A

THESIS

on

HYPNOTIC DERIVATIVES

of

BARBITURIC

ACID

By

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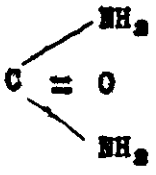
INTRODUCTION

This thesis has been an attempt on my part to amass in brief form the information on this large family of Barbiturates, as it is known and recorded from their introduction to the present time, and as it is contained in the libraries at my disposal. The references have been extracted briefly and to the point with the thought uppermost of indicating what information on the subject they contain. The barbitals have attained exceptional qualifications in their several fields, but, owing to their rapid multiplication, a thorough study and classification of their medicinal properties has been neglected. It is evident that what we need is not more hypnotic barbitals, but a more thorough understanding of the ones we have. May this thesis be of some assistance in attaining that end.

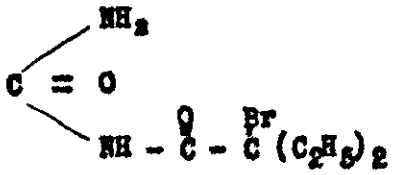
History

(1, 2, 4, 6, 9, 10, 11, 12, 13, 14, 17)

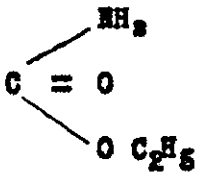
The barbiturates appeared first in 1903 when Emil Fischer and Von Mering (13, 2, 9) reported the hypnotic properties of diethylbarbituric acid, then called veronal. Barbital was isolated before by Conrad and Guthzeit (10) in 1882, but it was not until 1903 that the hypnotic properties were suspected. Their chemical relation to urea and other ureid hypnotics is indicated by the structural formulas (1, 2).



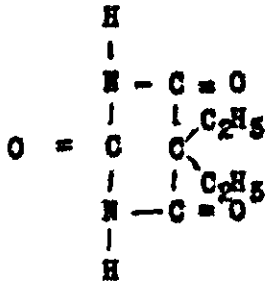
Urea



Carbromal



Urethane



Barbital

Sixty derivatives of barbituric acid are known (6), such as barbital, phenobarbital, amytol, etc., but there is possible as large a number as 1,225 with no more than six carbon atoms in the side chain. Many possible variations of the side chains have been prepared and tried since 1903, in an attempt to improve upon the hypnotic properties of barbital or to produce hypnotics covering other fields of hypnosis.

In 1918, Professor Stieglitz of the Federal Trade Commission of the U. S. A. urged that Barbital be the official name for the hypnotic then known as "veronal," (11). It was in the same year that Great Britain, realizing the increasing danger of allowing these important hypnotics to get into the hands of the laymen, had, through the Privy Council, all barbitals then known placed on the poison list (12), which permitted their sale only on an order from a doctor. As the newer hypnotics of this series were isolated, they were found to have properties

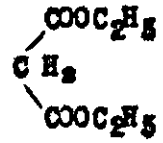
suitable for anaesthetic and pre-anaesthetic uses. The danger of barbitals increased as a result of these new uses, as they involved the use of intravenous injection. Thus it was that in 1935 the American Medical Association (14) made a rule allowing the injection of barbitals only where no other mode of administration was feasible and at the same time listed cases where the injection could or could not be used. All barbitals appeared on the Poison List on this continent in 1936 (4).

At the present time, as more is being learned about the action of the barbitals, they are coming to be classified according to their most satisfactory uses and some are used particularly for hypnotic action, some for sedatives, some for pre-anaesthesia and so on. An important field now entered by these hypnotics is that of obstetric amnesia. Pentobarbital, Pernocton and Rectidon (80, 265, 268) appear to be the ones best suited for this field.

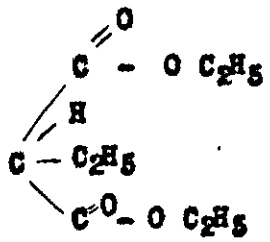
Chemistry

Preparation (4, 20, 21, 22, 25, 119, 155, 219, 220, 244, 246, 247, 252, 253, 257)

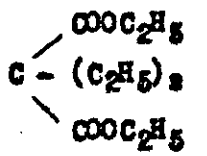
In general, the preparation of these compounds consists of the condensation of a di-ester of such a nature as to give the desired side chain with urea. In the case of Barbital, the diethyl ester of diethyl-malonic acid is the substance that is condensed with urea (20, 21). Until recently the chief problem was in finding a cheap suitable source for these complicated esters. The preparation of barbital is started with monochloracetic acid. This is treated with sodium cyanide and the resulting product hydrolysed with HCl in alcohol, yielding the ethyl ester of malonic acid.



This product is treated with the theoretical quantity of metallic sodium in absolute alcohol to get one of the hydrogen atoms replaced by an ethyl group -



With an excess of ethyl bromide the second hydrogen is replaced and diethyl ester of diethyl malonic acid results -



Diethyl cyanoacetic ester and diethylmalonyl chloride are other substances which, when condensed with urea or urea derivatives, produce barbital (21, 22, 25, 155). Cyanobutyric ester is a product which may be used for condensation with urea for barbital preparation, but is not commonly used, owing to the difficulty of its preparation (119).

The preparation of phenobarbital is now based commercially on the same basic principle as that for all barbiturate preparations, but the preparation of the condensing ester is more difficult. This is due to the fact that the phenyl group must be the one started with, as it is hard to introduce into a compound. Hence it is that in the preparation of phenobarbital (20) benzyl chloride is the starting point. Benzyl chloride is converted into phenyl acetic ester by treating it

first with sodium cyanide and then hydrolysing with acid in the presence of alcohol.

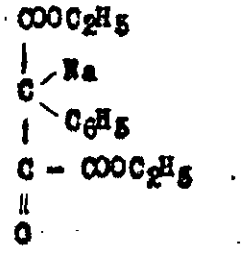
$$C_6H_5CH_2Cl + NaCN \longrightarrow C_6H_5CH_2CN + NaCl$$

Benzyl chloride — Benzyl cyanide

$$C_6H_5CH_2CN + C_2H_5OH + HCl \longrightarrow C_6H_5CH_2COOC_2H_5$$

Benzyl cyanide — Ethylphenyl-acetate

The ethylphenylacetate is condensed in the presence of alcohol and Na to form, with ethyl oxalate, sodium phenyl oxaloacetate -



This, when treated with HCl, removes CO and replaces the Na for H. This H is ethylated and the product condensed with urea to give phenobarbital.

Dial is prepared from the condensation of ethyl ester of diallylmalonic acid and urea (219). Neonal is prepared from the condensation of the esters of butylethylmalonic or butylethylcyanoacetic acids with urea (244, 246, 247). Ethyl ester of ethyl hexylmalonate is the product condensed with urea to produce Ortal (257).

Relation between Hypnotic Effect and Chemical Structure

(15, 77, 109, 140, 146)

On studying the chemical structure of these hypnotics, we find that we can identify the hypnotic effect with chemical groups present or their arrangement in the molecule. The hydrogen atoms on carbon 5 are very reactive and it is these on which the chief and most effective substitution takes place (15). If these hydrogens are replaced by halogens it is found that one of the halogens is more active than the other and it will react to form compounds with primary and secondary amines (115). The properties required in the side chains on carbon 5 may be summed up as follows :- (1) two hydrocarbon groups are required (110, 112), (2) the two groups must have a total of 4 carbons and not more than 8 carbons (112), (3) one must be an open chain, (4) not more than two alkyl groups should be aromatic in character (112), (5) benzyl group causes symptoms of tetanus (110) or convulsions (112), (6) any substitution in phenyl group on carbon 5 renders the drug inactive hypnotically (114, 115). Alkyl substitution on N reduces duration of action (151). There is a parallelism between the partition coefficient of the barbiturates and their hypnotic efficiency (109).

Many derivatives of barbituric acid have been prepared but in most cases physiological information on them has not been obtained, or, in some cases, that which has been obtained is not sufficient. Several thiobarbiturates have been prepared, both by substitution on carbon 5 and on other positions (116, 126, 130, 155). In some cases (130, 155) these thio derivatives have been reported as producing prompt sleep with rapid recovery. Fantus, in the 1956 Year Book of Therapeutics (130), evaluates pentothal sodium and accepts it as a suitable hypnotic and pre-anaesthetic.

Many other derivatives have been prepared showing hypnotic properties, but on the whole are not entirely satisfactory. Hill and Keach of Yale (125) prepared nine. Easterfield of Saskatchewan (158) prepared 2 ethoxy-barbituric acid, but it required exceedingly large doses for small depressant action. This same condition, together with variable toxicity, was found by Underhill and Johnson (129) who prepared other derivatives and classified them. N-mono or di- alkylated, 5 cyclo hexenyl or cyclopentenyl - 5 - alkylbarbituric acids have been prepared and are soporific (140), but no further report has been given.

Iso butyl - n - propyl barbituric acid (141) and N - amyl - ethyl barbituric acid, prepared by Dox and Jones of Parke-Davis Research Department (142), are powerful hypnotics. It has been found since that iso amyl ethyl barbituric acid (amytol) is a better hypnotic than the N-amyl (155).

Identification (24, 41, 154, 167)

Since much experimenting has been carried on in barbiturate research, many identification tests have been worked out for the purpose of barbital identification in tissue, blood and urine and for individual identification. In cases of identification in urine, blood and tissue, the extraction is made with chloroform from urine acidified with HCl and from blood after sodium tungstate and H_2SO_4 have been used as precipitants. The tissue is prepared for extraction by means of $CuSO_4$ or liquid air (25, 33). Once the extract is obtained, the presence of the barbiturate is identified colorimetrically with (a) cobalt acetate and isoprolamine (25, 33, 34, 36), (b) copper and baryta (26), (c) microsublimation method by Fischer and Reisch (28), (d) $NaNO_2$ and H_2SO_4, in which the depth of the straw or brown color is compared (40). Extracts are made from tissue by means of hot alcohol and tartaric acid (41).

In vitro the barbiturates are identified by their physical properties, crystalline structure (29, 154), and by their reactions to precipitants such as copper and baryta (26) and berberine sulphate (27). Derivatives, such as the xanthydrol and p-nitrobenzyl derivatives, are prepared (30, 31) and their physical properties are compared. The p-nitrobenzyl derivatives have proven the better for identification of this nature (31).

Pharmacology

Location of the Central Depression (2, 5, 36, 50, 54, 61, 221, 255)

In the large amount of work recently done on the hypnotic barbiturates, much material has been brought to light on the action of these drugs on the various organs and tissues of the body. Keeser (1927) places the scene of central depression in the cerebral cortex and probably also in the subcortical ganglia, especially the hypothalamic portion of the diencephalon (2, 5). Kopponyi found that on injection of anaesthetic doses of barbital the drug was found equally distributed in all parts of the central nervous system (5). Dille, Linegar and Kopponyi (50) claim that no organ has any specific affinity for the barbiturates, but barbital is less concentrated and pentobarbital more concentrated in the brain than in other organs. Phenobarbital does not act on the sympathetic or parasympathetic nervous system. Barbital, however, reinforces the excitability of sympathetic innervation and a paralysing action on the irritability of the parasympathetic innervation (61). Fabre (54) has shown that the placental membrane is perfectly permeable to barbiturates. Dial constricts the blood vessels in the brain (221), giving it a useful quality when used in anaesthesia for head operations. Ipral affects the higher cerebral centres (255).

Circulation (2, 43, 44, 45, 46, 47, 48, 57, 58, 60, 150, 164, 175, 196, 215)

Formerly it was believed (Impens) that there was a rise in blood pressure when barbitals were administered, but Gruber and Baskett of Washington (45) and Gruber and Roberts (44) and Anderson, Chen and Leake (48) claim they have reason to believe that blood pressure falls with the injection of the barbiturates. Barbital was the greatest offender in this respect, causing the greatest fall and slowing the heart beat at the same time (48, 60). Zorfas and McCullum, 1929, and Mason and Baker, 1930, (2) claim that the fall of blood pressure is due to the rapid injection and of too concentrated solutions. They maintain that with slow injection of dilute solutions no drop in blood pressure is observed. Although vaso constriction is possible with concentrated solutions which lower pH, it is usual to have vaso dilatation of the cerebral vessels with barbital, and phenobarbital, sodium, amytal, isopropyl allyl barbituric acid (45). These actions are directly in the walls of the blood vessels (45). It was found (46) that there was a lowering of blood sugar and a fall of coagulation time of the blood and a fall in anal temperature for some period of time, up to 44 hours, during barbital narcosis in pigeons and cats. Basaki noted also the delay in coagulation time in barbital and phenobarbital narcosis (57). No change in blood count is noticed even on long treatment with barbiturates (47). Pernocton, amytal and sandoptal are the most toxic to circulation (58). Phenobarbital and pentobarbital lower blood pressure (175, 196). Amytal strengthens the beat of the heart (215).

Respiration (2, 45, 48, 150, 164, 196, 208)

The respiratory centres are affected to a varying degree, depending on the size of dose, the mode of dosage and the rapidity of administration (Zorfos and McCullum (2)). As a rule, however, it is accepted that with intravenous injections of clinical doses of ipral, neonal, barbital, phondorn, amytal and dial, respiration is more shallow but slightly accelerated (2, 48). Phenobarbital and pentobarbital have a sedative action on the respiratory system. Phenobarbital kills by paralyzing the system (164, 196). It is claimed by some (150) that barbital is without effect on respiration and that amytal (205) diminishes it.

Smooth Muscles (2, 65, 65, 208, 259)

Smooth muscle is depressed to a varying degree with barbiturates. Clinical doses do not produce significant effects and even in full anaesthesia the depression is less than with ether. The contractions of the parturient uterus are not affected by the full analgesic dosage (2). There is a reduction in motility of the gastro-intestinal tract and loss of tonus and delay in the emptying time of the stomach (2), (Gruber, 65). Amytal does not affect rhythmic contraction of the uterus of guinea pigs (208). Ortal (259) is claimed to be more active in depressing excised smooth muscles than is amytal.

Basal Metabolism (2, 48, 260)

On the whole, the basal metabolism is not significantly changed even by full hypnotic doses (2). Ipral, sodium barbital, neonal and phenodorn decrease oxygen consumption and amytal and phenobarbital increase oxygen consumption, while dial has mixed effects (48). Pernocton and phenobarbital cause transitory inhibition of diuresis (260).

Temperature (2, 48, 196)

Due partly to depression of the medullary centres and partly to diminution of movement, there is a slight lowering of temperature in sedative doses and marked lowering in coma (2). There was a definite fall in anal temperature in narcosis of pigeons (46). Pentobarbital (196) lowers body temperature.

Fate and Excretion (2, 3, 4, 6, 36, 42, 55, 144, 154, 175, 254, 262)

The excretion of barbital occurs practically exclusively by the urine, the faeces containing only traces. The total recovered and the speed of excretion vary greatly, and these differences are chiefly responsible for the varying duration of the action (2, 3). The action of barbitals (6) depends on the effect of side chain oxidation ; the longer it takes for the drug to be oxidised to barbituric acid, if it is oxidised to the acid, the longer the action will persist. Barbituric acid is inert. Barbital is excreted unchanged, but only 25% of phenobarbital and 5% of phanodorm is excreted unchanged (4, 144). Dogs differ from man in that 70 to 85% of barbital is excreted in their urine unchanged (42). The products of the remaining barbital are not known. The rate and degree of excretion of these hypnotics are not affected by diuretics. Excretion decreases in order - dial, neonal, phenobarbital, pernocton and amytal (36, 154). Physiological salt solution or glucose solution have been found to be the best diuretics in cases of barbiturate poisoning (55). Ipral is known to persist in the body for twenty-four hours (254). Non toxic acetonyl compounds are the products formed in oxidation of noctal and pernocton (262). It has been shown (175) that phenobarbital is excreted by the mammary glands, so that care must be used during the nursing period.

Poisoning (2, 4, 7, 85-108, 154, 180, 181, 218, 219, 254)

Barbiturate poisoning is fairly common and though sometimes caused by over-susceptibility, is generally caused by over-dosage, either in therapeutic use or with suicidal intent. The symptoms of acute poisoning are those of mental confusion, nausea, muscular weakness, inco-ordination, and later, with marked fall in blood pressure, depression or even paralysis of respiration. Asphyxial convulsions and mydriasis may occur. Renal necrosis has been reported. Death is caused by paralysis of respiratory organs (2, 92, 94, 154). Chronic poisoning is symptomised by rashes, cyanosis, cerebration and cramp-like pains and near death broncho-pneumonia appears (4, 86, 180, 181, 182). Renal and hepatic insufficiency, hyperthyroidism and severe toxemia are conditions which make a person susceptible to poisoning (103). Amytal is claimed to be the least toxic of the barbitals (7), but has shown skin rashes, subjective nervous system, tachycardia and slight anaemia in certain cases (218). Luminal has frequently (180, 181, 182) caused symptoms of chronic poisoning. Evipan (93) has caused widespread paralysis following its use for general anaesthesia. Dial (219) has been known to cause skin rash and fever, while phanadorm (254) causes respiratory failure and lung edema in toxic doses.

In chronic poisoning removal of the drug seems to be sufficient to return the patient to normal, but in acute poisoning more rapid means of removing the drug from the system must be taken. The treatment should consist of evacuation if possible, and administration of stimulants. Picrotoxin (95, 99, 98) has attempted to attain the open market several times as an efficient antidote, as it is claimed (a) to cause a rise in blood pressure, (b) to prevent a steep fall, (c) to stimulate respiration, and (d) to maintain respiration even after cardiac stoppage. The American Medical Association (97), however, will not permit its free sale as yet, as they are not completely satisfied with the claims made for it by the manufacturer. Lumbar or cisternal drainage (104) is tried in very acute poisonings. Blood letting and artificial respiration are possible treatments (100, 96), together with the administration of adrenalin or ephedrine HCl or strychnine as antidotes. Coramine has been recommended as a suitable antidote (105), but alcohol is still superior to it (108). As yet the most reliable and commonly known antidote is strychnine. The statement has been made by one authority (85) that less than 1% of all suicides can be attributed to the barbitals.

Addiction (2, 5, 82, 89, 91, 101, 102, 164)

Addiction to barbiturates seems to be acquired fairly readily (2) and may lead to chronic poisoning which is characterised by confusion, mild dementia, debility, ataxia, gastro-intestinal irritation, anaemia and hematoporphyrin. Campbell (82) states that "fear of habit formation is much exaggerated;" other experimenters (5, 89, 101, 102, 164) definitely report addictiction, if not to all people, at least to a good many. However, long continued sedative therapy does not produce reduction in the original intelligence quotient (91), though barbital addiction is usually noticed in persons with lower than the average intelligence quotient.

Tolerance by Habituation (2, 51, 87, 234)

Repeated administration diminishes somewhat the hypnotic effect and raises the fatal dose to perhaps double (2). It seems to be a fact that continued sedative therapy with barbitals does produce a noticeable tolerance and this fact has been proven in the case of rats by Stanton (87). Ipral tolerance is not readily established (234). Eddy (51) claims that after repeated administration of barbital and phanodorm in cats, no tolerance was observed.

Therapeutic Uses

As Hypnotic (1, 2, 3, 7, 69, 75, 151, 152, 157, 159, 142, 150, 152, 162, 164, 168, 186-189, 200, 202, 219, 220, 234-245, 255, 264, 266, 267, 270)

Barbital and its derivatives are decidedly more actively hypnotic and somewhat more analgetic than chloral hydrate. Some of the derivatives are even more hypnotic than barbital itself, but usually their margin of safety is not as large. The action of these hypnotics is slower than with chloral hydrate, but more rapid than with sulfonemethane. In the absence of pain, small doses usually induce sleep within half an hour. The sleep lasts from 4 to 8 hours, depending on the individual, the drug and the dose. The patient generally awakens refreshed, but occasionally there is lassitude, vertigo, headache, nausea and diarrhea (1, 2, 3). Barbital produces a natural, dreamless sleep, lasting for 6 to 8 hours, while phenobarbital produces a natural sleep for 3 to 6 hours (2). Amytal and pentobarbital, on the other hand, produce a sleep of much shorter duration (6) and the patient has deeper lassitude and vertigo on awakening.

Barbital itself seems to be the most satisfactory hypnotic of this series for simple insomnia, nervous insomnia, and insomnia from cardiac disease (150). Only small doses of barbital are required for insomnia (152). Amytal is claimed by Lilly Research Laboratories (7) to be a better hypnotic than barbital, but practically, this has not yet been proven. It has a more valuable use in pre-anaesthesia. Phenobarbital (69, 162, 164) is also a good hypnotic. Its toxic properties are higher than those of barbital. The hypnotic properties of phenobarbital are improved when calcium is administered along with it (168). Amytal (200, 202), dial (219, 220), alurate (264), sandoptal (266) are all effective hypnotics with reasonable margins of safety. Their toxicity is higher and their after-effects more pronounced than the corresponding ones for barbital. Pentobarbital (187, 186, 188, 189(is effective in smaller doses than that required for barbital and its action is more rapid, lasting around four hours. Ipral produces a good sleep (234, 236, 237, 238), but due to its long remaining after-effects the patient is likely to sleep well the second night on the one dose. Nostal (239, 240, 242) is effective as a hypnotic (twice as much as barbital), but has undesirable after-effects. Neonal (245, 245, 249) is three times as active hypnotically as barbital. Ortal (255, 256) also is more effective than barbital, it has less toxic properties, but the effect is shorter. Hence it is not entirely suitable for simple hypnotic action. N-amyl ethyl barbituric acid (142) was introduced by Parke Davis (1928) and was claimed to have excellent hypnotic properties. Since then iso amyl ethyl barbituric acid has proven superior. The thio-barbituric acids (151), phenyl allyl barbituric acid (159) and ethylene N-N' bisbarbital have all laid claim to hypnotic properties. The latter, a di-molecular compound, is claimed to be three-fourths as hypnotic as barbital. Rectidon is a hypnotic

and administered rectally. It is claimed (270) that it has no effect on heart or blood pressure. Eldoral, ethyl pentamethylene uramil (267), is not claimed to be a hypnotic, but produces a preliminary condition for prevention of nervous insomnia.

As Sedative (1, 2, 5, 150, 162, 164, 200, 201, 202, 239, 245, 251, 266, 267)

This field is similar to that of the bromides but the barbiturates act much more promptly and may be used to produce much more profound effects. They are useful in toxic goiters to lower the nervous excitability, the muscular activity and the basal metabolism. The nervous vomiting of pregnancy has been treated successfully with these hypnotics, phenobarbital, in particular, one hour before meals and at bedtime, or hypodermically every four hours. This agent is similarly useful as a preventative of sea-sickness (1, 2, 5). All of the barbiturates have sedative properties to a greater or less extent. Their use as such is controlled, however, by their side-actions. Phenobarbital at present is the most suitable for straight sedative use (150, 162, 164). Amytal is claimed by Gorvan (202) to be unsatisfactory as a daytime sedative. Neonal, on the other hand, exerts a sedative action to an exceptional degree and is useful, therefore, in high nervous tension, neurosis and other conditions in which a sedative is required (245). In many cases of the short-acting hypnotics such as amytal, phanodorm, nostal, alurate, the sedative action is controlled by the dosage and the dosage in these drugs is kept quite low.

Epilepsy (1, 2, 5, 162, 164, 176, 271)

The barbiturates are active in diminishing the number and severity of the attacks, especially of the motor type, and thus indirectly improve the mental and physical condition of the patient. The improvement persists only during the medication. Acute attacks are controlled more efficiently than chronic or mild seizures and idiopathic and traumatic epilepsies are more amenable than the senile and syphilitic. The effects and efficiency are about the same as with bromides, but either may succeed when the other has become ineffective. The two medicaments are often combined to reduce the dosage of both. The barbiturates have several advantages over bromides in that the improvement is more rapid and the undesirable side actions are less (1, 2, 5). Phenobarbital is usually the hypnotic employed (2, 162, 164) and is most effective. Care must be taken when using it in this capacity as tolerance is apt to be established, necessitating increase in dosage. Serious relapse has been observed in epileptic patients following the withdrawal of phenobarbital (162). Cushny (176) believes phenobarbital's greatest action to be in the treatment of epilepsy. Rutonal (271) has been recommended in the treatment of epilepsy.

Anticonvulsant Action (2, 170, 176, 199, 202, 216, 217)

Convulsions of the central organs, such as those produced by strychnine poisoning, meningitis, tetanus, eclampsia, cocaine poisoning and insulin overdosage, are effectively controlled by the barbiturates. Tatum and Collins in 1925 showed the antagonistic action of barbiturates against cocaine poisoning in dogs (2). Phenobarbital (176) has been used effectively in the control of convulsions in strychnine and cocaine poisoning. Amytal (202, 216, 217) has proven more effective in the modern treatment of strychnine poisoning. The treatment consists chiefly in intravenous administration of sodium amytal during the premonitory stage or when the convulsions have begun. The dose is usually 7½ grams. Sodium pentobarbital is used intravenously in the same manner (199) but is less effective in equivalent doses.

Analgetic Action (2)

Ordinary hypnotic doses have limited analgetic properties. Clinically relief has been obtained in severe burns and in syphilitic gastric crises by pentobarbital, .5 to .8 grams. Migraine and paroxysmal and recurrent headaches respond fairly well to phenobarbital three times daily. The barbiturates are prescribed in combination with antipyretic analgesics in the treatment of headaches and neuralgic and neuritic pains (2).

Preliminary Tranquillisation (2, 150)

The barbiturates compete with morphine in this field and their action may be graded through a wider scale. If sleep is desired in a hurry before operation, it may be secured by intravenous injection. In local anaesthesia, the barbiturates have the additional advantage of being a prophylactic against acute poisoning by cocaine and procaine. A combination of morphine and barbiturates is effective. Pernocton cannot be used with morphine due to the danger of the additional depression. The long sleep and amnesia after the operation ease the ordeal for the patient, and those who have been subjected to several anaesthesias generally prefer the barbiturate and N_2O or ether sequence. The chief disadvantage of barbiturates consists in the varying susceptibility to the depression and in the duration of the post-anaesthetic stupor. When this is too prolonged it may be a positive advantage by resting the patient, as with pentobarbital ; but it limits the use of barbital and phenobarbital ; amytal and pernocton are intermediate.

In Anaesthesia (2, 5, 71, 72, 74, 80, 83, 84, 150, 166, 169, 186, 190, 193, 195, 200-206, 215, 221, 225-228, 251, 253)

The barbiturates have three prominent uses in anaesthesia. They may be used as basal anaesthetics (Fredel and Perlis, 1924 (2), as premedication to anaesthesia (Brumm, 1927, (2) or for obstetric amnesia (Diakin et al, 1929 (2). Of course, being non volatile they must be administered rectally, orally, hypodermically or by vein. This fact entails a more prolonged and continuous action, but allows no flexibility. One more disadvantage is the duration of stupor which may last for hours after the operation. On the whole, except in experimental work, the use of the barbitals for basal anaesthesia is not justified, as their advantages do not outweigh their disadvantages. Swanson (193) has classified sodium pentobarbital equal to sodium amytal in basal anaesthetic properties, but both are more satisfactory than either sodium phenobarbital or sodium barbital. Kleindorfer and Halsey (74) also believe sodium amytal to be efficient, but maintain that dial and iso propyl allyl barbituric acid should be used with caution as basal anaesthetics. Desplas (84) has recommended ethobutylethylbarbituric acid as a satisfactory basal anaesthetic when administered intravenously. Fantus, in his 1936 Year Book (150), lists the advantages of pentothal sodium as a basal anaesthetic. He claims it is safe, rapidly broken down, is smoother and causes less twitching than does evipal. It has no effect on the blood pressure, but is depressive to respiration. The recovery is slower than with nitrous oxide and there is no vomiting. This material is from clinical data supplied by Jarman and Abel.

Even greater use is now being made of the barbiturates in conjunction with a surgical anaesthetic (2, 5). They are used as premedication to the volatile anaesthetics, ether, ethylene or nitrous oxide. Their use with the latter has proven most effective and is a definite accession to anaesthetic technique. When these hypnotics are administered before volatile anaesthetics, the patient has no sense of suffocation or induction of general anaesthesia (166). The amount of N_2O or other general anaesthetic can be decreased and a larger oxygen supply maintained, thus eliminating cyanosis. Post operatively the patients are free from nausea, vomiting and laryngeal mucus. Stormont, Lampe and Barlow (71) have determined allonal, dial and neonal to be the most efficient in nitrous oxide anaesthesia as a 30 minute anaesthesia may be obtained with 30% M.L.D. with 85-15% mixture of the gas and oxygen, whereas with barbital and amytal 45% of M.L.D. was required. Barlow, Duncan and Gledhill (72) with a 80-20% mixture of gas found 30% M.L.D. of pentobarbital was required, 37.5% M.L.D. of panodorm and 45-50% M.L.D. pernocton. Sodium amytal used as pre-anaesthetic medicant (201, 205, 205) produces a quiet sleep of several hours after the operation. Pentobarbital (190, 193, 169) synergizes with morphine when both are used. Morphine, on the other hand potentiates amytal. In pre-anaesthesia pentobarbital may be administered orally or rectally. It may be used to advantage prior to local or spinal anaesthesia (186). Evipal (227, 226) has been highly recommended as a pre-anaesthetic medicant, but its advantages

are not sufficient to warrant its acceptance by the medical profession (225). Patients must be prone, not old or feeble and a constant airway must be maintained with this hypnotic (228, 253). Evipal has been found efficient in anaesthesia for radium therapy (251). Spinal reflexes remain active when dial is used (221).

Obstetric Amnesia (2, 80, 81, 191, 192, 261, 263, 268, 269)

The barbiturates have shown their effectiveness recently in producing obstetric amnesia. They are used not with the intention of total anaesthesia but to induce a condition where the patient is drowsy and drops off to sleep between pains. The pains are not diminished but are little felt and not remembered. The labor is not delayed, circulation, respiration and temperature remain normal, the babies are not narcotized and breathe promptly. This effect requires a full hypnotic dosage of the drug by mouth or rectum at the beginning of labor and repeated when the cervix has dilated 5 or 4 cm. (2). Barbiturates, it is stated (81), are less valuable when used alone than when used with other drugs. When using Pentobarbital, 5 grains, the patient sleeps or doses between pains and the uterine contractions are unaffected. Complete amnesia may be produced with larger doses (191, 192). Pentobarbital has proven more efficient than barbital and amytal in combination with ether in producing obstetric amnesia, due to its large ratio (2.7) of the M.F.D. to M.E.D. (80). Pernocton (261, 263) has been used and also rectidon with no ill effects to mother or child. The latter (268, 269) is administered by rectum.

General Properties

(2, 19, 156, 162, 165, 185, 184, 274, 275)

The barbiturates are crystalline or hygroscopic powders, odorless, colorless, with a taste slightly bitter. Their melting points range from 122° to 203°. The acids are sparingly soluble in water but readily soluble in ether, alcohol, chloroform, solutions of alkali carbonates and alkali hydroxides. The sodium salts, which have an action similar to the parent hypnotic and are used for solutions internally and intravenously, are readily soluble in water, sparingly soluble in alcohol and insoluble in ether or chloroform. The tests for purity include chiefly those for chlorides, sulphates, readily carbonizable substances, salts of heavy metals and, in the case of the sodium salts, a limit of the free acid. (Complete physical properties are given in the official references under each drug.)

In dispensing, the sodium salts of barbital and phenobarbital may be dispensed interchangeably with barbital and phenobarbital, where their physical properties indicate. For hypnotic use these drugs are dispensed in tablet or capsule form, for mixtures the sodium salts are used. In the case of intravenous injection, when the substance must be sterile, the sodium salt is used and the sterilizing is done by tyndalization (156, 162, 165). The "acids" decompose on heating with alkali carbonates or hydroxides and solutions of them and calomel darken slowly (158). The sodium salts are incompatible with ammonium salts, acid salts, morphine HCl, Tr. Cinchona and fruit essences (158, 162, 165). The end products of phenobarbital decomposition in aqueous solution have been studied (184, 185) and phenyl ethyl acetyl carbamide and carbon dioxide have been identified. Glycerin is a good vehicle for the barbitals and disguises the taste nicely (19, 274, 275).

The mode of administration, whether by mouth, rectum, subcutaneously or by vein, is determined by factors of the particular case. It is usual to use oral administration for simple insomnia. In anaesthesia the usual methods of administration are intravenous and rectal. Oral administration is the safest and the one preferred, except when rapid results are required and then intravenous administration may be employed. The choice of the drug is determined by (a) its safety margin (2, 5), that is the margin allowed by the difference between the minimum effective dose and the minimum toxic or fatal dose, and (b) duration of effect. Pentobarbital ranks high in both criteria, having a large safety index and short duration, when considered as a pre-anaesthetic. There is, on the whole, a wider range of M.E.D. to M.L.D. (67) for amytal than for barbital. In the case of administering for premedication, a hypnotic dose is given the night before the operation. One and a half or two hours before the operation pentobarbital sodium, 5 to 7½ grains, is given orally, or sodium amytal, 5 to 9 grains. Morphine is then administered one half to three quarters of an hour before the operation.

If the barbitals are injected intravenously, the procedure is reversed and morphine is given first, followed ten minutes before the operation by the barbiturate, injected slowly by vein as a 10% aqueous solution of the sodium salt (2). In obstetric amnesia a full hypnotic dose is given orally before labor commences, then after the dilation of the cervix a further dose is given intravenously (2). For sedative action the barbiturate is administered in tablet form three times a day.

Advantages of the Barbiturates

1. The effect of the barbitals is prompt, securing dreamless sleep in 20-30 minutes after oral administration and immediately with intravenous injection.

2. The degree of action may be easily graded by the dosage, from slightly sedative to complete coma.

3. The circulation, respiration, metabolism, smooth muscle remain practically normal with full anaesthetic dose, not being disturbed until near toxic dose is reached.

4. No undesirable after-effects are noted after the duration of narcosis.

5. The drugs may be administered by all channels, mouth, rectum, hypodermically or by vein, since they cause no serious local irritation.

6. There is no danger of serious accumulation, practically no habituation and small liability of addiction.

Disadvantages of the Barbiturates

1. Individuals vary in their response to the drugs, some to a marked extent.

2. Frequently there is a period of excitement and inebriation before the true hypnotic effect becomes operative.

3. The sleep and hebetude may be prolonged to an undesirable degree.

4. Severe cholera-like diarrhea has been reported.

5. In some individuals marked skin reactions occur.

6. In exceptional cases collapse occurs.

Conclusion

(98, 99, 89, 105, 118, 125, 129, 151, 157, 158, 140, 141, 146, 147)

It appears that, though we have numerous hypnotic derivatives of barbituric acid on the market, their true values have not received the wide recognition that is due them. This, in part at least, may be because of the improper use of many, due to lack of complete information concerning them. It is a fact that more physiological information is required before the average practitioner can choose the one drug that is best suited for the particular case he has in hand.

To attempt to produce a new hypnotic that is related to these, requires a study of the relation of hypnosis to the chemical groups in the present barbitals. In this connection one might point out that (a) the benzyl group cannot be used, (b) the ether derivatives on carbon 5 have been prepared and have not proven satisfactory (125, 129, 158), (c) N - substituted derivatives (117, 151) and tertiary alkyl derivatives (118) have good possibilities, (d) the Br CH : C Me CH_3 group on carbon 5 has been suggested (157) and (e) the thiobarbituric acid derivatives warrant a closer study. Other compounds that have been prepared and recognized as hypnotics, but apparently not studied physiologically, are iso-butyl-N-propyl barbituric acid (141), phenyl allyl barbituric acid (146), crotylallylbarbituric acid (147), N-alkylated 5 cyclopentenyl or 5 cyclohexenyl barbituric acids (140). The study of the use of barbitals in drug withdrawal from addicts (185) might be suggested, or the search for a reliable antidote to barbital poisoning, as suggested in coramine (105) or picrotoxin (98, 99) might be commenced. In our future study of these compounds let it be remembered that man is more susceptible than animals (89) and that testing the products in the open market is a slow and dangerous method of proving the doubtful value of the drug.

Drug	Chemical Name	Synonym	Where Official	Dose	Remarks
Amytal ✓	iso amyl, ethyl		N.N.R.	1.5 to 12 g.	sedative, hypnotic, pre-anaesthet
Barbital ✓	di ethyl	Veronal	B.P., U.S.P., N.N.R.	1½ to 8 g.	hypnotic, with analgesics
Dial-Ciba ✓	di allyl	Dial	N.N.R., B.P.C.	½ to 4½ g.	sedative hypnotic
Ipral Calcium ✓	calcium ethyl isopropyl	Ipral	N.N.R.	2 to 4 g.	hypnotic
Neonal ✓	N-butyl ethyl	Soneryl	N.N.R.	¾ to 6 g.	hypnotic, sedative
Nostal (Noctal) ✓	iso propyl-(β) β brom allyl		N.N.R.	¾ to 4½ g.	sedative, hypnotic
Ortal-Sodium ✓	Na, n-hexylethyl	Ortal	N.N.R.	5 to 6 g.	hypnotic
Pentobarbital-Sodium ✓	Na, ethyl (1 methyl butyl)	Pentobarbital, Nembutal	N.N.R.	½ to 6 g.	hypnotic, pre-anaesthetic, infant analgesia
Phanodorm	Δ Cyclo-hexenyl ethyl		N.N.R.	1½ to 6 g.	hypnotic
Phenobarbital	phenyl, ethyl	Luminal, Gardinal	B.P., U.S.P., N.N.R.	¼ to 10 g.	sedative, hypnotic, epilepsy
Phenobarbital Na	Na, phenyl, ethyl	Luminal Sod.	B.P., U.S.P., N.N.R.	¼ to 11 g.	for hypodermic injections
Sandoptal	iso butyl allyl		N.N.R.	3 to 12 g.	hypnotic
Sod. Amytal	Na, iso amyl ethyl	Amytal Sodium	N.N.R.	3 to 12 g.	hypnotic, pre-anaesthetic
Soluble Barbital	Na, di ethyl	Medinal, Veronal Sod.	B.P., U.S.P., N.N.R.	1½ to 8 g.	sedative, hypnotic, injection
Alurate	allyl isopropyl	allonal	N.N.R.	1 to 2 g.	hypnotic
Sod. Alurate	Na, allyl isopropyl		N.N.R.	1 to 10 g.	hypnotic, pre-anaesthetic
Ipral Sodium	Na, ethyl isopropyl		N.N.R.	2 to 4 g.	hypnotic
Seconal	allyl (methyl butyl)				
Pentothal	Et (methyl butyl) thio				

Kalmal hypnotic — β brom allyl isopropyl

Evipal — me cyclohexenyl N Me

Reference Number 1

New and Non-official Remedies 1936

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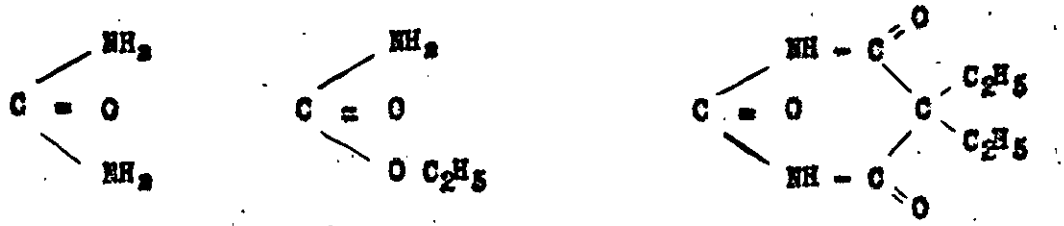
Barbituric Acid Derivatives

Barbital is chemically diethylbarbituric acid which is related to urea and the carbamate hypnotics.



Urea — Ethyl carbamate "Urethane" — Diethyl barbituric acid "Barbital"

The ethyl groups may be replaced by other alkyl or aryl radicals to form a large number of derivatives. Compounds in which one of the ethyl groups of diethylbarbituric acid is replaced by an isoamyl group (amytal), a normal butyl group (neonal), an iso-propyl group (ipral), a cyclo-hexenyl group (phanodorm), an n-hexyl group (ortal), a 1-methyl butyl group (pentobarbital) and a phenyl group (phenobarbital, luminal) etc., are accepted for the N. N. R.

These "acids" are sparingly soluble in water, but freely soluble compounds are formed by substitution of sodium for the hydrogen of one of the NH groups of such acids to make sodium barbital (soluble barbital U.S.P.), sodium phenobarbital (soluble phenobarbital U.S.P.) and others.

Actions and Uses -m Barbital and its derivatives are effective sedatives and hypnotics, and are used as such in simple insomnia, hysteria, neurasthenia, thyroid disease and chorea, in epilepsy in the intervals between the seizures, in mental disturbances and in pending delirium tremens. They also augment the action of analgesics such as aminopyrine, acetophenetidin and acetyl salicylic acid, and they are used in combination with these analgesics for the relief of pain, especially of neuralgic character.

They are decidedly more actively hypnotic and somewhat more analgetic than chloral hydrate ; they do not produce local irritation and the taste is not disagreeable. The margin between the ordinary therapeutic dose and the toxic dose is somewhat wider than that with chloral hydrate, and small therapeutic doses have little effect on blood pressure and respiration. Several of the derivatives

of barbital are more actively hypnotic than the parent substance and may be preferred, especially as a sedative ; but there is no satisfactory evidence that the margin between the therapeutic and toxic doses of these derivatives is wider than in the case of barbital itself. The action is somewhat slower than with chloral hydrate, but more rapid than with sulfonmethane. In the absence of pain small doses usually induce sleep within half an hour. The sleep lasts for four to eight hours, varying with individuals, with the drug used and with the dose. The patient generally wakens refreshed, but occasionally there is lassitude, vertigo, headache, nausea and diarrhea on the following day even after moderate doses. Skin eruptions are sometimes observed. Fatal collapse (by peripheral paralysis of the blood vessels) has occurred after relatively small doses. Toxic doses cause lowered body temperature, depression of the respiration and circulation, and feeble heart beat. There is long-continued stupor, sometimes interrupted by excitement. The condition has been confused with uremia, epidemic encephalitis and opium poisoning. The slower the excretion of the various members of this group, the more lasting is the action, and with very slow excretion ordinary doses may produce cumulative toxic effects after some time. It is therefore safter to intermit the administration at least weekly. Continued use may lead to habitual addiction. Barbital preparations are usually administered orally or rectally. In rare instances intravenous injections may be used (J.A.M.A. 97 : 1886, Dec. 19, 1931 ; 101 : 208, July 15, 1933) but this method does not offer any advantages, except when oral administration is not feasible or when unusually prompt action is imperative. Recent experimental work indicates that fairly large doses are effective against poisoning by local anaesthetics like cocaine and prococaine, and their salts, and against strychnine and picrotoxin.

Reference Number 2

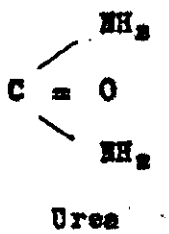
Manual of Pharmacology. Torvald Sollmann, M.D.

Page 769.

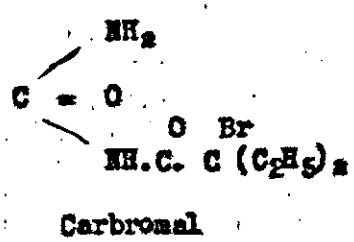
Barbital and Other Barbituric Acid Derivatives

Chemical Structure :-

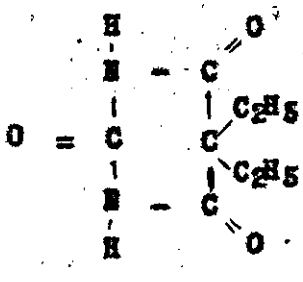
Barbital was introduced in 1903 by Emil Fischer and Von Mering under the name of Veronal. Its chemical relation to urea and to other ureid hypnotics is indicated by the structural formulas :



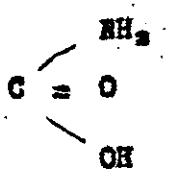
Urea



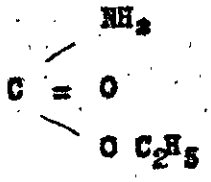
Carbromal



Barbitol



Carbamic Acid



Urethane (ethyl carbamate)

The "acids" are only sparingly soluble, but their salts are readily soluble.

The numerous barbitals have in general the same actions and in a therapeutic sense may almost be considered as different preparations or forms of one substance. They differ in dosage, in duration of action, and somewhat in breadth of the therapeutic zone ($\frac{\text{fatal dose}}{\text{therapeutic}}$). The relation of the substituted groups to the degree of pharmacologic action appears complex. In general, the effectiveness follows the Meyer-Overton Law, increasing with the partition coefficient ($\frac{\text{solubility in oil}}{\text{solubility in water}}$) ; and decreasing less consistently with the surface tension. Some compounds, however, fall out of order.

Therapeutic Uses :-

The barbiturates are used extensively for securing calmness and sleep, to suppress convulsions, and for partial and even complete anaesthesia. Sedative doses are not markedly analgetic, but their addition to other analgetics renders these most effective, presumably by reducing the apprehension of pain.

Advantages of Barbiturates :-

The degree of action may be easily graded by the dosage, from slightly sedative to complete coma. The effect is prompt, securing dreamless sleep in twenty to thirty minutes after oral administration and immediately with intravenous injection. Even the full anaesthetic dosage produces little if any disturbance of other functions ; the respiration, circulation, metabolism and the smooth muscles remain quite or practically normal until the fatal dosage is approached. There are no undesirable after-effects beyond the duration of the narcosis. There is no serious local irritation, so that the drugs may be administered by all channels, by mouth or rectum, hypodermically or by vein. There is no dangerous cumulation and practically no habituation, no need for increase of dosage, and relatively small liability of addiction, none beyond that entailed by the desire for easy sleep.

Disadvantages of the Barbiturates :-

The response is rather variable and quite markedly so in some individuals. The hypnotic effect is often preceded by considerable excitement, inebriation and even delirium, and the sleep and hebetude may be undesirably prolonged. Collapse occurs exceptionally. Severe cholera-like diarrhea has been reported. In some individuals the barbiturates produce marked skin reactions, resembling urticaria, purpura, measles or scarlatina.

Location of the Central Depression :-

This is on the cerebral cortex and probably also on the subcortical ganglia (E. & J. Keeser, 1927), especially the hypothalmic portion of the diencephalon. The bulbo-spinal reflexes are very little affected (Pearcy and Weaver, 1927).

Respiration :-

With oral administration, hypnotic doses produce slight slowing, chiefly through the sleep. Larger doses depress the respiratory centre directly, reducing the depth and rate, often with irregularities (Page and Coryllis, 1926). With intravenous injection of clinical doses, the respiration becomes more shallow and often slightly accelerated, but it remains regular (Zerfos and McCullum). Even hypnotic doses may paralyse the respiratory centre if injected too rapidly.

Circulation :-

Anaesthetic doses cause no significant change in the circulation, clinically or in animals, with oral or hypodermic or slow intravenous administration. The blood pressure remains normal ; the heart rate may be slightly quickened ; the color of the skin is generally unchanged, sometimes pale or slightly cyanotic. With rapid intravenous injection, there is a prompt fall of blood pressure, averaging 30 mm. in clinical cases, generally with prompt recovery to the normal level. It is probably due to the temporary flocculation of the sparingly soluble barbituric acids, at the reaction of the blood ; it may therefore be prevented by slow injection of dilute and alkalinized solutions (Zerfas and McCullum, 1929 ; Mason and Baker, 1930).

Smooth Muscle :-

This is always depressed by adequate doses but in varying degree. Clinical doses do not produce significant effects, and even in full anaesthesia the depression is much less than with ether. The contractions of the parturient uterus are not affected by the full analgesic dosage. The uterine response to pituitary remains normal.

The motility of the gastro-intestinal tract of dogs, cats and rabbits is significantly reduced, and the emptying time of the stomach is markedly delayed ; but adequate stimuli, for instance distention or pilocarpine, evoke normal peristalsis ; also of the ureter.

Temperature :-

This is lowered slightly by sedative doses and markedly in coma, due partly to depression of the medullary centers, partly to diminution of movement.

Basal Metabolism :-

This is not significantly changed even by full hypnotic doses.

Fate and Excretion :-

The excretion of the barbitals occurs practically exclusively by the urine ; the faeces contain only traces. In the urine they occur partly unchanged and partly split. The total recovered and the speed of excretion vary greatly, and these differences are chiefly responsible for the varying duration of the action ; differences in the speed of absorption also play a part.

Tolerance by Habituation :-

Repeated administration diminishes somewhat the hypnotic effect and raises the fatal dose to perhaps double.

Addiction :-

This is fairly readily acquired and may lead to chronic poisoning : confusion, mild dementia, debility, ataxia, gastro-intestinal irritation, anaemia and hematoporphyrin.

Acute Poisoning by the Barbiturates :-

This is fairly common, sometimes by over-susceptibility, but generally by overdosage, through suicidal intent or in the therapeutic use of the larger doses in connection with anaesthesia, especially by vein. The phenomena consists in coma (sometimes with preceding excitement), marked fall of blood pressure, depression or even paralysis of respiration and fall of temperature. The reflexes are preserved, but greatly diminished. Asphyxial convulsions and mydriosis may occur, although the pupils are usually constricted. Renal necrosis has been reported. The heart may beat for some time after respiration has stopped. The treatment should consist in evacuation if possible. Stimulants would be indicated, but caffeine, camphor, metrogal etc. are not very effective. Picrotoxin has given good results on animals.

Toxic and Clinical Doses of Some of the More Important Barbiturates

Compound	Ordinary Clinical Dose	Severe Intoxication but with Recovery	Generally Fatal
Allonal	.5 gm.	10 gm.	> 15 gm.
Amytal	.1 to .3 gm.	1.5 to 2 gm.	2 to 3 gm.
Barbital	.5 gm.	3 to > 10 gm.	5 to > 20 gm.
Dial	.1 to .3 gm.	2 to 2.5 gm.	> 2.5 gm.
Pentobarbital	.1 to .3 gm.	> .5 gm.	(?)
Pernocton	.2 to .5 gm.	.5 to 1 gm.	.5 to > 1 gm.
Phanodorm	.1 to .3 gm.	1.2 gm.	> 10 gm.
Phenobarbital	.18 to .2 gm.	4 to 7 gm.	> 6 to 9 gm.

Therapeutic Uses :-

The sedative action of the barbiturates receives a wide variety of applications. To secure sleep, to dull worry and apprehension, and to clam nervousness and obtain tranquility and rest in conditions ranging from "overwrought nerves" through drug addiction, hyperthyroidism, mania, chorea and epilepsy ; and to produce partial or complete unconsciousness in anaesthesia. The effects can be readily graded in intensity by dosage and in duration by the

selection of the appropriate type of barbiturate. The barbituric acids may be administered by mouth as capsules, or the sodium salts may be dispensed as capsules or powders, and dissolved in hot water, milk or a little tea. Administration by hypodermic and intravenous injection is especially important in obstreperous and maniacal patients. With some patients, on the other hand, considerable excitement precedes the sedative effect. There is some danger of addiction and of acute poisoning ; the latter is perhaps especially frequent with phenobarbital (Taddei, 1923).

Use as Hypnotic :-

The hypnotic dosage of barbital or phenobarbital or their sodium salts, at bedtime, generally ensures a natural, dreamless sleep, beginning in twenty to thirty minutes and lasting six to eight hours. The patient awakens refreshed, but is not as alert as usual and some lassitude persists during the day. With other barbiturates the duration of the after inertia is shorter. With phenobarbital the total action lasts only three to six hours, which is often too brief.

Use as a Sedative :-

This field is similar to that of the bromides but the barbiturates act much more promptly and may be pushed to more profound effects. Skin eruptions occur only in especially susceptible individuals. In temperamental excitability or in emotional stress, barbiturates should be avoided for fear of habituation. They are useful in toxic goiter to lower the nervous excitability, the muscular activity and the basal metabolism; they allay the apprehension and greatly reduce the risk of operation. The barbiturates have also been used successfully against the nervous vomiting of pregnancy, especially phenobarbital, an hour before each meal and at bedtime, or hypodermically every four hours. This agent is similarly useful as a preventative of seasickness. Infantile pylorospasm, pyloric stenosis and severe colic has been treated successfully with phenobarbital, crushed and given before or with each cereal feeding. A minim of atropine solution 1 : 1000 may be added.

Epilepsy :-

The barbiturates diminish the number and severity of the attacks, especially of the motor type, and thus indirectly improve the mental and physical condition of the patient. The improvement persists only during the medication. Acute attacks are controlled more efficiently than chronic or mild seizures and idiopathic and traumatic epilepsies are more amenable than the senile and syphilitic. The effects and efficiency are about the same as with bromides, but either may succeed when the other has become ineffective. The two medications are often combined to reduce the dosage of both. The barbiturates have several advantages over bromide in that the improvement is more rapid, and the undesirable side-actions are less ; they avoid the progressive psychoses of bromide and the acne, fetid breath and dietary restriction. Phenobarbital is usually employed, partly because it was the first to be introduced for this purpose.

Anticonvulsant Action :-

The barbiturates may be used clinically as well as experimentally to suppress most if not all varieties of convulsions of the central origin ; asurmatic tetanus, strychnine poisoning, meningitis, chorea, status epilepticus, tetany, eclampsia, cocaine poisoning, insulin overdosage. The antagonism of barbiturates towards acute cocaine poisoning and other local anaesthetic drugs was shown on dogs and monkeys by Tatum and Collins, 1925. Sulfonal and trional are also effective. Not only are the convulsions suppressed, but the respriatory depression is decreased and the minimal fatal dose is materially increased. Similar observations have been made on man. In case of collapse by the local anaesthetic agents, the barbiturate may be administered by vein. Phenobarbital may be used prophylactically before local anaesthesia, especially with hypersensitive subjects.

Analgetic Action :-

Ordinary and hypnotic doses are anagetic to a limited degree. In normal men the sensory irritability to foradic stimulation appears somewhat depressed. Clinically satisfactory relief has been reported in severe burns and in syphilitic gastric crises with pentobarbital, .5 to .8 gm. Migraine and other paroxysmal and recurrent headaches respond fairly well to phenobarbital three times daily ; it may be necessary to continue the medication over long periods. In the treatment of headaches and neuralgic and neuritic pains, the barbiturates are prescribed together with the antipyretic analgesics. Mixtures with amidopyrin have been especially exploited under coinced names. Although objective clinical experiments are difficult to devise, it may be presumed that the tranquilizing effect of the hypnotics renders the patient more amneable to the analgetic action of the antipyretics, so as to constitute a kind of potentiation.

Barbiturates in Anaesthesia :-

Since the central effects of the barbitals do not differ in principle from those of other aliphatic narcotics, they may be used alone, or in combination, to secure general anaesthesia (Fredet and Perlis, 1924) ; or as premedication to anaesthesia (Brumm, 1927) ; or for obstetric amnesia (Drabkin et al, 1929). The chief difference from ether lies in their non-volatility ; they cannot, of course, be administered by inhalation, but by mouth, rectum, hypodermically or by vein. The non-volatility also precludes their excretion by the lungs and entails a more prolonged and continuous action. This secures steadiness of anaesthesia, but restricts flexibility. Safety can only be ensured by doses which require to be supplemented by volatile anaesthetics. Another disadvantage of the fixed anaesthesias, especially with the full anaesthetic dosage, is the duration of the stupor, which may last for hours. The prolongation of a profound narcosis may be presumed to be generally injurious ; it disposes to pulmonary complications ; it makes difficult the judging of the

rallying of the patient from the operation ; and it makes excessive demands on the nursing personnel, since the patient must be watched continuously to prevent obstruction of breathing. Basal anaesthesia by barbiturates, i.e. their use as the chief agent of the anaesthesia, is now generally conceded to be unjustified.

Barbiturates in Conjunction with Inhalation Anaesthesia :-

Their use in this connection is a definite accession to anaesthetic technique. They may be administered simply to assure sleep on the night preceding the operation, to tranquilise the patient, to remove nervousness and apprehension and to secure smoother induction, or finally, to take a more or less equal share in the anaesthesia itself.

Preliminary Tranquilization :-

In this field the barbiturates compete with morphine, and their action may be graded through a wider scale, but preferably so that the patient is actually in a normal sleep when the inhalation is started. In emergencies, such as in painful accidents or caesarian section, this sleep may be secured immediately by intravenous injection. In local anaesthesia, the barbiturates have the additional advantage of being a prophylactic against acute poisoning by cocaine or procaine. Many anaesthetic ists give morphine along with barbiturate, thereby enhancing the sedative action, before and during the operation, diminishing the after-pain and lessening the tendency to excitement during recovery from the anaesthetic. It is inadvisable to use morphine with pernocton, because the additional depression of respiration may become dangerous.

For combination anaesthesia, i.e. with dosages that give the barbiturates a more or less equal share in the anaesthesia, they diminish correspondingly the amount of the inhalation agent, and therefore diminish the undesirable side-actions. The induction is tranquil, even more than after morphine ; the blood pressure, heart and respiration remain more nearly normal than with any other anaesthesia (except for the tendency to respiratory depression with pernocton). Nitrous oxide is potentiated, so that surgical anaesthesia may be maintained with an 80 : 20 mixture, allowing sufficient oxygen to prevent anoxemia and to secure adequate relaxation. The reduction in the ether generally prevents vomiting and post anaesthetic nausea. The long sleep and amnesia after the operation ease the ordeal for the patient, and those who have been subjected to several anaesthesias generally prefer the barbiturate and nitrous oxide or ether sequence. The chief disadvantage of barbiturates consists in the varying susceptibility to the depression, and particularly in occasional excitement, and in the duration of the post-anaesthetic stupor. When this is too prolonged, it may be a positive advantage by resting the patient, as with pentobarbital ; but it limits the use of barbital and phenobarbital : amytal and pernocton are intermediate.

Channel of Administration ;

Oral administration should be preferred, because of its greater safety, unless there are special indications against its use, although the slower absorption entails the disadvantages of greater variability of response, and longer duration of excitement. Rectal and hypodermic injections are not often used, since the alkaline solutions are somewhat irritant. Intravenous injection offers the tempting advantage of immediate effects and better control of immediate dosage. However there is a danger of underestimating the eventual depression by the immediate response ; and unless the injection is made very slowly, there may be an alarming fall in blood pressure to shock level, 50 or even 70 mm., but it is usually of short duration. This is probably due to precipitation of the barbituric acids on contact of the strong solutions with the blood ; it may be minimized by alkalising the solutions with a buffer, but best by injecting very slowly. Altogether, intravenous administration appears justified only if immediate effects are imperative.

Choice of Preparations :-

This involves chiefly the duration of the effects, the toxicity, i.e. the margin between the therapeutic and fatal dose, and the personal experience of the physician with the drug. Of these, the duration of action is clinically more important than the margin of safety, since the differences in the latter are not sufficiently large to appear practically important.

The duration of the stupor is clinically notably shorter with pentobarbital and pernocton than with the other barbiturates. The margin of safety may be expressed by the ratio $\frac{\text{minimal fatal dose}}{\text{therapeutic dose}}$, the safety increasing with the index. In relation to mixed anaesthesia, the therapeutic efficiency may be measured on rats as the dosage which permits the maintenance of anaesthesia with an 85 : 15 per cent N_2O : O_2 gas mixture, which is not anaesthetic for undrugged rats. On this basis, the barbiturates fall into two groups : (1) those with the higher index of safety of 1 : 5.5 to 1 : 4, namely, pentobarbital, neonal, dial, alurate ; and (2) those with the lower safety index of 1.9 to 2.65, namely, barbital, phenobarbital, pernocton, amytal and phanodorm (Barlow et al, 1950, 1951).

Pentobarbital alone ranks high with both criteria, brief duration and safety index. Pernocton ranks next according to duration, but lowest as to safety, and in this case the difference is material. Amytal ranks next as to duration, and belongs to the lower group as to safety. All the others are undesirable for anaesthesia because of long duration. Fitch, Waters and Tatum, 1950, group the general desirability in a similar order, except that they place pernocton at the head.

Procedure in Premedication :-

This may be shaped as follows : On the evening before the operation, an ordinary hypnotic dose of any barbiturate is administered to ensure rest. An hour and a half or two hours before the operation, the fasting patient receives orally sodium pentobarbital, 5 to 7½ grains ; or sodium amytal, 5 to 9 grains. One-half to three-fourths of an hour before the operation, morphine may be administered hypodermically, one sixth to one quarter grain, with or without atropine. This is followed in due course by nitrous oxide : oxygen mixture, 80 : 20, or by ether.

If the barbiturates are used intravenously, the order is reversed ; the morphine is administered first, followed ten minutes before operation by the barbiturate, as a ten per cent watery solution of the sodium salt, injected slowly, in not less than two to five minutes. The dosage should not exceed the quantity cited above for oral administration, and may require to be reduced according to age and weight, physical and emotional condition, etc.

Obstetric Amnesia :-

In this, it is aimed to induce a condition in which the patient is not actually unconscious, but tranquilised and drowsy, so that she drops off to sleep between pains and the pains, although of undiminished force, are but little felt and not remembered. Morphine may be omitted or reduced to half. The labor is not delayed, the circulation, respiration and temperature remain normal, the babies are not noticeably narcotised and breathe promptly. This effect requires a full hypnotic dosage, pentobarbital 5 grains,or amytal 4 grains, by mouth or rectum, at the beginning of labor, and repeated when the cervix has dilated 3 or 4 cm. The latter dose may be injected hypodermically or intravenously. Pernocton has been used in a single dose of 2.5 to 6 cc. of the ten per cent solution by vein at this stage. The barbiturates may also be added to the Gwathmey rectal anaesthetic mixtures.

Reference Number 2 (Cont.)

Name		Formula	M.F.D. ratio mgs. per kg. hypo	Min. Anaesth dose, ratio mgs. per kg. hypo	Therap. Breadth M.F.D./M.A.D.	Order of Therap. Breadth	Premedication efficiency in relation to N_2O anaesthesia
Trade Name	Chemical Ester						
Barbital	di ethyl	$R = \begin{matrix} C_2H_5 \\ C_2H_5 \end{matrix}$	310	190	1.63	5	2
Phanodorm	cyclohexenyl ethyl	$R = \begin{matrix} C_6H_9 \\ C_2H_5 \end{matrix}$	220	90	2.44	7	6
Neonal	N-butyl ethyl	$R = \begin{matrix} C_4H_9 \\ C_2H_5 \end{matrix}$	190	80	2.37	5	7
Dial	diallyl	$R = \begin{matrix} C_3H_5 \\ C_2H_5 \end{matrix}$	150	60	2.5	9	8
Phenobarbital	phenyl, ethyl	$R = \begin{matrix} C_6H_5 \\ C_2H_5 \end{matrix}$	140	110	1.27	2	4
Amytal	iso-amyl, ethyl	$R = \begin{matrix} C_5H_9 \\ C_2H_5 \end{matrix}$	140	57	2.45	8	5
Pernocton	2 butyl brom-ethyl	$R = \begin{matrix} C_4H_9 \\ C_2H_4Br \end{matrix}$	124	56-65	2.1	4	1
Pentobarbital	ethyl (1methyl butyl)	$R = \begin{matrix} C_2H_5 \\ CH_2CH_2CH_2CH \\ CH_3 \end{matrix}$	120	50	2.4	6	9
Ipral	calcium ethyl iso propyl	$R = \begin{matrix} C_3H_7 \\ C_2H_5 \end{matrix}$	110	90	1.22	1	5

Reference No. 3

Pharmacology and Therapeutics — Arthur R. Cushny

Substances Acting after Absorption.
Barbituric Acid Group

p. 567.

Pharmacological Action :-

Keeser and Keeser, using barbital, phenobarbital and dial, found the greatest concentration when small doses were used, in the diencephalon, especially in the thalmus - in contrast to the cerebral hemispheres, and suggest that the former region is of particular significance in the phenomenon of sleep.

Koppanyi and his co-workers found that on intravenous injections of anaesthetic doses of sodium barbital the drug was equally distributed in every portion of the central nervous system.

Poisoning, Habit Formation and Tolerance :-

Much is to be learned about the idiosyncrasies and overdosage of the newer compounds, but there is reason to believe that they differ markedly from those of barbital and phenobarbital. Habit formation is now a recognised problem and tolerance from prolonged use a recognised fact.

Excretion :-

Barbituric acid derivatives are excreted in the urine in varying amounts, only traces being found in the faeces.

Synergism and Antagonism :-

Convulsions may be controlled by intravenous injections and the lethal dose of strychnine and cocaine in animals may be increased from two to four times.

Combinations of barbituric acid hypnotics and antipyretic drugs such as antipyrine and acetylsalicylic acid are advantageous clinically.

Therapeutic Uses :-

The barbituric acid derivatives are used as hypnotics, mild sedatives to the central nervous system, particularly associated with motor disturbances, and in the treatment of epilepsy.

Use in Anaesthesia :-

Barbiturates were recommended for use in large intravenous doses to produce complete surgical anaesthesia, but now they are used to better advantage for pre-anaesthetic medication and in conjunction with nitrous oxide and ether. They are used also preliminary to administration of local anaesthetics, procaine or cocaine.

Reference Number 4

Hypnotics — Ralph G. Harry

The Manufacturing Chemist, Feb. 1937, page 45.

The Barbituric Acids

The author deals with the preparation, properties and physiological action of modern hypnotics, one class of which is the barbiturates. He describes the preparation of barbital and phenobarbital as typical of the group. They are the same preparations as those outlined in Remington (20).

"The intensity of action of these hypnotics varies according to the nature of the substituents. No hypnotic action is evident if both the H's are substituted by methyl groups."

Therapeutics and Toxicology of the Barbiturates

"Luminal is twice as poisonous to man as veronal and may cause death in doses as little as 4 gm. Dial in a dose of 2.4 gm. has been known to lead to severe poisoning, whilst some people become inebriated even after doses of .3 to .4 gms."

Barbitone is excreted, unchanged, slowly and may lead to accumulative poisoning, characterized by erythematous rashes, cyanosis, and defective cerebration.

Women are more susceptible than men to this group of drugs. Owing to their slow excretion, they should never be used in renal disease. Luminal produces obvious effect for several days, then drowsiness appears, and about one week after starting treatment, a morbilliform rash and pyrexia appears, the clinical picture being remarkably like an attack of measles, the symptoms disappearing in about four days, provided the medicine is discontinued.

"In cases of death, symptoms of broncho-pneumonia with breakdown of kidney function are common features.

"The chief source of excretion of these drugs is the urine, about 70 per cent veronal and up to 25 per cent luminal escape combustion in the body. Phanodorm undergoes oxidation, however, and only 5 percent escapes in the urine.

Reference Number 4 - continued

Poison Restrictions on Barbiturates :-

"By the 1936 Poisons List and Rules "Barbituric Acid, its salts ; derivatives of barbituric acid, their salts ; compounds of barbituric acid, its salts, its derivatives, their salts with any other substance" are included in Schedule I, and, further, "can only be sold on prescription."

Reference Number 5

Journ. Pharmacol. and Exp. Therapeutics.
5, 26, 371 (1925).

A comparative study of hypnotics of the barbituric acid series is given by Nielsen, Higgins and Spruth of the Abbot Laboratories. A list of fifteen barbiturates was studied. The authors found experimentally that dogs and cats and rabbits were unsatisfactory and the albino rat was used for their final results.

Toxicity, efficiency and safety subcutaneously in albino rats

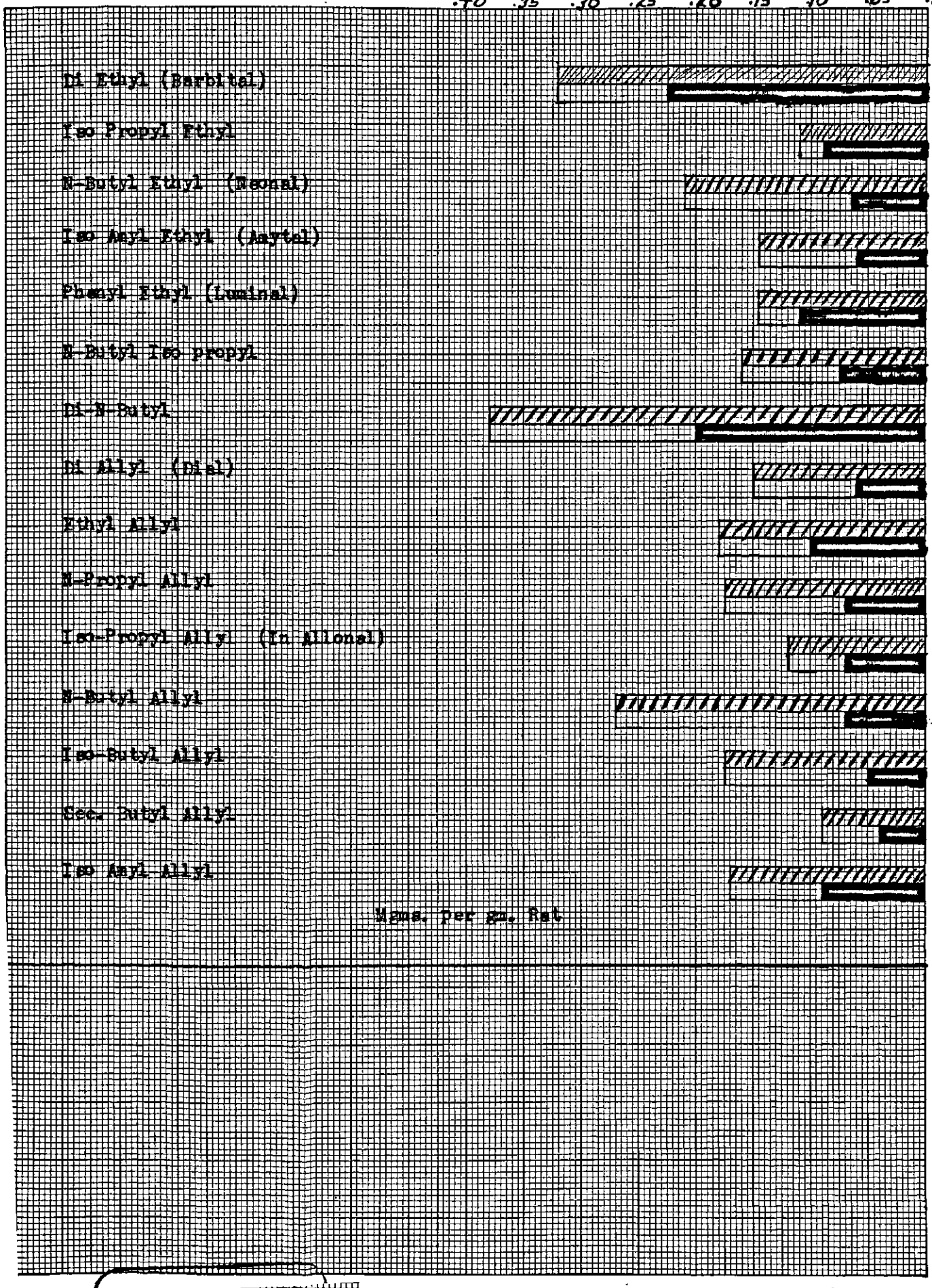
	Min. fatal dose in mgm. per gm. rat	Ratio of Toxicity (Barbital = 1)	Min. effective dose, in mgm. per gm. rat	Ratio of efficiency (Barbital 1)	Safety Margin %
Diethyl barbituric acid (Barbital	.51	1	.225	1	27
Isopropyl ethyl barbituric acid	.11	2.8	.09	2.5	18
n-butyl ethyl barbituric acid (Neonal)	.19	1.68	.0625	3.66	67
Isoamyl ethyl barbituric acid (Amytal)	.14	2.2	.0575	3.9	59
Phenyl ethyl barbituric acid (Luminal)	.14	2.2	.11	2	21
Benzyl ethyl barbituric acid		Produced convulsions			
n-butyl iso propyl barbituric acid	.16	2	.0725	3.1	55
Di n-butyl barbituric acid	.38	.8	.2	1.125	47
Diallyl barbituric acid (Diel)	.15	2	.06	3.75	60
Ethyl allyl barbituric acid	.18	1.7	.1025	2.2	43
n-propyl allyl barbituric acid	.175	1.7	.072	3.125	59
Iso propyl allyl barbituric acid (Allonal)	.125	2.5	.0525	4.25	58
n-butyl allyl barbituric acid	.27	1.1428	.075	3	72
Iso-butyl allyl barbituric acid	.175	1.7	.0525	4.25	70
Sec. butyl allyl barbituric acid	.09	3.5	.0375	6	58
Iso-amyl allyl barbituric acid	.17	1.8	.085	2.66	50

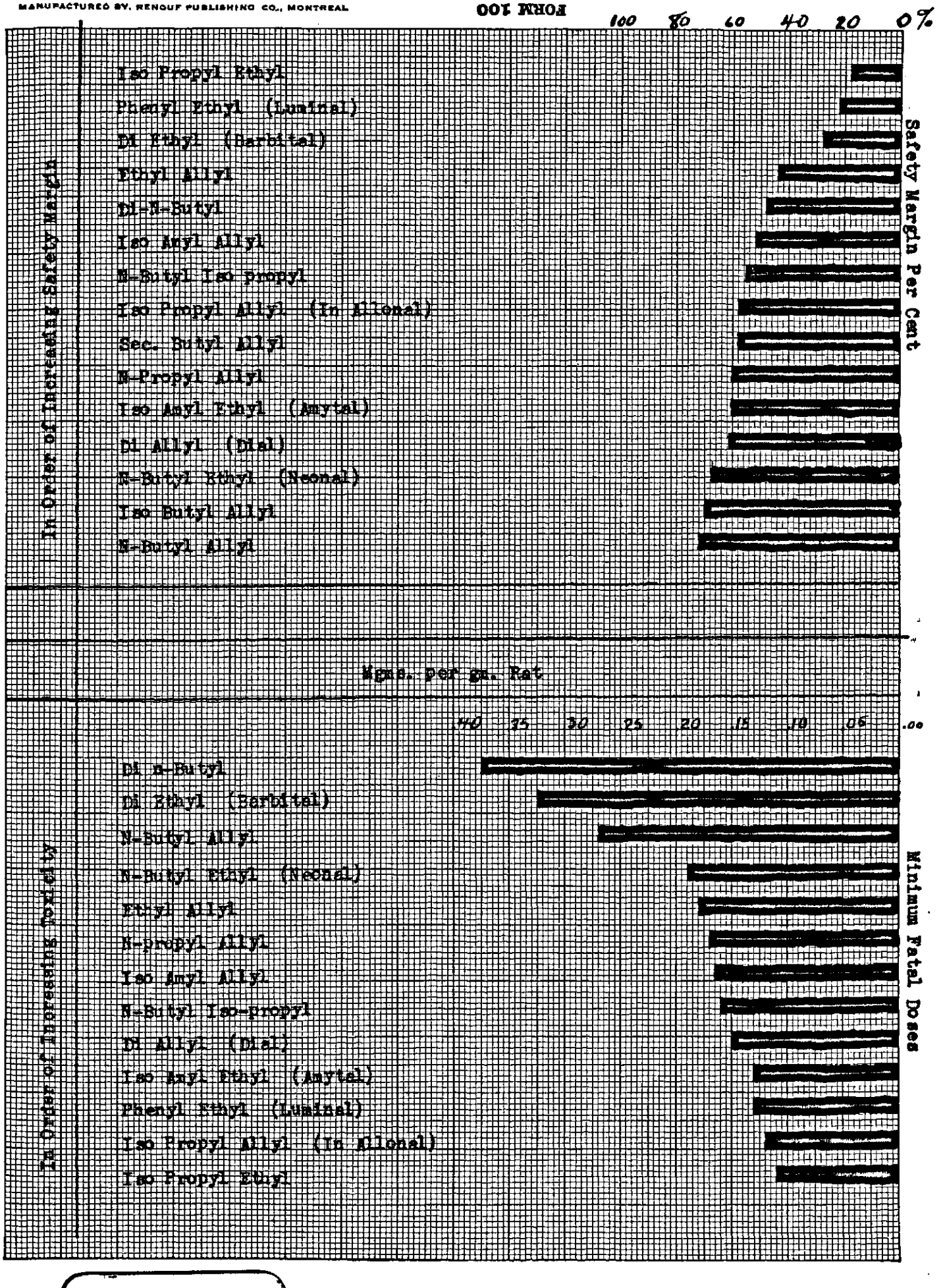
Minimum Fatal Dose
Minimum Effective Dose
Safety Margin

MANUFACTURED BY RENOUF PUBLISHING CO., MONTREAL

Mgms. per gm. Rat

.40 .35 .30 .25 .20 .15 .10 .05 .00





Mgms. per gm. Rat

.40 .35 .30 .25 .20 .15 .10 .05 .00

Di-Ethyl (Barbital)

Di - N - Butyl

Phenyl Ethyl (Luminal)

Ethyl Allyl

Iso Propyl Ethyl

Iso Amyl Allyl

N - Butyl Allyl

N-Butyl Iso-Propyl

N-Propyl Allyl

N-Butyl Ethyl (Neonal)

Di Allyl (Diel)

Iso Amyl Ethyl (Amytal)

Iso Propyl Allyl (In Allonal)

Iso Butyl Allyl

Sec. Butyl Allyl

Minimum effective dose

In order of increasing efficiency

Reference Number 6

Applied Pharmacology A. J. Clark

Page 189

About sixty derivatives of barbituric acid are known, but this is a very small fraction of the possible variations, of which there are 1,225, none with more than six carbon atoms in a side chain.

Barbituric acid is inert, and hence these drugs are rendered inert by the oxidation of their side chains ; and the drugs with the least stable side chains produce the shortest actions.

Barbitone and sodium barbitone have a somewhat shorter action, and are widely used as hypnotics. Only about half of the hypnotic dose of barbitone is excreted in twenty-four hours, and three days are required for its complete excretion. The drug will therefore produce cumulative effects if taken daily.

Amytal and nembutal are short acting drugs, because they are rapidly broken down in the body. For this reason they are finding extensive employment for pre-anaesthetic medication.

Reference Number 7

Journal American Chemical Society, 45 : Pages 243-249 (1925)

A report from the Eli Lilly Research Laboratories on new hypnotics of the barbituric acid series. Among those described in the article, with physical properties and relative hypnotic properties, are - diethyl barbituric acid (barbital), iso propyl ethyl (ipral), iso butyl ethyl, iso amyl ethyl (amytal), n-butyl ethyl (neonal), benzyl ethyl, phenyl ethyl (phenobarbital) and di n-butyl ethyl.

Amytal was found to be the most active and least toxic of this series, being even better as an hypnotic than di propyl barbituric acid (proponal) which was claimed by Fischer and Mering, Med. Klinik, 1 : 1527 (1904-5), to have twice the activity of barbital.

Reference Number 8

Chemical Abstracts, 25, 1 (1923) : Page 1471.

In Am. J. Pharm., 100 : 692-7 (1928) occurs a review and discussion of the then popular hypnotics of the barbituric acid series. The list includes veronal, dial, proponal, luminal, neonal (soneryl), sandoptal, allonal, ipral, phanodorm, amytal and noctal.

Reference Number 9

Recent Advances in Organic Chemistry, Vol. I. A. W. Stewart

Page 305

Fischer first synthesized barbituric acid by the reaction of malonic acid and urea, in his attempt to prove the structure of uric acid.

Reference Number 10

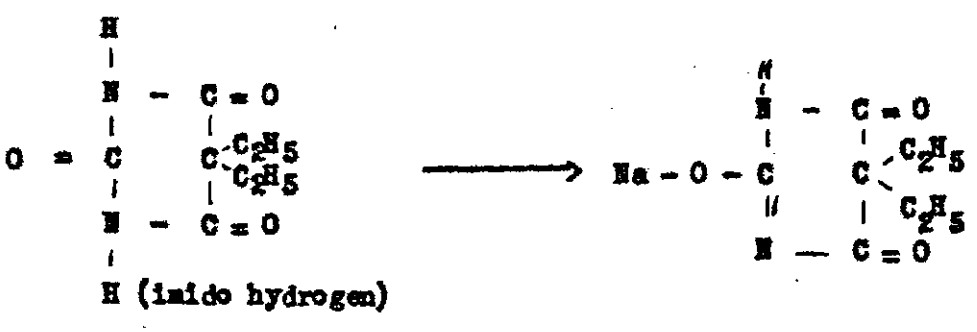
Organic Chemistry Julius Schmidt

Page 300

Barbital was isolated in 1882 by Conrad and Guthzeit by the action of ethyl iodide on the silver salt of barbituric acid. It was not until 1903 that Fischer and Von Mehring showed that it had excellent hypnotic properties.

The ureides are for the most part beautifully crystalline compounds whose character as amides is shown by the fact that on prolonged warming with dilute alkalis they take up 2 mols H_2O to yield a dibasic acid and urea.

Ureides are "acidic" in character and the imido hydrogen is replaced by metals.



Reference Number 11

Year Book American Pharmaceutical Association, No. 7 (1918)
Page 398

Official American Names for Synthetic Drugs

Prof. Stieglitz urges the use of the official name (Federal Trade Commission) of Barbital for the drug marketed as veronal and of Barbital-Sodium for the drug marketed as medinal and veronal sodium.

Reference Number 12

Year Book American Pharmaceutical Association, No. 7 (1918)
Page 495

The Privy Council of Great Britain has classified as poisons barbital and other alkyl, aryl or metallic derivatives of barbituric acid. As a result veronal will be dispensed only on a physician's order and a record of sales will be kept.

- J. Am. Med. Assoc. 70 (1918), 955.

Reference Number 13

Chemistry of Barbital and its Derivatives Collins and Leech
Journ. Am. Med. Assoc. 1931, 96, 1869.

Barbital, the first of the "barbital series" was introduced into medicine by E. Fischer and Von Mering in 1903. Since then a large number of other derivatives of barbituric acid have been put on the market. The two hydrogen atoms attached to carbon are very reactive and may be substituted by an almost unlimited number of groups.

Reference Number 14

Quarterly Journal Pharmacy and Pharmacology, 6 (1933)

The Council of the American Medical Association in a report here said that the intravenous injection of barbitals should only be used where it was not feasible to use the oral method. Cases were given in the report in which the intravenous administration may be used.

Reference Number 15

Chemical Abstracts, 21, 1 (1927) Page 1515.

Kaer and Loewe in Arch. exptl. Path. Pharmakol., 118, 108-114 (1926), claim that acetylsalicylic acid is antagonistic to certain of the partial effects of veronal, as is antipyrine. With ceronal and pyramidon, injected in different regions of the body, a similar antagonism is shown.

Reference Number 16

Quarterly Journal Pharmacy and Pharmacology, 8, 4 (1935) Page 748.

"Veramon", a mixture of barbitone (28%) and amidopyrine, has an excellent analgesic effect approaching that of morphine.

Reference Number 17

American Journal of Pharmacy, Dec. 1934. Page 489.

Phenobarbitone and Soluble Phenobarbitone :-

"Barbitone and Phenobarbitone : an equal weight of soluble barbitone or soluble phenobarbitone is dispensed if the other ingredients of the prescription are soluble and compatible with them.

"Soluble Barbitone and soluble Phenobarbitone : An equal weight of the insoluble equivalents are dispensed and suspended if the other ingredients of the prescription would precipitate the insoluble drugs. Tragacanth 5 grains to each fluid ounce is used."

Reference Number 18

Quarterly Journal Pharmacy and Pharmacology, 7 (1934) Page 507.

In cases where rhubarb is administered after the administration of barbitals it was found that the laxative action of the rhubarb is decreased, while the effect of the barbituric acid on the heart is increased.

Reference Number 19

Journal American Pharmaceutical Association, Nov. 1936. Page 995.

"While barbital as well as phenobarbital is best given in solid dosage form (capsule or tablet), should administration in liquid dosage form be desired, glycerin is the best vehicle. It has a better disguising effect upon soluble barbiturates than alcohol has upon the insoluble barbiturates, with the difference that the glycerin solution

Reference Number 19 (Continued)

will tolerate indefinite dilution. Hence, especially when the barbiturate is intended for a child, soluble barbital in glycerin solution may be recommended."

Reference Number 20

Remington's Practice of Pharmacy Page 985.

Gives the discussion of the barbitals as contained in the N. N. R.

Barbitalum

Preparation :-

Monochloracetic acid is treated with sodium cyanide, the resulting cyanacetic acid is hydrolyzed with hydrochloric acid in the presence of alcohol, yielding the ethyl ester of malonic acid.

$$\underset{\text{monochloracetic acid}}{CH_2ClCOOH} + \underset{\text{sodium cyanide}}{NaCN} \longrightarrow \underset{\text{cyanacetic acid}}{CH_2CNCOOH} + \underset{\text{sodium chloride}}{NaCl}$$

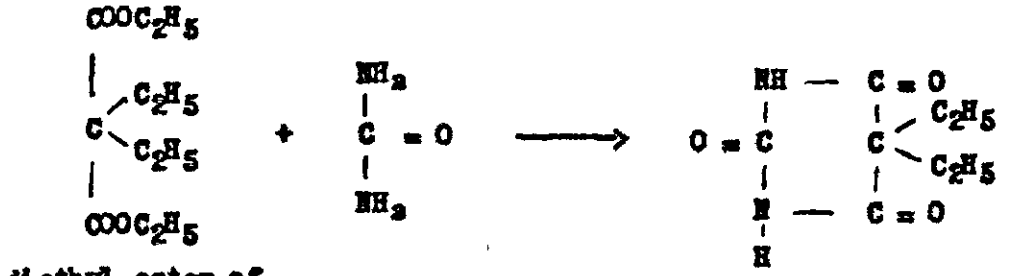
$$\underset{\text{cyanacetic acid}}{CH_2CHCOOH} + 2\,C_2H_5OH + HCl \longrightarrow \begin{matrix} COOC_2H_5 \\ | \\ CH_2 \\ | \\ COOC_2H_5 \end{matrix} + NH_4Cl$$

alcohol

The ester in absolute alcohol solution is treated with the theoretical quantity of metallic sodium to replace one hydrogen of the CH_2 group, and thereupon a slight excess of the theoretical amount of an ethylating agent, such as ethyl bromide, is added. The second hydrogen is then similarly ethylated. The diethyl ester of diethyl malonic acid thus obtained is formed, from which the barbital is liberated with hydrochloric acid.

$$\begin{matrix} COOC_2H_5 \\ | \\ CNa_2 \\ | \\ COOC_2H_5 \end{matrix} + 2\,C_2H_5Br \longrightarrow \begin{matrix} COOC_2H_5 \\ | \quad C_2H_5 \\ C \\ | \quad C_2H_5 \\ COOC_2H_5 \end{matrix}$$

diethyl malonate sodium — ethyl bromide — diethyl ester of diethyl malonic acid

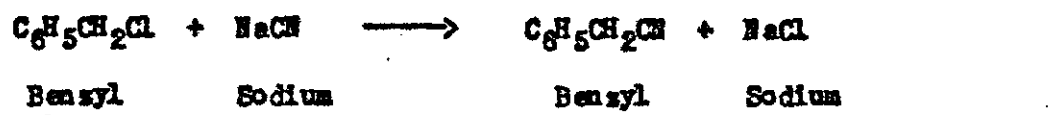


diethyl ester of diethyl malonic acid

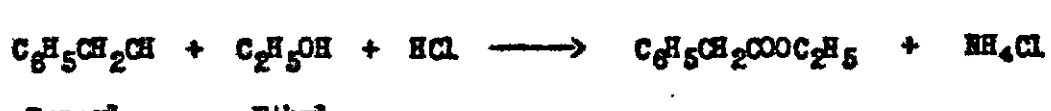
Phenobarbitalum U.S.P.

Preparation :-

Benzyl chloride is converted into phenyl-acetic ester by treating first with sodium cyanide and then hydrolyzing with acid in the presence of alcohol.

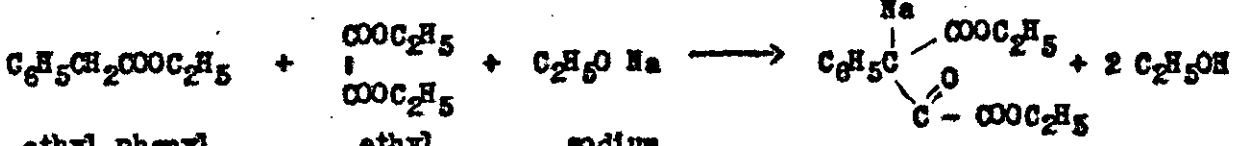


Benzyl Chloride — Sodium Cyanide — Benzyl Cyanide — Sodium Chloride



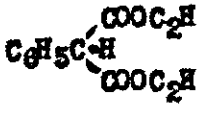
Benzyl Cyanide — Ethyl Alcohol — Ethylphenylacetate

The ethyl phenyl acetate is condensed in the presence of alcoholand metallic sodium with ethyl oxalate, forming sodium phenyl oxalo-acetate.



ethyl phenyl acetate — ethyl oxalate — sodium ethylate — sodium phenyl oxalo-acetate

Hydrochloric acid is added to liberate the liquid condensation product which, on being distilled at about 180°, splits off carbon monoxide and phenyl malonic ester –



The hydrogen of the CH in the phenyl malonic ester is then ethylated and condensed with urea, as described under barbital.

Reference Number 21

Organic Medicinal Chemicals — Barrowcliff and Carr

Page 43.

Veronal

The two methods of preparation, whichare of greatest technical importance, are described in detail, the others are merely enumerated.

(1) By condensation of diethylmalonic ester and urea. Sodium, 52 parts (3 mols.) is dissolved in absolute alcohol (600 parts), and to the colled solution 40 parts of dry urea and 100 parts (1 mol.) of diethylmalonic ester are added. The mixture is heated under pressure in an autoclave at 100°-110° for 4-5 hours. After cooling, the sodium salt of diethyl barbituric aid is filtered off and the filtrate reheated, when another crop may be obtained. The sodium veronal is dissolved in water and the solution acidified with HCl.

(2) From diethyl-cyanoacetic ester. Sodium is dissolved in absolute alcohol and after cooling, powdered urea and diethyl cyanoacetic ester are added and the mixture refluxed for 3 hours. Sodium barbital is the product.

(3) From diethylmalonyl chloride and urea.

Reference Number 22

Chemistry of Synthetic Drugs — Percy May

Page 57.

Veronal is prepared by allowing dialkyl derivatives of malonic ester to react with urea or alkyl substituted ureas in the presence of sodium ethoxide or other metallic ethoxides.

Reference Number 23

Chemical Abstracts, 24,2 (1930) — Page 2544.

Production of Barbital - by Schwyzer, Pharm. Ztg. 75, 337-340 (1930)

Two different commercial procedures for the preparation of barbital are discussed in connection with detailed methods for producing monethylmalonic ester, diethylmalonic ester and urea, together with the apparatus used in the several operations.

Reference Number 24

Journal of American Pharmaceutical Association. Oct. 1955. Page 847.

Studies in Barbiturates. XI. Further Contributions to Methods of Barbital Research

The authors describe several methods for preparing urine, blood and tissue for an analysis on them for barbiturates. Research is carried on in barbiturates chiefly by analysing for their contents in urine, blood and tissue.

Reference Number 25

Journal of American Pharmaceutical Association, Nov. 1954. Page 1074.

Studies of Barbiturates II. Contributions to methods of Barbital Research.

- By Theodore Koppanyi, James M. Dille, William S. Murphy and Stephen Krop.

I. Methods of Extraction :-

Urine - The urine is rendered acid with hydrochloric acid and extracted with chloroform. Colored and concentrated urines have first to be cleared by means of a copper sulphate solution.

Blood - (1) Sodium Tungstate Method - Here sodium tungstate and .67 N H_2SO_4 are used as precipitants.

(2) Myers and Wardell's Method (Adapted).

Tissues - (1) Copper Sulphate Precipitation method.
(2) Liquid Air Method.

The tissues are frozen with liquid air and pulverized, then extracted with chloroform.

II. Methods of Colorimetry :-

(a) The Macro Test. - Colorimetric tests are run on the chloroform extracts of each tissue. Cobalt acetate solution and barium hydroxide are the reagents used in the color test. A blue color indicates a positive test.

Standard barbital solutions are prepared and used to compare the blue colors with that of the unknown.

(b) The Micro Test. - Cobalt acetate and lithium hydroxide are the ingredients used here.

(c) Isoprolamine Test. - Cobalt acetate and Isoprolamine solution are the reagents used in this test.

Reference Number 26

Quarterly Journal of Pharmacy and Pharmacology, 7, (1934) Page 115.

Identification of Barbituric Acid Derivatives, by Rosenthaler, Apothekerztg., 1933, 48, 793.

General reactions which indicate their presence are their solubility in alkali, formation of a blue or violet color with Zwikker's cobalt reagent, the formation of a precipitate with mercuric nitrate, and the production of ammonia on boiling with alkali. For individual identification, the following plan is proposed.

(1) Beilstein's copper test positive : Noctal, Pernocton.
(2) Beilstein's copper test negative :

A. Dissolve in baryta water :-
Veronal : Lead acetate to solid gives four cornered rods and plates.
Luminal : no crystals with lead acetate : ammonium phosphate solution in potassium hydroxide gives spheres and sheaves of branched needles.
Allylisopropylbarbituric acid : no crystals with lead acetate ; ammonium phosphate gives prisms, needles and rods, the latter mostly in tufts.

B. Crystals with baryta water :-
Diel : Thallium acetate to solution in ammonia gives crystals.
Sandoptal, Prominal : Thallium acetate gives no crystals.

C. Amorphous forms with baryta water :-
Evipan-sodium : Immediate amorphous granules.
Phenodorm : No immediate change with baryta water. Thallium acetate gives with the ammoniacal solution spherules, then sheaves and double hemispheres formed of spears.

Reference Number 27

Chemical Abstracts, 30, 16 (1936) Page 5524.

Berberine as Microchemical Reagent, by C. von Zijp, Pharm. Weekblad., 73, Pages 764-767 (1936).

Berberine sulphate as a reagent may be used to identify phenobarbital, dial, barbital and rutonal.

Reference Number 28

Chemical Abstracts, 29, 2 (1935).

Testing for Soporifics, especially Barbiturates in Cerebrospinal Fluid and Blood. Fischer and Reisch, Z. ges. exptl. Med., 95, 739-55 (1935)

The purified ether extract from the tissue is subjected to microsublimation. The concentration of barbituric acid derivatives produced in blood and cerebro-spinal fluid by therapeutic doses can be detected.

Reference Number 29

Chemical Abstracts, 30, 6 (1936)

Optical Crystallographic Study of some Derivatives of Barbital and Phenobarbital. Hultquist and Poe, Ind. Eng. Chem., Anal. Ed., 7 : 398-399 (1935).

The crystalline structure and preparation of some twenty rare derivatives of barbital and phenobarbital are described. The data include that on the benzyl and phenacyl derivatives of barbital and phenobarbital.

Reference Number 30

Journal of the Chemical Society, London, 121-122 (Nov. 1922), 11, 795.

Fabre, in J. Pharm. Chim., 1922, 26, 241-249, pointed out that veronal and other barbituric acid hypnotics condensed with xanthydrol to form crystalline derivatives. Similar derivatives are not formed by other hypnotics, therefore the reaction is of value in the identification of barbituric acid hypnotics.

Reference Number 31

Quarterly Journal Pharmacy and Pharmacology, 7 (1934) Page 681.

Identification of Barbituric Acid Derivatives, by Jespersen and Larsen, Dansk. Tidss. Farm, 8, 212 (1934).

The identification of the barbiturates was undertaken by first preparing the xanthydrol and p-nitrobenzyl derivatives. A chart is given showing the different physical properties of the barbiturates and the prepared compounds. The p-nitrobenzyl derivatives were found more suitable than the xanthydrol derivatives for the identification.

Reference Number 32

Journal of American Pharmaceutical Association, Dec. 1933, Page 1251.

The Identification of Some Hypnotics of the Barbituric Acid Series. - By George W. Hargreaves and H. W. Nixon.

Contains a summary of the literature showing several tests used for identifying various members of the barbital family. Among the experimental tests are solubility tests, melting points, p-nitro benzyl derivatives, permanganate test and precipitation tests. Those listed under color reactions are concentrated sulphuric acid, formalin sulphuric acid and nitrite sulphuric acid tests.

Reference Number 33

Quarterly Journal of Pharmacy. 1 (1928) Page 111.

Detection of Small Quantities of Veronal in Blood and Urine. Fischer, Pharm. Zeit. 1928, 73 : 222.

The ether extract is introduced with the aid of a capillary funnel into a sublimation tube to evaporate. It is sublimed from an oil bath at 145°C on a cover-glass cooled with moistened filter paper, when it may be identified microscopically with Denige's reagent.

Reference Number 34

American Journal of Pharmacy, March 1936. Page 117.

Rapid Method of Determining the Amount of Barbital Derivatives in Urine and Medicinal Products. H. Oettel, Arch. Pharmaz.

"The quantitative estimation is based on the colorimetric reaction of cobalt acetate with the barbituric acid derivative, a blue color being produced."

Reference Number 35

Chemical Abstracts, 29, 1 (1935) Page 291.

Estimation of Barbital in Admixture with Acid Substances, by Titration, especially in the Examination of Organs. By Fuchs, Scientia Pharm., 5 : 93-95 (1934).

The procedure of Viebŏck and Fuchs (C.A. 28, 5834) in somewhat modified form is suggested as permitting the estimation of barbital in the presence of other acidic substances. For isolation of barbital from organic tissues, a suitable extraction and purification procedure has been developed.

Reference Number 36

Chemical Abstracts, 28, 1 (1934) Page 826.

Studies on Barbiturates, by Koppanyi, Murphy and Krop. Arch. intern. Pharmacodynamie, 46, 76-96 (1933).

Barbiturates can be detected colorimetrically by adding $Co(Ac)_2$ and $Ba(OH)_2$, dissolved in absolute MeOH, to a $CHCl_3$ extract of the unknown. Human beings, dogs and cats excrete 40-90% of barbital taken by mouth in the urine. The rate and degree of excretion are not affected by diuretics. The excretion of the other barbiturates (dial, neonal, phenobarbital, pernocton and amytal) is less than that of barbital, decreasing in the order named. The brain does not store more barbital than any other organs.

Reference Number 37

Chemical Abstracts, 28, 1 (1934) Page 3128.

Presence and Detection of Diethylbarbituric Acid in Cerebrospinal Fluid, Vitte, Bull. soc. pharm. Bordeaux, 70 : 255-6 (1932).

A procedure for the separation of barbital from the spinal fluid in the case of barbital poisoning is described.

Reference Number 38

Chemical Abstracts, 18 (1924) Page 5252.

Analyses of veronal and phenobarbital are given by Clycert, J. Assoc. Official Agr. Chem. 8 : 47-49 (1924), a description of their properties and the method of analysis is described.

Reference Number 39

Chemical Abstracts, 24, 5 (1930) Page 5934.

Itallie and Steenhauer in Pharm. Weekblad, 67 : 777-785 (1930) described, with charts, etc., methods of distinguishing such barbituric acids as barbital, proponal, dial, allonal, soneryl (butyl-ethyl), luminal, rutonal, phanodorm and sandoptal, one from the other.

Reference Number 40

Chemical Abstracts, 20 (1926) Page 477

Zamparo in Boll Chim. Farm., 64 : 257-8 (1925), reports a means of identifying alkyl derivatives of barbituric acid. One cc. of H_2SO_4 and two drops of 2% $NaNO_2$ added to 1 gm. of the substance gives no reaction with barbital, gradually appearing a faint yellow color with dial in the cold (pink in the heat) and with phenobarbital gives yellow-orange color in hot or cold, which disappears on dilution.

Reference Number 41

Quarterly Journal of Pharmacy 1 (1928) Page 111

Detection in the Cadaver of Vegetable Poisons and Medicines, Brumig and Kroft, Arch. Pharm., 1927, 9 : 712.

Veronal is best extracted from a suitable part of the cadaver with hot alcohol, acidified with tartaric acid. Hot water and alcohol are used for the purification of the alcoholic extract. Veronal can still be detected after one and a half years in spite of strong putrefaction of the body. When death takes place several days after a fatal dose of veronal has been taken, all the veronal can be still detected.

Reference Number 42

British Chemical Abstracts, A (1927) Page 1219

Elimination and Toxicology of Veronal, Sensi, Annali Chim. Appl. (1927), 17 : 447-456.

The author shows that 70-85% of the veronal administered to dogs is eliminated in the urine. Animal metabolism undoubtedly exerts a destructive action on veronal, and putrefaction of the organs results in gradual disappearance of the drug ; the nature of the resultant products is unknown. These results contradict those of Ipsen (Wien. Med. Wochenschr., 74 : 2025).

Reference Number 43

The Journal of Pharmac. and Experimental Therapeutics, 5, 25 (1925)

Page 219.

The Effect of Phenobarbital and Phenobarbital Sodium upon Blood Pressure and Respiration. By Gruber and Baskett of the Washington University School of Medicine.

The authors, in summing up the previous literature, point out that Impens (1912) found phenobarbital to have a sedative action upon the respiratory system and to cause the blood pressure to rise ; Wetzel found in possible to cause narcosis but to have no change in blood pressure.

In their experimental results, only two cases out of the 164 injections showed anything but a pure fall in blood pressure. Whether given intravenously or intraperitoneally or orally the same depression of blood pressure occurred.

Sodium phenobarbital in small and moderate doses caused acceleration of respiration with decreased depth in most instances. After the acceleration, however, the rate slowed and depth increased.

Large doses of phenobarbital or sodium phenobarbital cause paralysis of respiration. The heart continues to beat for minutes even after cessation of respiration.

Reference Number 44

Journal of Pharmacology and Experimental Therapeutics, 27, 4 : 527-54 (1926)

The Effect of Na Phenobarbital and other Barbituric Acid Derivatives upon Coronary Circulation. By Gruber and Roberts.

The drugs studied were barbital, phenobarbital, Na phenobarbital, amytal and iso propyl allyl barbituric acid ("sanonifer").

The methods of procedure and charts of the blood pressures are given. In the summary the authors state that all the barbiturates tested in dilute solutions produce coronary vaso-dilatation when injected into the perfusate of an isolated cat or rabbit heart.

Concentrated solutions produce variable results, but these they believe are due to the change in pH of the perfusion fluid.

Amytal, when injected intravenously in saturated solutions, materially lowers the arterial blood pressure in experimental animals.

Reference Number 45

Journal of Pharmacology and Experimental Therapeutics, 27, 4 (1926)

Page 349.

The Effect of Phenobarbital and Other Barbituric Acid Derivatives upon Cerebral Circulation. By Gruber and Roberts.

The compounds used were barbital, phenobarbital and sodium phenobarbital, amytal and iso propyl allyl barbituric acid.

The authors conclude that all the barbiturates tested cause dilatation of the cerebral vessels. Vaso constriction, which was noted in certain types of injection, was due to the change in pH of the fluid perfusing through the brain.

Fluids with a pH less than the perfusate when injected cause vaso dilatation and when those injected have a pH greater than the perfusate vaso constriction results.

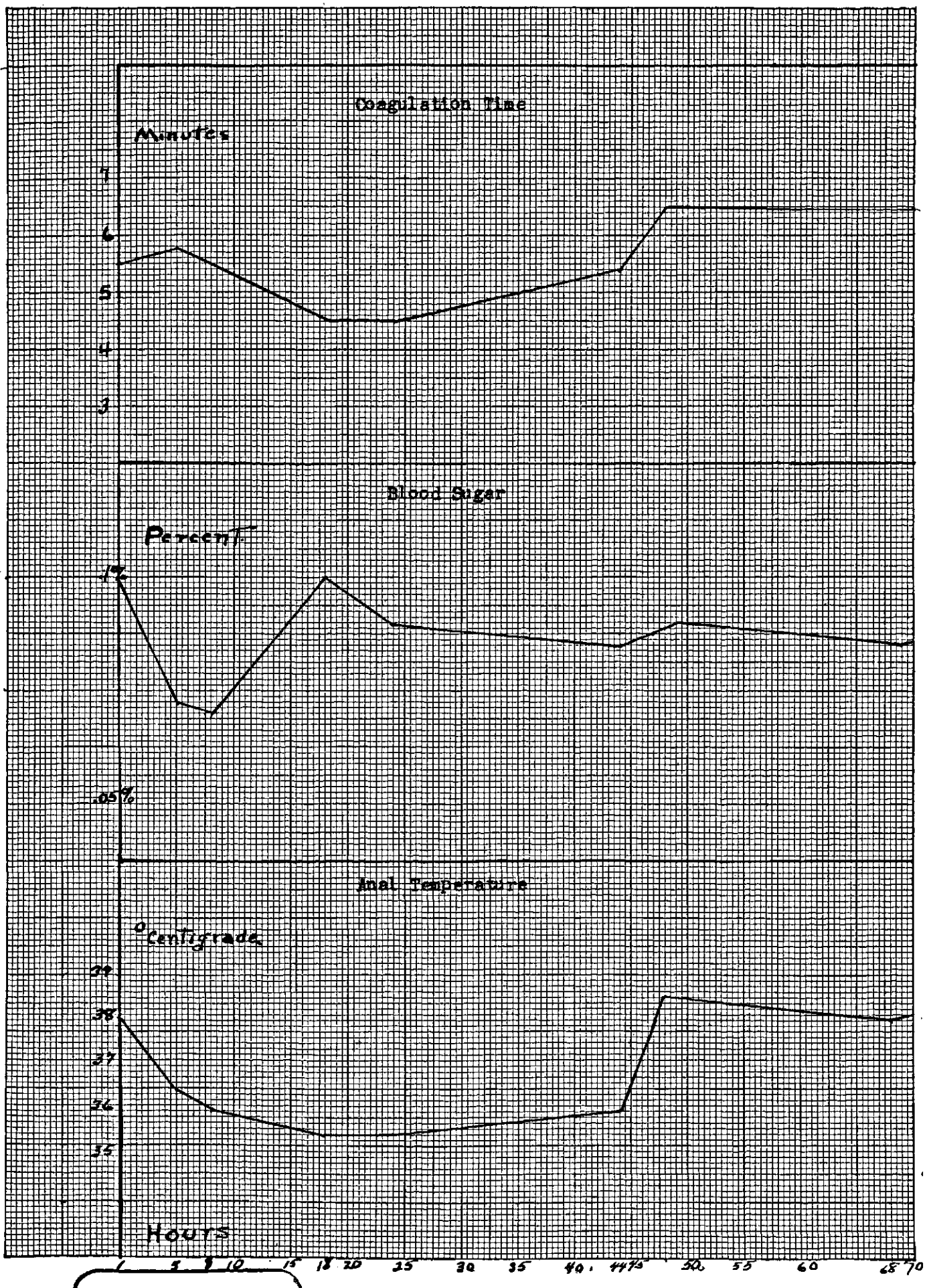
The barbituric acid derivatives in the brain, as in other organs, act directly on the vessel wall to produce vaso dilatation. The beneficial results in epilepsy are believed to be due to the vaso-dilator action.

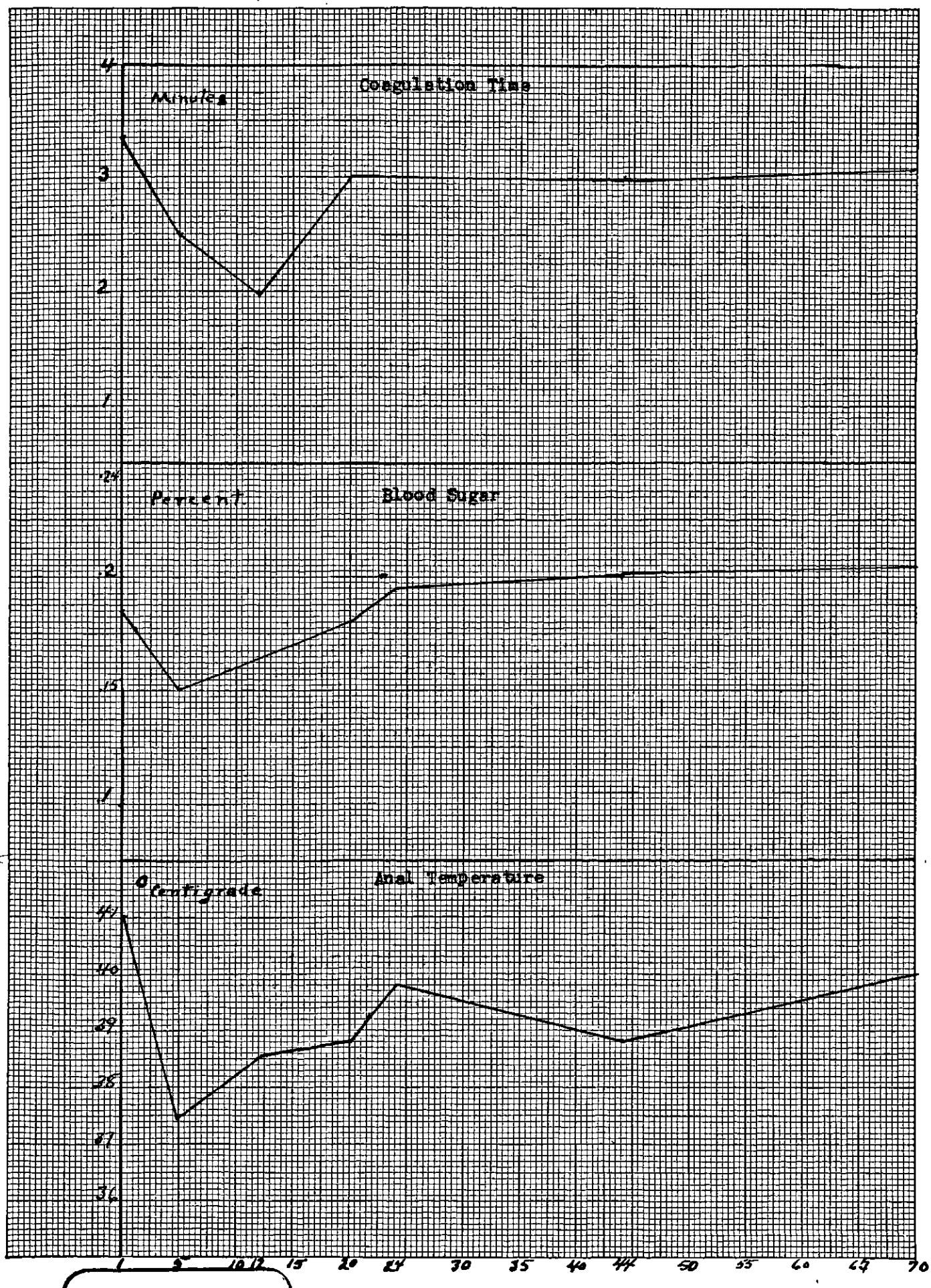
Reference Number 46

Journal of Pharmacology and Experimental Therapeutics, 24, 4 (1924)

Barbital Narcosis

Barbital narcosis was studied in pigeons and cats, a record of blood coagulation time, sugar content and body temperature was kept during the period. In the first few hours of barbital narcosis in pigeons and in cats, a lowering of blood sugar level was observed. The blood sugar level returned slowly to normal by the end of the forty-fourth hour. The coagulation time of the blood was shortened during the first few hours of barbital narcosis, and returned to normal between the twentieth and forty-fourth hours.





Reference Number 47

Journal American Medical Association, Feb. 1, 1936. Page 421
Kansas Medical Society Journal, Topeka, 56 : 485-526 (Dec. 1955)

Effects of Aminopyrine and Phenobarbital on Blood Count, page 500. - by S. J. Wilson.

The author reports that after watching the blood count of rats after the injection of aminopyrine and phenobarbital and combinations of each, there was no change in the blood pictures of the series in which phenobarbital alone was used.

Reference Number 48

Journal of Pharmacology and Experimental Therapeutics, 40 : 215-228, (1930)

The Effects of Barbituric Acid Hypnotics on Basal Metabolism in Humans - by Anderson, Chen and Leake.

Sodium barbital, ipral, neonal, phanodorm, caused decreased O_2 consumption. Amytal and phenobarbital increased O_2 consumption, while dial had inconsistent effects. Barbital had a more consistent effect in decreasing the pulse rate and lowering the blood pressure than the other drugs. All the drugs decreased tactile discrimination and increased respiratory rate.

Reference Number 49

Chemical Abstracts, 50, 5 (1956) Page 1443.

Pharmacology of Nicotine, by Gold and Brown, J. Pharmacol. 54 : 463-76, (1955)

Barbital antagonizes the action of nicotine, although it does not prevent death from two fatal doses. Such death is without convulsions. The emetic action of nicotine is not abolished by barbital.

Reference Number 50

Chemical Abstracts, 30, 5 (1936) Page 1445.

Barbiturates and Factors Governing their Distribution, - by Dille, Linegar and Koppanyi.

Barbiturates can be detected in the blood as long as they are in the tissues, and no organ tissue has any specific affinity for them, although barbital is less concentrated in the brain and pentobarbital sodium more concentrated in the brain than in other organs.

Reference Number 51

Chemical Abstracts, 24, 2 (1930) Page 2198.

The Effect of the Repeated Administration of diethylbarbituric acid and of cyclohexenylethyl-barbituric acid. - by Eddy, J. Pharmacol. 37 : 261-71 (1929).

Eddy describes the tests used to follow tolerance of cats to continued doses of the two barbitals. He claims no tolerance of either drug was observed.

Reference Number 52

Chemical Abstracts, 24, 2 (1930) Page 2181.

Kugel and Epstein in Arch. Epl. Path. Pharmakol., 142, 1929, described their results obtained in diuresis from the administration of hypnotics. The amount of water and of salt increase is given comparatively for sandoptal, luminal, veronal and paraldehyde, etc.

Reference Number 53

American Pharmaceutical Association Year Book 1933. Page 140.

Barbital Poisoning, - by W. E. Gower and J. Van De Erve, J. Pharmacol. and Exper. Therap. 1933.

Various methods of fluid administration to cause diuresis was tried in attempting to recover dogs from anaesthetic doses of sodium barbital. Physiological salt solution by vein was found superior to glucose solution. In several cases diuresis exerted no apparent influence in recovery from amytal.

Reference Number 54

American Pharmaceutical Association Year Book 1933. Page 141.

Barbituric Acid Derivatives, - by M. R. Fabre, J. Pharm. et Chim., 18 (1933), 417.

Veronal was used as an example to demonstrate that placental membrane is perfectly permeable to the barbituric acid series.

Reference Number 55

Chemical Abstracts, 30, 11 (1936) Page 5885.

Effects of Different Narcotics on the Spontaneous and Reflex Electrical Activities of the Cerebral Cortex, - by Bremer, Compt. rend. soc. biol., 121 : 861-866 (1936).

Cats were used. The cortical oscillograms obtained during anaesthesia with Et_2O or $CHCl_3$ were quite different from those obtained during hypnosis by barbiturates.

Reference Number 56

Chemical Abstracts, 30, 19 (1936) Page 6827.

Pyramolone and Barbituric Acid Derivatives are Causes of Primary Agranulocytosis, - by Taeger, Sammlung Vergiftungsfällen 5, Abt. C, 61 (1934) : Chem. Zentr. 1935, II : 2086.

A summary with extensive references. According to the observations of American and Scandinavian authors the continued use of Pyramidon is supposed to lead to agranulocytosis, but these findings must not be regarded as clearly understood.

Reference Number 57

Chemical Abstracts, 26, 5 (1932) Page 4873.

The Influence of Various Narcotics on the Blood Coagulation as well as on the Coagulation Components of the Blood, - by Basaki, Folia Pharmacol. Japan, 14, No. 2, Opera orig. 14-19 (1932)

Veronal and luminal delay and retard coagulation of the blood. The coagulation components are also decreased.

Luminal and veronal act directly on the mid-brain centre and secondarily on the centre in the cerebrum.

Reference Number 58

Chemical Abstracts, 24, 5 (1930) Page 5864.

Comparative Studies on Circulatory Damage and Narcotic Effect of Various Barbituric Acid Derivatives, - by Marthe Vogt. Arch. exptl. Path. Pharmakol. 152, 541-60 (1930)

The derivatives were found to have similar toxic effects on circulation.

Veronal has slower but larger narcotic effect. Phanodorm and amytal and particularly noctal and pernocton induce very brief narcosis.

Veronal is least toxic for circulation ; pernocton, amytal, proponal and sandoptal are most toxic ; numal, dial, luminal and phanodorm are intermediate. The margin between the lethal and narcotic dose for rats is widest with phanodorm and amytal, least with noctal and pernocton and intermediate with the others.

Reference Number 59

Chemical Abstracts, 17, 2 (1923) Page 2004.

Wiki, in his report in Arch. intern. pharmacodynamie 27 : 117-161 (1922), gives a detailed report of his study of veronal, luminal and dial. The toxicity, anaesthetic properties and effects on blood pressure and on respiration were studied. Luminal is to be used with the greatest caution. Dial and allylisopropyl barbituric acid (alurate) are preferable in their mode of action to veronal. Alurate and dial were found to be almost identical in action and dosages.

Reference Number 60

Chemical Abstracts, 17, 2 (1923) Page 2148.

Klin. Wochschr. 1, 944-947 (1922)

Sodium barbital has an action on blood vessels of reducing temporarily the blood pressure, like that action of papaverine.

Reference Number 61

Chemical Abstracts, 22, 1 (1928) Page 261.

The Importance of Sodium Diethylmalonylurea and Sodium Phenylethylmalonylurea in the Study of Sympathetic and Paresympathetic Iniation, as listed in Compt. rend. soc. biol. 95, 1046 (1926) by Arnell.

Phenobarbital sodium is without action upon sympathetic or

Reference Number 61 (Continued)

parasympathetic innervation, nor does it modify the reaction of adrenaline upon either intestine or uterus. Barbital reinforces excitability of the sympathetic innervation and exercises a paralysing action on the irritability of the parasympathetic innervation.

Reference Number 62

Chemical Abstracts, 29, 3 (1935) Page 8130.

Barbiturates and the Mammalian Heart - by Roth, Arch. intern. pharmacodynamie 51 : 179-184 (1935)

Perfusion of the isolated heart of white rats with Na barbital, Na phenobarbital, Na amytal and Na ethyl (1 methyl-butyl) barbiturate caused a brief stimulation followed by the characteristic depression. The stimulation was not prolonged and the depression least marked with Na barbital.

Reference Number 63

Chemical Abstracts, 29, 2 (1935) Page 6309.

The Effect of Some Barbituric Acid Derivatives on the Intestine of a Cat, - by Dreyer and Hebb, Proc. Nova Scotian Inst. Sci. 18 : 282-5, (1933-34).

The sodium salts of phenobarbital, amytal, veronal, dial, phanodorm and pentobarbital were injected intravenously into decerebrated cats and in all cases the gastric and intestinal movements were stimulated until doses became so large that respiration or circulation failed. The action was peripheral.

Reference Number 64

American Pharmaceutical Association Year Book, 1933. Page 141.

Barbituric Acid Derivatives, - by Coste and Bolgert, Bull. Mem. Soc. Med. Hop. Paris, 49 (1933) 779, through Squibb Abstr. Bull. 6, (1933), A-1106.

"Two cases are reported in which lesions followed or coincided with a state of coma induced by a barbituric acid derivative."

"The Authors discuss the possibilities of central or peripheral disturbance as an explanation of the pathology."

Reference Number 65

Chemical Abstracts, 20 (1926) Page 3045.

Gruber reports that there is a loss of tonus and complete cessation of peristaltic movements in smooth muscles produced by concentrated solutions of the barbiturates.

Reference Number 66

Chemical Abstracts, 28, 5 (1934) Page 7366.

Barbiturates IV. Effect of Barbiturates in Experimental Nephrosis. Murphy and Koppanyi, J. Pharmacol. 52.: 70-77 (1934).

Barbiturates VI. The Elimination of Amytal and Neonal. Koppanyi and Krop, Ibid. pp. 87-90.

Barbiturates VII. Experimental Analysis of Barbital Actions. Koppanyi and Dille, Ibid., pp. 91-100.

Reference Number 67

Journal of Pharmacology and Experimental Therapeutics, 1, 51 (1927) Page 1.

The Comparative Anaesthetic Efficacy of Isoamylethyl barbituric acid and Diethyl barbituric acid, - by Swanson and Page of the Lilly Research Laboratories.

The minimum fatal dose and minimum effective dose of these two compounds have been studied by the authors. In the article charts are given showing the M.F.D. when given orally to cats is 110 mgm. per kilogram for amytal and 280 mgm. per kilogram for barbital. When the subcutaneous injection in rabbits was compared, the M.F.D. was found to be 110 mgm. for amytal and 290 mgm. for barbital. Comparing the drugs by subcutaneous injection in rats, it was found that the M.F.D. for amytal was 100 mgm. and for barbital 510 mgm.

The minimum effective dose for amytal was found to be 40 mgm. and for barbital was found to be 200 mgm.

The guinea pig is not a satisfactory animal for the standardization of these anaesthetics.

The M.E.D. was obtained by subcutaneous injection in rabbits. It was 45 mgm. for amytal and 155 mgm. for barbital. The time of induction seems to be less than one hour shorter for amytal than for barbital.

There is a wider range found between the M.E.D. and the M.L.D. with amytal than with barbital.

Reference Number 68

Journal of the American Medical Association, June 29, 1935. Page 2318.

The Clinical Use of Anaesthetic Agents and Methods, - by John S. Lundy, M.D.

Derivatives of Barbituric Acid ;

"In certain emergency cases any practising physician is justified in using the barbiturates in large doses ; for example in cases of tetanus, eclampsia of pregnancy, or convulsions caused by meningitis or by strychnine poisoning. A derivative of barbituric acid is most effective when given intravenously. When given intravenously, the rate of injection should be slow enough so that marked depression of respiration does not occur ; since individuals vary, no rule can be given other than that the respiration must be watched. Perhaps as important as the rate of injection is the initial assurance that the stomach is empty and thereafter the maintenance of a good airway. A sterile soluble salt should be used for injection. If the soluble salt is not available, the insoluble salt may be given by mouth or rectum.

It is now apparent that these drugs are habit forming to certain types of individuals and I feel that if the patient becomes addicted to the use of a barbiturate, that patient may possibly be emotionally unstable and constitutionally inferior, with psychopathic tendencies.

As pre-operative or post-operative medication, these drugs are valuable and are safely used in small doses in the majority of cases.

Intravenous injection of the barbiturates to produce surgical anaesthesia should be confined to minor operations of short duration, and administration should be by experienced persons. These injunctions should hold until it has been definitely shown that the drug has a wide margin of safety and that fatalities are unlikely to occur from moderate overdosage. The latter requirement for safety, in all probability, never can be met, and so I advise against the giving of barbiturates intravenously by those inexperienced in their administration whenever another anaesthetic agent can be used instead."

Reference Number 69

American Pharmaceutical Association Year Book 1930. Page 115.

Therapeutics of Barbituric Acid Derivatives, - by S. Weiss, Am. J. Med. Sci. (Sept. 1929) through Clin. Med. and Surg. 57 (1930) p. 72.

The author lists his conclusions based on personal and clinical experience. He finds that -

1. Man is more susceptible than animals.
2. Marked individual variations exist in response of patients to identical doses.
3. Sodium luminal injected intravenously stops convulsions, produces muscular relaxation, and induces sleep.

Reference Number 69 (Continued)

4. Intravenous administration of sodium luminal and other barbituric acid compounds has been found beneficial in treating severe status epilepticus, eclampsia, etc.
5. Intravenous routine use of barbituric compounds for surgical anaesthesia in certain psychoses is dangerous.
6. The mechanism of their solution is different from that of ether, chloroform and nitrous oxide.
7. In administration of barbituric acid compounds one must carefully observe the patient's condition.

Reference Number 70

American Journal of Pharmacy, Jan. 1936. Page 38.

Duration of Action of Barbiturates

"The long acting barbiturates upon intravenous administration produce little immediate toxic or fatal effect. The rapid intravenous injection of short acting barbiturates is followed by acute toxic effects, often resulting in the immediate arrest of the heart beat and respiration.

Fifteen minutes were required after the intravenous injection of barbital or phenobarbital to attain the same degree of anaesthesia that was reached in one to three minutes with pentobarbital."

Reference Number 71

Journal of Pharmacology and Experimental Therapeutics, 59 (1936) Page 165.

Comparison of Premedication Values of Several Barbituric Acid Derivatives in Relation to Nitrous Oxide Anaesthesia. - by Stormont, Lampe and Barlow.

The authors studied the relative efficiency of a series of barbituric acid derivatives as premedication agents for N_2O anaesthesia in rats. Rats are not anaesthetized at all by an 85-15% mixture, and show only mild analgesia with a 90-10% mixture. Anaesthesia is readily induced with a 95-5% mixture. In the tests the animals were anaesthetized with a 95-5% mixture and the duration of the anaesthesia determined under an 85-15% mixture.

Conclusions : Allonal, neonal and dial are most efficient in prolonging the anaesthetic effect of N_2O. All three will give at least 30 minutes anaesthesia with 85-15% mixture, using 30% of their M.L.D. A similar duration of anaesthesia with phenobarbital, barbital and amytal could only be produced with 45% of the M. L. D.

Reference Number 72

Journal of Pharmacology and Experimental Therapeutics, 41 : 367-78 (1931).

The Premedication Values of Nembutal, Phanodorm, Pernocton, in Relationship to Nitrous Oxide Anaesthesia, - by Barlow, Duncan and Gledhill.

Complete anaesthesia could be obtained with 50% of the M.L.D. of nembutal or with 37.5% of the M.L.D. of phanodorm, and an 80-20% gas mixture. Pernocton was effective only in doses of 45-52% of the M.L.D. and the toxicity was very great.

Reference Number 73

Chemical Abstracts, 30, 6 (1936) Page 1943.

Paraldehyde and Other Preliminary Hypnotics, - by Albert H. Miller, Anesthesia and Analgesia, 15, 14-21 (1936).

A comparison of paraldehyde with barbiturate, avertin, morphine, with and without atropine, as a preanesthetic.

Reference Number 74

Journal of Pharmacology, 43 (1931) Pages 449-456.

A Study of the Relative Efficiency as Basal Anaesthetics of Avertin, Amytal, Chloral, Dial and Isopropylallylbarbituric Acid, - by Kleindorfer and Halsey.

"Amytal should be a safe and efficient basal anaesthetic. Dial and isopropylallylbarbituric acid should only be used with caution."

Reference Number 75

Journal of Pharmacology and Experimental Therapeutics, 6, 24 (1925) Page 451.

It was found by Hirschfelder and Rice, of the Department of Pharmacology of the University of Minnesota, that in rats in a frightened condition the soporific action of sod. barbital definitely diminishes. Rabbits were used as the frightening agent and it was found that when larger doses were given to the rats the effect was a gradual narcosis rather than a natural sleep. All possible means, therefore, should be used to place the patient's state of mind at rest during the administration of a sopporific.

Reference Number 76

Chemical Abstracts, 27, 2 (1933) Page 3008.

The Determination of Toxicity Constants and the Activity of Some Barbituric Derivatives. Principles of Comparison. Results. - by Launoy, J. physiol. pathol. gen. 30, 564-578 (1932)

Launoy describes the positions assumed by rabbits in different degrees of anaesthesia after neonal, amytal, phanodorm, etc. He gives the standard dose of barbital, nembutal amytal, neonal, phenodorm, dial, ipral, gardenal and rutonal ; the toxic units ; the narcotic units ; narcotic values and toxic values, compared to barbital = 1.

Reference Number 77

Journal American Medical Association. Dec. 26, 1936. Page 2104.

The Clinical Use and Dangers of Hypnotics. - by Sonia Weiss, M.D.

The author deals in quite a general manner with all hypnotics in use. They are classified according to their relationships to other drugs, the type of sleep desired, chemical structure, administration and dosage, untoward effects and chronic intoxication.

Some features of chronic poisoning by barbiturates are dealt with, particularly the diagnostic side of it.

Reference Number 78

Journal American Medical Association, Oct. 24, 1936. Page 1581.

The Pharmacopeia and the Physician : The Use of Hypnotics. - by G. P. Grabfield, M.D.

The article deals, in a general manner, with all hypnotics, - how they act on the central nervous system and conditions indicating their use.

"Pentobarbital has proved very useful for quick action of short duration."

"Barbital is still probably the most satisfactory drug when more prolonged and less prompt action is desired.

Where sleep is disturbed by motor restlessness not directly associated with cerebral activity, phenobarbital is useful, the author suggests."

Reference Number 79

Journal American Medical Association, Nov. 23, 1935. Page 1721.
Journal of Pharmacology and Experimental Therapeutics, 54 (Sept.) 1935.

Relative Efficiency of a Series of Analeptics as Antidotes to Sublethal and Lethal Dosages of Pentobarbital, Chloral Hydrate and Avertin. - by Barlow.

The report represents in excess of 1,600 experiments, under such conditions that any recoveries noted could be attributed to the effects of the analeptic measures alone.

Reference Number 80

Journal American Medical Association, Dec. 21, 1935. Page 2044.

Ether-Oil Rectal Analgesia in Obstetrics. - by James T. Gwathmey, M.D. and C. O. McCormick, M.D.

In this article the doctors describe fully their modified technique used in analgesia in obstetrics. Pentobarbital sodium in 1½ gr. doses, repeated as necessary, is given as a basal anaesthetic.

Relative Toxicity of Drugs.

	Minimum Effective Dose	Minimum Fatal Dose	Ratio
Pentobarbital Sod.	40	110	2.7
Barbital	225	510	1.57
Amytal	72	180	2.5

Reference Number 81

Journal American Medical Association, June 22, 1935. Page 2296.

Barbiturates in Primiparous Labors

The drugs used by Tritsch and Brown in their study were diallylbarbituric acid (dial), sodium iso amyl ethyl barbiturate (amytal) and morphine, sodium iso amyl ethyl barbiturate (amytal) and rectal ether, sodium allylisopropyl barbiturate with scopolamine.

The authors conclude that the barbiturates used above are apparently of less value for the relief of pain during labor and for production of amnesia in labor than they are when combined with other drugs. Barbiturates combined with sedative or amnesia-producing drugs appear to accentuate and prolong their action.

Reference Number 82

Handbook of Therapeutics David Campbell

Page 205.

The barbituric acid compounds used in treatment of diseases of the nervous system are given. Barbitone (veronal) and its sodium salt, medenal, are the best known representatives of this class. Phenobarbital (luminal) is also used in nervous treatment.

The author thinks that the fear of habit formation is very much exaggerated and that habituation to hypnotics depends more on the mentality of the patient than on the particular drug.

Reference Number 83

Manufacturing Chemist, Feb. 1935. Page 57.

Barbiturate Intoxication.

Manufacturing Chemist, Jan. 1932. Page 9.

Anaesthetics

Barbituric acid derivatives have been subjected to research to find a stable compound suitable for injection before volatile anaesthetics. Nembutal "844" (sodium ethyl methyl-butyl barbituric acid) and amytal sodium were found useful.

Reference Number 84

Journal American Medical Association, Jan. 11, 1936. Page 165.
Paris Medical. 2 : 525-540 (Oct. 26, 1935).

Anaesthesia obtained by intravenous administration of ethobutylethylmalonylurea is described by Desplas and his associates, according to their experiments on fifty-two cases.

Reference Number 85

Manufacturing Chemist, March 1934. Page 72.

Battle of the Barbiturates

"Physicians argue that no other drugs can take the place of the barbiturates for promoting sleep and calming down over-activity of the nervous system such as convulsions, and they insist that their use is essential."

Reference Number 85 (Continued)

"On the other hand, we have the smaller, no less important group, which holds these drugs are dangerous, that they are frequently used for suicide, and that addiction is so easy and so fatal that their use should be limited by the most stringent legislation."

It has been said that less than 1% of all suicides can be attributed to these drugs.

Reference Number 86

Manufacturing Chemist, Dec. 1954. Page 595.

Barbiturate After-Effects

"Rashes may occur during the first days of barbiturate medication, but pain does not come for a considerable time. As a rule the pain was cramp-like, with intolerable bouts refractory to such well-known antirheumatic drugs as aspirin, antipyrin and sodium salicylate.

Reference Number 87

American Journal of Pharmacy, 108, 18 (1936) Page 545.

Addiction and Tolerance to Barbiturates. The Effects of Daily Administration and Abrupt Withdrawal of Phenobarbital Sodium and Pentobarbital on the Albino Rat. - Stanton, J. Pharmacol. and Exp. Therap., 57 (1936) page 245.

Since the introduction of barbiturates in 1903, indiscriminate use by the public has led to an increasing number of reported cases of habituation with either acute or chronic poisoning as the result. Few data exist, however, concerning the occurrence of true addiction to these compounds in the sense of hyperirritability and other abstinence symptoms following their withdrawal.

The author carried out a series of experiments on albino rats, using two members of the barbituric acid series : phenobarbital-sodium, an example of a long acting barbiturate, and pentobarbital-sodium, an example of a short acting hypnotic.

The method used was a determination of the twenty-four hour abstinence irritability of the rat receiving daily injections of the drug, irritability being objectively measured by recording the struggle response of the rat to a uniformly uncomfortable situation. Tolerance, by this method, is indicated by a progressive weekly increase in the level of response one hour after injection of the drug. Such an increase indicates a lessened tranquilising power of the drug, and hence a tolerance on the part of the animal.

Reference Number 87 (Continued)

The results show that following daily injection of both compounds there was no increase in abstinence irritability. On the contrary, the irritability progressively decreased, especially with the larger doses, and this extended to a considerable degree into the withdrawal period. Rats therefore do not become addicted to phenobarbital-sodium or to pentobarbital-sodium in the sense of increased irritability following withdrawal of the drug, but tend rather to show evidence of some cumulation of depressive effect.

The courses of injection induced only a very minor degree of tolerance to the maximal effects of pentobarbital-sodium, as indicated by the struggle response of rats one hour after injection, but the duration of the somnifacient action appeared to be markedly shortened at the end of the injection period.

Reference Number 88

Journal American Pharmaceutical Association, July 1936. Page 597.

The Toxicity of Barbital Derivatives

The toxicity in rabbits and the comparative efficiency were studied for amytal, barbital, dial, neonal, pentobarbital, phanodorm and phenobarbital, using both oral and intraperitoneal routes.

Some of the figures for the minimum lethal dose differ markedly from those found in the literature. Apparently the general ratio of efficiency to toxicity is approximately the same for the seven compounds, except that amytal and pentobarbital seem to be extremely safe by oral administration.

Reference Number 89

Year Book American Pharmaceutical Association, 9 (1920) Page 584.

Barbital Addiction

The constant use of even small doses of barbital effects the central nervous system. Those taking the drug habitually become much debilitated and seem less able to stand moderate doses. Death has occurred from a 5 gm. dose in addicts.

Reference Number 90

Year Book American Pharmaceutical Association, 1926. Page 177.

Expedient to Prevent Barbiturism

The author quotes Cimbal, who prescribes simultaneously

Reference Number 90 (Continued)

powdered ipecacuanha. If the prescribed dose is exceeded, vomiting is produced.

- Levant. Gaz. Des. Hopitaux, 80 (1926), page 479.

Reference Number 91

Therapeutic Notes, Feb. 1935. Page 65.

Barbiturates in Epilepsy

Patients studied had been taking phenobarbital in doses of from 2 to 6 grains daily over a period of years. As these patients showed no significant deterioration, it is suggested that long-continued sedative therapy does not produce reduction in the intelligence quotient.

Reference Number 92

Journal of American Medical Association, Dec. 8, 1934. Page 1815.
Presse Medicale, Paris.

Barbituric Arthralgias and Myalgias

"Castin and Gardien report six cases in which joint muscle pains developed in the course of barbiturate administration.

The pains seem to occur only after prolonged administration of the drug.

The authors state that as a general rule the barbituric algesias are no more a contradiction to the use of this drug than are the skin eruptions and other reported complications."

Reference Number 93

Journal American Medical Association, Jan. 19, 1935. Page 262.
British Medical Journal, London, 2 ; 929-976 (Nov. 24, 1934).

Barbituric Acid Paralysis

Londor and Sallek report a case of widespread paralysis following the use of a derivative of barbituric acid (evipan) for general anaesthesia with no premedication.

Reference Number 94

Year Book American Pharmaceutical Association, 1951-52. Page 115.

Chronic Experimental Barbital Poisoning, - by M. H. Seevers and A. L. Tatum, J. Pharmacol. 42 (1951), page 217.

The authors administered barbital to dogs over a period of three years and summarised their findings with regard to tolerance, and damage to central nervous system.

Reference Number 95

Chemical Abstracts, 50, 5 (1956) Page 775.

The Nature of the Barbiturate-Picrotoxin Antagonism, - by Linegar, Dille and Koppanyi, Science 82 (1955), page 576-7.

The antidotal effect of different doses of picrotoxin was manifested in four different ways : (a) occasional rise in blood pressure, (b) prevention of steep fall and hastening of the recovery from a fall in blood pressure produced by intravenous barbiturate injection, (c) stimulation of respiration, (d) maintenance of respiration after barbiturate injection even after cardiac stoppage.

Reference Number 96

Chemical Abstracts, 50, 4 (1956) Page 1122.

Treatment of Coma Caused by Barbiturates, - by Flandin, Presse Med. 45 : 805-4 (1955).

High doses of strychnine, blood letting, artificial respiration, and adrenaline by rectum are recommended.

Reference Number 97

Journal American Medical Association, Aug. 1, 1956. Page 554.

Status of Picrotoxin

The American Medical Association, as referee, pointed out that wide differences in effectiveness had been found by Maloney in the use of picrotoxin against different barbiturates, negligible, for instance, against phenobarbital, and many times greater against nostal.

"The council does not wish to imply a belief that picrotoxin is of no value in the treatment of barbital poisoning. It awaits the development of further evidence in the work of competent investigators."

Reference Number 98

Quarterly Journal of Pharmacy and Pharmacology, 6 (1933) Page 727

Maloney (J. Pharmacol. 49 ; 155, 1933) claims picrotoxin is more efficient as an antidote to veronal poisoning than cocaine or strychnine.

Reference Number 99

Chemical Abstracts, 25, 5 (1931) Page 4959.

Picrotoxin as an Antidote in Acute Poisoning by the Shorter Acting Barbiturates, - by Maloney, Fitch and Tatum, J. Pharmacol. 41 ; 465-82 (1931)

Animals having had barbiturates will tolerate a much larger dose of picrotoxin than a normal animal. The use of picrotoxin as an antidote in barbiturate poisoning is suggested.

Reference Number 100

Chemical Abstracts, 26, 2 (1932) Page 3842.

Nembutal ; An Antidote, - by Cameron and McCulloch, Can. Med. Assoc. J. 26 ; 415-415 (1932).

Large doses of nembutal produce death by respiratory failure in guinea pigs. In rats cocaine HCl did not give any protection against nembutal poisoning. Ephedrine HCl, given intravenously 15 minutes after a lethal dose of nembutal, affords a marked protection.

Reference Number 101

Chemical Abstracts, 24, 1 (1930) Page 158.

Veronal is a dangerous habit forming drug states Super, in an extract from Hahnemannian Monthly, 64 ; 695-700 (1929), who also describes a treatment for the habit, the symptoms of which are abnormality of speech, muscular inco-ordination and hypnosis.

Reference Number 102

Chemical Abstracts, 29, 1 (1935) Page 844.

A Comparative Study of the Habitual Use of Barbiturates and Coal Tar Derivatives, as Furnished by Reports from Various Hospitals Throughout the United States, - by Lowy, Can. Med. Assoc. J. 31 ; 638-41 (1934).

Contains data giving addiction to, poisoning by and death from, barbital and phenobarbital.

Reference Number 103

Quarterly Journal Pharmacy and Pharmacology, 7 (1934), Page 624.

Poisoning by Barbital and Allied Drugs, - by Stewart and Willcox, Lancet, London, 226, 6 (1934)

Cases of hyperthyroidism, severe toxemia, and renal and hepatic insufficiency are unduly susceptible to barbiturate poisoning. Colonic and stomachich lavage should be repeated frequently as the elimination of the poison is most important.

Reference Number 104

Chemical Abstracts, 28, 2 (1934) Page 5795.

Poisoning by Barbital and Allied Drugs, Its Treatment by Lumbar and Cisternal Drainage, Purvis, Stewart and Willcox, Lancet 1 ; 15-16 (1934).

Reference Number 105

The 1936 Year Book of General Therapeutics Fantus, p. 286.

Antidotal Effect of Coramine in Barbituric Acid Narcosis

"From the results reported it may be inferred that Coramine is of value in counteracting the effects of a wide range of barbiturates with a wide range of dosages."

Reference Number 106

Chemical Abstracts, 29, 2 (1935) Page 1816.

Cocaine, Alcohol, Dinitrophenol and Methylene Blue in Experimental Intoxication with Barbiturates, - by Allegri, Boll. soc. ital. biol. sper. 10 ; 48-51 (1935)

These four substances and procaine were tried on dogs, cats and rabbits to show their inhibitory effects on the animals when toxic doses of phenobarbital and barbital were given.

Reference Number 107

Journal American Medical Association, Aug. 17, 1935. Page 502.

The Antidotal Action of Potassium Permanganate, - by R. Hatcher, M.D.

"Potassium permanganate may be useful in washing the stomach after poisoning by alurate, dial and possibly some others ; not after phenobarbital, barbital, amytal or neonal."

Reference Number 108

Chemist and Druggist, 1933. Page 57.

Le Barbiturisme Aigu (ed.) - Barbiturate Intoxication.

"They claim that alcohol is superior to coramine and strychnine as an antidote ..... But strychnine etc. is still safer."

Reference Number 109.

Journal American Chemical Society, 55 : 528-532, Jan. 1933.

Physiochemical Properties and Hypnotic Action of Substituted Barbituric Acids. - Tabern and Shelberg.

Through experiments with fifteen barbiturates, the authors established certain facts relating their hypnotic properties to their chemical properties.

One table listed shows a definite parallelism between the partition coefficients and hypnotic efficiency.

They deal also with the surface tension factor and its relationship to hypnosis.

Certain groups or side chains have been identified with specific reactions by the authors.

Reference Number 110

Journal American Chemical Society, 44 : 1141-45 (1922) - Dox and Yoder. (Contribution from Parke Davis and Company)

"The fact has been repeatedly demonstrated that two hydrocarbon radicals on the 5 carbon atom are necessary to confer sleep-producing properties on barbituric acid. The two radicals may or may not be identical, but one alone is not sufficient."

The authors attempted to combine the antispasmodic properties of the benzyl derivatives and the hypnotic properties of barbituric acid. They prepared a series of alkylbenzyl barbituric acids, with the alkyl radical derived from the primary aliphatic alcohols. Previously no such derivatives had been described.

Ethyl benzyl barbituric acid was found to have the strongest physiological action.

"Contrary to our expectations, the hypnotic effect was accompanied by symptoms of tetanus instead of the antispasmodic effect commonly attributed to the benzyl group."

Reference Number 111

Quarterly Journal of Pharmacy and Pharmacology, 5 (1932) page 141.

Modification of Hypnotic Action through Change in Chemical Structure, - by Schonle (Ind. Eng. Chem. 23 : 1104, 1931)

A maximum hypnotic effect is reached at the amyl group as the alkyl chain is lengthened in the alkyl ethyl combination. A further increase in molecular weight diminishes the hypnotic effect.

Reference Number 112

Chemical Abstracts, 18 (1924) page 882.

Dox, in J. Am. Pharm. Assoc. 12 : 602-9 (1923), reports his attempts to find the hypnotic radical of the barbiturates. The two alkyl groups on 5 carbon should have a total C of 4 and not more than 8. One of the groups must be an open chain. The benzyl group has a tendency to cause convulsions. Not more than two alkyl groups should be aromatic in character.

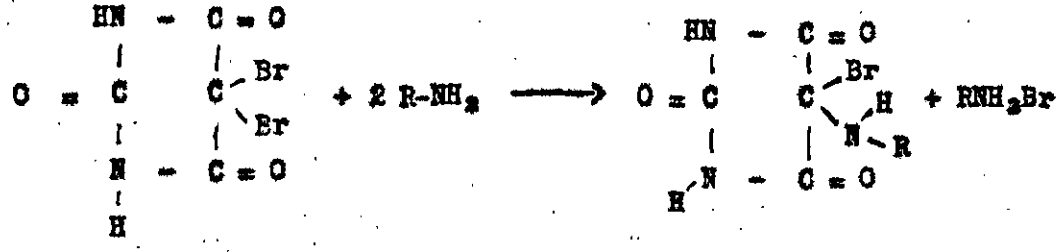
Reference Number 113

Journal American Chemical Society, 54 : 256-9 (1932)

Some Reactions of Di-halogen Barbituric Acids, - Dorothy Nightingale and Schaifer.

One halogen of the di-halogen derivatives of barbituric acid is more reactive than the other. The chloride derivative is much less reactive than the bromo compound.

The bromo compound reacts with primary and secondary amines as follows :



Nitrogen and halogen analyses are given for many of the derivatives prepared in this manner.

Reference Number 114

Journal American Chemical Society, 52 : 224-9 (1930) Bousquet and Adams.

The authors of the extract, describing their experiences, claim that all the substituted phenyl ethyl barbituric acids prepared by them were inert physiologically. These derivatives were made by placing radicals in the phenyl radical of phenobarbital.

Reference Number 115

Chemical Abstracts, 26, 1 (1932) Page 1660.

The Influence of Nitration and Amination on the Physical and Physiological Properties of Methyl-phenyl-malonyl-urea (Rutonal) and Ethyl-phenyl-malonyl-urea (Luminal), - by Louflier and Postic, Compt. rend. 193 : 1478 (1931)

The substitution of a nitrate or amino group in the benzene nucleus of hypnotics of the barbituric acid series causes the hypnotic properties to disappear. The derived amines cause a slow fall in temperature and are less toxic.

Reference Number 116

Chemical Abstracts, 50, 10 (1956) Page 5945.

Thiobarbiturates II, - by Miller, Munck, Crossley, Hartung, J.A.C.S. 58 : 1091-1 (1936)

The following five 5-disubstituted thiobarbituric acids were prepared from the proper malonic ester and $CS(NH_2)_2$ with EtONa, refluxing 6-7 hours.

Et Pr, m. 174.5°	Et iso-Bu, m. 170.5°
Pr iso-Pr, m. 168.5°	Pr Allyl m. 158°
Pr Bu m. 155.5°	Pr iso-Bu, m. 152°
Pr sec-Bu., m. 165°	Pr hexyl, m. 114.4°
iso Pr allyl, m. 176.5°	iso-Pr Am., m. 98.5°
Allyl Bu, m. 180-1°	Allyl iso-Bu, m. 147°
Allyl Am, m. 112.5°	

The yields are somewhat higher than those obtained from the O analogs.

Reference Number 117

Journal American Chemical Society, 58 : 794-6 (1936)

Some Nitrogen Substituted Barbituric Acids and Their Derivatives. - by Dorothy Nightingale and Claude Alexander.

Twenty-seven nitrogen substituted barbituric acids and their derivatives are listed, together with their melting points.

Reference Number 118

Journal American Chemical Society, 58 : 751-2 (1936)

Dox and Bywater list nine tert-alkyl ethyl derivatives with their melting points, as prepared by them.

Reference Number 119

Chemical Abstracts, 29, 1 (1935) Page 2913.

Preparation of Cyanobutyric Ester from Butyric Acid and Veronal from Cyanobutyric Ester. - Takeichi Nishikawa, Mem. Ryojun Coll. Eng. Inouye Commeration. Vol. 1934 : 389-92.

Complete description of the esterification and the condensation, together with quantities and yield, is given.

Reference Number 120

Year Book American Pharmaceutical Association, 1935. Page 208.

A. W. Dox synthesized homodesoxyveronal, the 7 membered heterocycle homologous to desoxyveronal. (J.A.C.S. 55 : 5871, 1935)

Reference Number 121

Organic Syntheses XII, page 58-9 (1932) Sheppard and Hartmann

Preparation of Nitrobarbituric Acid

Barbituric acid added to fuming HNO_3 below 40°C during two hours, stirring continued for one hour. A yield of 85-90% is obtained.

Reference Number 122

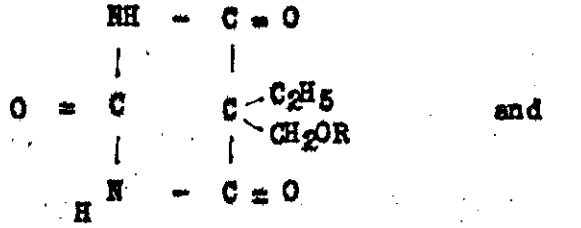
Organic Syntheses Vol. XII (1932) Sheppard and Hartmann.
Page 84-5.

Nitrobarbituric acid is reduced by tin and concentrated HCl on a boiling water bath. A 65-70% yield is obtained.

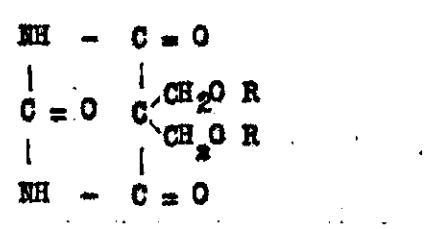
Reference Number 123

Journal American Chemical Society, 48 : 257-62 (1926)

In a contribution from the Department of Chemistry of Yale University, Hill and Keach described their experiments in obtaining ether substituted derivatives of barbituric acid. Nine were synthesized of the types -



and



The therapeutic properties were not given in this report.

Reference Number 124

Journal American Chemical Society, 48, 2 : 2571 (1926)

Easterfield, Woods and Wright of the University of Saskatchewan in 1926, during their study of substituted urethans, prepared a barbituric acid derivative, 1, 5 - diphenyl - 2 - imino-barbituric acid. A description of the preparation is given but no reference is made to possible hypnotic properties.

Reference Number 125

Chemical Abstracts, 10 (1916) Page 2715.

Methods are described for preparing amino derivatives of barbituric acids. No reports as to the hypnotic possibilities of the products are given.

Reference Number 126

Journal American Chemical Society, 58 : 2164-6 (1916)

Condensation of Thiobarbituric Acid with Aromatic Aldehydes, - by Dox and Plaisance.

Benzalmalonylthiourea, hydroxybenzalmalonylthiourea, nitrobenzalmalonylthiourea, cinnamylidenemalonylthiourea, are described with their preparation. No physiological properties, if any, are given.

Reference Number 127

Chemical Abstracts, 10 (1916) Page 2715.

Methods are described for preparing amino derivatives of barbituric acids. No reports as to the hypnotic possibilities of the products are given.

Reference Number 128

Journal American Chemical Society, 55 : 1110 (1933) - M. S. Taggart and G. H. Richter.

Imidazole derivatives of barbituric acid have been prepared but no report was given on their hypnotic value.

Reference Number 129

Quarterly Journal of Pharmacy, 11 : 553 (1929)

A Comparative Study of New Ether Derivatives of Barbituric Acid - by Underhill and Johnson, J. Pharmac. & Exp. Therap. 55 : 441, 1929.

The toxicity of the six new ether derivatives in ascending order was -

ethyl methoxymethyl-barbituric acid
ethyl ethoxymethyl-barbituric acid
ethyl-N. butoxymethyl barbituric acid
ethyl-propoxybarbituric acid
ethyl-iso butoxymethyl-barbituric acid
ethyl - benzyloxymethyl-barbituric acid

Reference Number 129 (Continued)

The order of increasing efficiency as hypnotics for rats was -

ethyl-benzyloxymethyl-barbituric acid
ethyl-propoxymethyl-barbituric acid
ethyl-isobutoxymethyl-barbituric acid

Ethyl-N.butoxymethyl-barbituric acid and ethyl-methoxymethyl-barbituric acid are ineffective.

The order of increasing lethal dose was -

ethyl-methoxymethyl barbituric acid
ethyl-ethoxymethyl-barbituric acid
ethyl N-butoxymethyl-barbituric acid
ethyl propoxymethyl-barbituric acid
ethyl-iso butoxymethyl-barbituric acid
ethyl-benzyloxymethyl barbituric acid

Of the six derivatives studied, ethyl-benzyloxymethyl-barbituric acid is nearest to barbitone in effectiveness. Administered intravenously to the dog, it has a toxic action of the heart ; given orally this is still found, but the action is not fatal. In both cases the blood pressure is lowered.

Reference Number 130

The 1936 Year Book of General Therapeutics Fantus

pp. 257-264

Pentothal Sodium for Intravenous Anesthesia

From experience, Jarman and Abel (Lancet, 1 : 422-25, Feb. 22, 1936) regard pentothal sodium (thio barbiturate pentothal sodium) as safe and satisfactory for intravenous anesthesia.

It is rapidly broken down and only the minimum dose is required for surgical anesthesia for minor operations. Usually 5 ccs. is sufficient.

It is a yellow crystalline powder, giving off H_2S when mixed with water.

On page 258 a description of the induction period is given and compared to evipal. Pentothal is smoother, causes less twitching and the fall in blood pressure is less noticeable. Pentothal is more depressant to the respiratory centre.

There follows a description of the method of intravenous injection and of the signs to watch for indications of anesthesia. Recovery is not as rapid as with nitrous oxide, but is more pleasant. Vomiting is absent.

Reference Number 151

Journal American Pharmaceutical Association, Oct. 1936. Page 858.

Fourteen barbiturate compounds were studied in which an alkyl substitution was made on the N. The duration of action, and the ratio of the minimum lethal dose to the minimal anesthetic dose were studied on albino rats.

The duration of action was found to be distinctly reduced by the substitution of an alkyl radical on the nitrogen of the barbituric acid compounds.

Reference Number 152

Journal American Chemical Society, 55 : 1230 (1933) A. W. Dox

Ethylene-N, N'-Barbital

This di-molecular barbital with hypnotic properties has been prepared by the author. In tests on white mice it was shown to have a hypnotic potency three-fourths that of barbital.

Reference Number 153

Journal American Chemical Society, 57 : 1961-5 (1935)

Sulphur Containing Barbiturate Hypnotics Tabern and Volwiler

Several of these thio compounds are powerful hypnotics. When injected intravenously into animals, they produce very prompt sleep, from which the animals recover rapidly. Data on twelve compounds are given.

Reference Number 154

The Yaar Book of the American Pharmaceutical Association 1930. Page 165.

Microchemical Reactions of Barbituric Acid Derivatives, - by L. van Itallie and A. J. Steenhauer.

A description, with some illustrations of the crystals obtained, is given of the microchemical reactions of the following compounds : diethyl-barbituric acid, dipropyl-barbituric acid, diallyl-barbituric acid, allylisopropyl-barbituric acid, butylethyl-barbituric acid, phenobarbital, phenylmethyl-barbituric acid, cyclohexenyl-ethyl-barbituric acid and isobutylallyl-barbituric acid. The procedure is given in detail.

Reference Number 155

Journal American Chemical Society, 52 : 1676 (1930) - E. H. Volwiler and D. L. Rabern

Preparation of 5, 5-substituted Barbituric Acids

The authors describe the experimental work necessary to prepare a series of isomeric amyl substituted barbituric acids. They have studied these compounds pharmacologically and compared their hypnotic activities to their chemical composition. Certain physical constants of the compounds and the intermediates are described in the paper.

Reference Number 156

Chemical Abstracts, 30, 11 : 2209 (1936)

Barbituric Acid

Barbituric acid of the general formula R_1R_2 C.CO.NR_3CO.NH.CO, in which R_1 and R_2 are aliphatic or alicyclic residues and R_3 an unsated aliphatic residue of 3 or 4 C atoms chlorinated or brominated at the double bond, are obtained by heating C-di-substituted barbituric acid in the form of an aqueous solution of its alkali salt with 1, 2-dihalo 2-alkylenes containing 3 or 4 C atoms.

Reference Number 157

Chemical Abstracts, 30, 17 : 4998 (1936)

Barbituric Acid Derivatives - Chem. Fab. Joachim Wiernik & Co. A-G. Ger. 629, 575, May 5, 1936 (Cl. 12p.701)

Three methods are given for the preparation of soporifics substituting barbituric acid in the 5-position with the group BrCH : C $MeCH_2$ and also with an alkyl or aryl group.

Reference Number 158

Chemical Abstracts, 17 : 2015 (1923)

Stewart Basterfield in J. Pharmacol. 20 : 451-61 (1923) reports that 2-ethoxy barbituric acid in large doses caused some depressant action in mice, but in moderate doses was ineffective in larger animals.

Reference Number 139

Chemical Abstracts, 29, 2 : 6702 (1935)

A New Hypnotic , - Maria Leinzinger, Magyar Orvosi Arch. 36 : 195 (1935)

Phenyl allyl-barbituric acid has a better effect than phenobarbital, the toxicity of both drugs being the same. Phenyl-allyl-barbituric acid is eliminated faster than phenobarbital.

Reference Number 140

Chemical Abstracts, 28, 1 : 2850 (1934)

Barbituric Acid Derivatives, - Farbenind and Brit. 401, 695 (Nov. 17, 1933)

N mono or di-alkylated 5 cyclohexenyl or cyclopentenyl-5-alkylbarbituric acids and their salts are prepared by a known process for the manufacture of barbituric acid derivatives. The products are soporific.

Reference Number 141

Chemical Abstracts, 23, 5 : 5012 (1929)

Chem. Fab. vorm. Sandos. Swiss 132, 149, Nov. 29, 1927, reports the preparation of a new barbituric acid with powerful hypnotic properties. It is iso-butyl-n-propyl barbituric acid and is prepared by condensing iso-butyl n-propyldialkylmalonic ester with urea.

Reference Number 142

Journal American Chemical Society, 50 : 2035-6 (1928)

Among the derivatives of barbituric acid reported by Dox and Jones of Parke-Davis Research Department is N amyl ethyl barbituric acid, which they claim to have several times the potency of barbital.

Reference Number 145

Chemical Abstracts, 17 : 2887 (1923)

Sefton-Jones of the firm of Wulfing reports the preparation of the Ca and Mg salts of barbital and phenobarbital. Salts thus obtained are easily absorbable and give permanent mixtures with the alkali-earth salts of acetylsalicylic acid.

Reference Number 144

Chemical Abstracts, 17 : 3073 (1923)

Quade reports the preparation of the Mg salt of barbital as being water soluble and adapted for dispensing in a mixture with acetylsalicylic acid.

Reference Number 145

Chemical Abstracts, 21, 2 : 2907 (1927)

Volwiler, July 19, patented n-butyl-allylbarbituric acid which may be used as an hypnotic.

Reference Number 146

Chemical Abstracts, 7 : 1785 (1913)

Phenylallylbarbituric acid is reported to have hypnotic properties. It is made by heating phenyl-allyl-malonate with Na, absolute alcohol and urea, and treating the product with HCl.

Reference Number 147

Chemical Abstracts, 19 : 153 (1925)

Crotylallylbarbituric acid is reported by Taub, Schutz and Meisenburg as being an hypnotic and its preparation is described.

Reference Number 148

Barbitone B.P.

Barbitone, synonym Barbital, is a white crystalline powder, odorless, taste faintly bitter.

It is soluble in 170 parts water, in alcohol, in ether, in chloroform, and in aqueous solutions of alkali hydroxides and of alkali carbonates.

Tests for Identity : A saturated aqueous solution is acid to litmus and a gelatinous precipitate is produced when $AgNO_3$ is added to a solution acidified with HNO_3. Ammonia is evolved on boiling with alkali.

Tests for Purity : M.P. 189°-192°. Limit tests for carbonizable substances. Limit of neutral and basic substances and leaves on incineration not more than .05% residue.

Dose 5 to 10 grains, .3 to .6 grams.

Reference Number 149

Barbitonum Solubile B.P.

Soluble Barbital (synonym) may be obtained by the reaction of barbitone and sodium hydroxide. It contains not less than 97 per cent of $C_8H_{11}O_3N_2Na$.

It is a white, crystalline powder, odourless, taste bitter. Soluble in about 6 parts of water, slightly soluble in alcohol, insoluble in ether and in chloroform.

Tests for Identity : An aqueous solution is alkaline to litmus and yields a crystalline precipitate of barbitone on the addition of dilute HCl. The residue after incineration yields reactions characteristic of sodium.

Tests for Purity : Limit test for free barbitone and of neutral and basic substances.

An assay for $C_8H_{11}O_3N_2Na$ is described.

Soluble Barbitone should be kept in a well-closed container. A solution of soluble barbitone for injection is sterilized by heating in an autoclave or by Tyndalization, or by filtration.

Dose : 5 to 10 grains, .3 to .6 grams.

Reference Number 150

Barbitonum B.P.C.

Properties listed are same as those of the B.P. Soluble in water, 1 in 170, boiling water, 1 in 12, alcohol 1 in 8.5, ether, chloroform and acetone. Standards are those listed in the B.P.

Action and Uses :

Barbitone is an hypnotic which is said to act only on the central nervous system and has been found especially suitable for use in nervous insomnia and insomnia associated with cardiac disease. In ordinary doses it does not affect the medullary centres to an appreciable degree and therefore blood pressure and respiration are not influenced. Barbitone belongs to the group of indifferent hypnotics, which owe their action to their physical property of relative solubility in brain lipoid and insolubility in water. It is excreted slowly, so that cumulation may occur : eight grains require three or four days for complete excretion. Regular administration, like that of other cumulative drugs, leads to sudden poisonous symptoms, such as rash, sickness, headache and delirium. In acute poisoning, coma and all the symptoms of collapse may result, often with rise of temperature, and may be followed by broncho-pneumonia. The bowels and kidneys should be functioning properly when barbitone is administered, because it is excreted slowly. It should be given with caution in cardio - renal affections. Barbitone is of value in seasickness and has been given as a sedative before ether or chloroform anaesthesia.

Many derivatives of barbituric acid are used for the same purpose as barbitone, but, generally speaking, they are more powerful and therefore more potentially dangerous. These hypnotics in ordinary doses are of little use when sleeplessness is due to pain. In such cases they are generally combined with drugs such as amidopyrine and acetyl-salicylic acid, which possess analgesic properties. Barbitone is best administered in cachets, swallowed with a draught of hot liquid.

In cases of poisoning, the stomach should be washed with warm water, strychnine in full doses and adrenaline, or pituitary extract injected, and the usual means taken to prevent collapse and ensure efficient respiration. If coma is prolonged, food may be given by the stomach tube and dextrose-saline injected rectally. Lumbar or cisternal puncture may be necessary to remove the poison from the brain, and drainage, especially if pneumonia has commenced.

Preparation - Tabella Barbitoni et Amidopyrinae, B.P.C.

Reference Number 151

Barbitonum Soluble B.P.C.

Synonyms - Soluble Barbital ; Barbitone Sodium.

Standards, solubilities and characters are those given in the B.P.

Action and Uses :

The properties are similar to those of barbitone, but its action is claimed to be more rapid owing to its greater solubility. For this reason it has been administered rectally (1 in 20 solution) and hypodermically (1 in 10 solution).

Reference Number 152

New and Non-Official Remedies page 100.

Barbital

Diethyl barbituric Acid Barbitone - Diethyl Malonylurea

See B.P. for standards.

Actions and Uses :

Described under Barbital and Barbital compounds N.N.R. Barbital is quickly absorbed, especially when it is given in solution. Small doses induce sleep, apparently with little other effect, and are relatively safe, but fatalities have followed its indiscriminate use.

Dosage :

As hypnotic 8 grains, best prescribed in the form of a powder to be given in hot fluid, such as hot milk, half an hour before bedtime. Pills or tablets should be crushed before swallowing, to ensure absorption. From 1½ to 2 grains is used with analgesics for the relief of pain.

Veronal : a brand of barbital U.S.P., manufactured by Winthrop Chemical Co.

Reference No. 153

Barbital Sodium N.N.R.

Soluble Barbital - Sodium Diethylbarbiturate
Soluble Barbitone - Sodium Diethylmalonylurea

"It yields, when dried to a constant weight at 100°C, not less than 88% and not more than 90% of barbital." U.S.P.

Reference Number 153 (Continued)

Actions and Uses :

The same as those of barbital. It is claimed, however, that this drug acts more rapidly on account of its greater solubility. Because of its solubility, administration by rectal injection and also by subcutaneous injection has been proposed.

Dosage :

The same as that of barbital. It should be administered in aqueous solution.

Medinal : A brand of soluble barbital U.S.P. manufactured by Schering and Glatz.

Veronal-Sodium : A brand of soluble barbital U.S.P. manufactured by Winthrop Chemical Co.

Reference Number 154

Pharmacology and Therapeutics — Cushny

Barbital or Barbitone

Barbital and its sodium salt are devoid of action except on the central nervous system, and thus approach the ideal soporific more closely than some others.

They produce natural sleep in doses of 5-10 grains, larger quantities deepening and lengthening unconsciousness with only the organs of the central nervous system being involved. Fatal poisoning has occurred, the lowest dose being 10 grains, but recovery has been reported from doses as high as 125 grains. The symptoms are those of mental confusion, nausea, muscular weakness and incoördination, the heart and respiration remaining normal until near the end.

Owing to widespread abuse of the drug, chronic poisoning is common. The patient shows erythematous rash, cyanotic skin, mental depression, drowsiness or visual hallucinations. Constipation is common.

The drug is eliminated mainly by the kidney, 50 to 90% having been recovered.

Reference Number 155

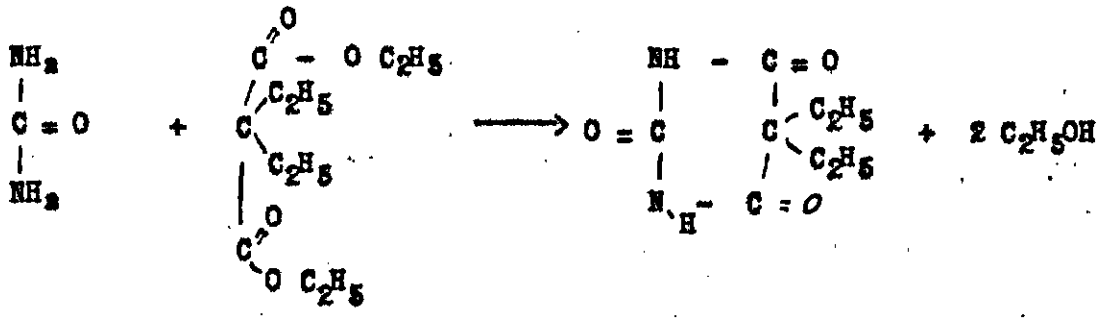
Pharmaceutical Chemistry — Bentley and Driver

Page 561

Barbitone

Sometimes known as veronal, it is prepared by the interaction of urea with either the acid chloride or the ethyl ester of diethylmalonic acid.

Reference Number 155 (Continued)



Urea — ethyl diethyl-malonate — Barbitone — ethyl alcohol

Phenobarbitone, known under the trade name of luminal, is made in a similar way to barbitone, except that the acid chloride or ester of phenyl-ethyl-malonic acid is used.

Reference Number 156

American Journal of Pharmacy, Jan. 1935, No. 1

Sterilization of Barbital Sodium Solution, - C. J. T. Madsen

A 10% solution of Sod. Barbital after 60 minutes at 100°C loses 2.5% by decomposition into barbital, and the original pH of 10.1 falls to 9.3. Diethyl acetylurea forms $CH(C_2H_5)COOH$, and the latter gives off CO_2 and NH_3. The rate of decomposition is decreased by decrease in pH. A 10% solution of sod. barbital, pH 8.9, after 60 minutes at 100°C loses 1.5% by decomposition.

Reference Number 157

Chemical Abstracts, 30, 11 : 5885 (1936)

Lustig and Wachtel,(Z. Krebsforsch 43 : 54-65, 1935), found barbital to be effective, in vitro, in investigating the therapeutic effectiveness of substances in carcinonia.

Reference Number 158

Journal of American Pharmaceutical Association, Sept. 1951. Page 691.

Incompatibilities of Some Important Newer Chemicals, - by Charles F. Lanwermeyer.

Barbital :

Barbital and acetphenetidin are antagonistic physiologically, as tested in guinea pigs. Antipyrin is antagonistic to the sedative effect of barbital, but the stimulating effect of the two is synergistic. Heating with alkali carbonates or hydroxides decomposes it, liberating ammonia. It darkens with calomel slowly, but when moist or if sodium bicarbonate is present, it darkens immediately.

Barbital Sodium :

Barbital Sodium is incompatible with ammonium salts giving off ammonia and precipitating barbital. It is incompatible with acid salts, morphine hydrochloride, and with solutions containing fruit essences, on account of the acid present. With Tr. of Cinchona it precipitates out the alkaloids, but the reaction takes 24 hours.

Reference Number 159

Manufacturing Chemist, May 1952 Page 101

Purity of Veronal

Dutch Pharmacopoeia - a solution of veronal in alkali should remain bright on addition of bromine water, while luminal gives immediately a white crystalline precipitate. Van Arkel (Pharm. Weekblad, 1952, Vol. 69, p. 86) says that veronal also gives a white crystalline precipitate, but on longer standing and in the presence of too much alkali. Suggests that the bromine derivative be made, and the melting point and bromine content be compared with the pure veronal or luminal derivative.

Reference Number 160

Phenobarbitonum B.P.

Phenobarbital (synonym) is a white crystalline powder, odourless, taste slightly bitter. Soluble in about 1000 parts of water, in alcohol, in ether, in chloroform, and in aqueous solutions of alkali hydroxide and alkali carbonates.

Tests for Identity : A saturated aqueous solution is acid to litmus and when fused with caustic alkali, ammonia is given off.

Tests for Purity : M.P. 175-177°. Limit test for readily carbonisable substances. Limit test for neutral or basic substances. Test for the absence of phenyl barbituric acid. On incineration, it leaves not more than .05 per cent of residue.

Dose : .03 to .12 grams, ½ to 2 grains.

Reference Number 161

Phenobarbitonum Solubile B.P.

Soluble Phenobarbital (synonym) is the monosodium derivative of phenyl ethyl barbituric acid, and may be obtained by the interaction of phenobarbitone and sodium hydroxide. It contains not less than 95 per cent $C_{12}H_{11}O_3N_2Na$.

Characters : A white hygroscopic powder, odourless, taste bitter. Very soluble in water, soluble in alcohol, indoluble in ether and in chloroform.

Tests for Identity : An aqueous solution is alkaline to litmus and yields phenobarbitone on addition of dilute hydrochloric acid. The residue left after incineration gives reactions of sodium.

Tests for Purity : Tests for presence of barbitone. Limit tests for free phenobarbitone, and neutral and basic substances.

An assay is described for presence of $C_{12}H_{11}O_3N_2Na$.

Soluble phenobarbital should be kept in a well-closed container.

Dose : .03 to .12 grams, ½ to 2 grains.

Reference Number 162

Phenobarbitonum B.P.C.

Synonym - Phenobarbital.

Soluble in water 1-1000, in alcohol 1-15, ether and chloroform.

Standards - the same as those in B.P.

Action and Uses :

Phenobarbitone has properties similar to those of barbitone, but its action is intensified, owing to the replacement of an ethyl group by a phenyl group. It is a useful hypnotic and sedative in nervous insomnia and is employed to relieve migraine. The toxic action of procaine

Reference Number 162 (Continued)

and other local anaesthetics may be reduced by the previous administration of a dose of phenobarbitone. Phenobarbitone is used more especially in the treatment of epilepsy, but care should be exercised, as tolerance is apt to be established, necessitating increase in dosage. Serious relapse has often been observed in epileptic patients following the withdrawal of this drug. It should be noted that there is only a small margin between the maximum therapeutic dose and minimum lethal dose.

Phenobarbitone is contra-indicated in arteriorsclerosis, pulmonary and cardiac disease and in nephritis. In some individuals, a skin rash may be produced by phenobarbitone, necessitating withdrawal of the drug. Poisoning for phenobarbitone should be treated as outlined for Barbitonum.

Preparations : Elixir Phenobarbitoni B.P.C.
Tabellae Phenobarbitoni et Theobrominae B.P.C.

Reference Number 165

Phenobarbitone Solubile B.P.C.

Synonyms - Soluble Phenobarbital ; Phenobarbitone-Sodium.

Standards and characteristics are those given in B.P.

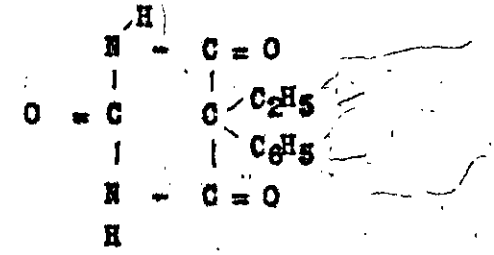
Action and Uses :

Phenobarbitone-Sodium has properties similar to those of phenobarbitone, but differs in being freely soluble in water. Solutions for injection may be sterilized by Tyndallisation or by filtration. It is incompatible with ammonium bromide and other ammonium salts. When the two are dispensed together, a white crystalline precipitate of phenobarbitone is deposited, and the supernatant liquid is alkaline and smells of ammonia.

Reference Number 164

Phenobarbital N.N.R. 110

Phenylethylmalonylurea - Phenobarbitone - Phenylethylbarbituric acid.



Actions and Uses :

The introduction of the phenyl group increases the hypnotic and sedative action of phenobarbital over that of barbital. The toxicity seems to be increased in about the same ratio. The sleep may be preceded by a period of excitement. Moderately large therapeutic doses sometimes cause severe circulatory depression. The formation of a habit has been reported.

Phenobarbital has a sedative action on respiration, lessening the frequency of breathing. It kills by respiratory paralysis. It is eliminated by the kidneys, a certain portion being decomposed in the organism. No gastric disturbances have been observed.

Phenobarbital is used as a useful hypnotic in nervous insomnia and conditions of excitement of the nervous system, its chief use in this field being as a sedative and antispasmodic in the treatment of epilepsy, in which it lessens the frequency and severity of seizures. Its use as a sedative has also been proposed in chorea, neurasthenia, cardiac and gastric neurosis, climacteric disorders, depmenorrhea, exophthalmic goiter, and preoperative and postoperative cases, but it should be remembered that the drug has no curative action in such conditions.

Dosage : From ¼ to 5 grains, increased if necessary to 10 grains. The average dose is 1½ grain. A maximum dose of 10 grains should not be exceeded.

Characteristics, tests for identity and purity are given by the British Pharmacopoeia, where it is listed under the title of Phenobarbitonum.

Luminal, a brand of phenobarbital manufactured by Winthrop Chemical Co.

Reference Number 165

Phenobarbital Sodium N.N.R.

Soluble Phenobarbital, Soluble Phenobarbitone

"When dried at 140°C for six hours, contains not less than 90.4 per cent and not more than 91.4 per cent of Phenobarbital U.S.P."

Actions and Uses : The same as those of phenobarbital.

Dosage : For hypodermic injection phenobarbital sodium is used in the form of a 20 per cent solution, prepared by dissolving the salt in boiled and cooled distilled water ; 30 minims of the solution contain six grains of phenobarbital sodium. The dose of phenobarbital sodium is 10 per cent greater than that of phenobarbital.

Phenobarbital sodium may be given hypodermically in doses of 1½ to 5 grains.

Caution : Aqueous solutions of phenobarbital sodium are not stable,, but decompose on standing ; on boiling a precipitation occurs.

Purity tests include those for chlorides, sulphates, salts of heavy metals, readily carbonizable substances and uncombined phenylethylbarbituric acid.

Luminal sodium is a brand manufactured by Winthrop Chemical Co.

Reference Number 166

Phenobarbital as Pre-Anaesthetic Medication, - by Bartlett and Bartlett, Jr. Surg. Gyn and Ob,1930, 51 : 217.

Administer .8 to 3.0 grams three hours before operation, chiefly under N_2O or ethylene anaesthesia. Patient has no sense of suffocation or induction of general anaesthesia. Smaller quantity and lower concentration of gas necessary. Postoperative nausea and vomiting rare ; patient usually easily able to take fluids by mouth ; patient sleeps for hours, usually has little recollection of events immediately pre- or post operative. Only toxic results were occasional skin rashes.

Reference Number 167

Journal of American Pharmaceutical Association, Jan. 1934. Page 18.

A Reaction for Phenobarbital, - by George Al. Beal and C. R. Smalkowski.

Mohler's reaction may be used to distinguish phenobarbital from barbital. The progress of the reaction differs slightly from that with benzoic acid. In the latter case the reddish brown ring diffuses to form a solution of the same color, and on heating changes to a yellowish green solution. With phenobarbital, on the other hand, the reddish brown

Reference Number 167 (Continued)

ring diffuses to form an orange-colored mixture which is turbid. Upon heating the color becomes more intense, shading into orange red, and eventually becomes greenish yellow, the precipitate persisting.

Reference Number 168

Journal American Medical Association, Feb. 1, 1936. Page 419.
Indiana State Medical Association Journal, 28 : page 662, Dec. 1, 1935.

Improved Hypnotic and Sedative Due to Synergistic Action of Calcium with Phenobarbital, - by Robinson.

The author reports that an earlier, more uniform action was obtained from a combination of phenobarbital and calcium phosphate than from phenobarbital and acetylsalicylic acid.

Reference Number 169

Chemical Abstracts, 25, 5 (1931) Page 4516.

Use of Phenobarbital in Surgery, - by Graham in Can. Med. Assoc. J. 24 : 671-5 (1931)

"There is evidence that it decreases the amount of morphine necessary post-operatively, and the amount of intestinal derangement. Less ether is required for anesthesia."

Reference Number 170

Chemical Abstracts, 25, 2 (1931) Page 2768.

Use of Phenobarbital in Infant Feeding, - by Barbour, Arch. Pediatrics, 48 : 55-60 (1931).

"Phenobarbital is safe and effective for the control of infant vomiting and more satisfactory than atropine."

Reference Number 171

Chemical Abstracts, 6 (1912) Page 1809.

Geisaler, in Münch. Med. Wochschr. 59 : 922-4, announces luminal to be a new strongly acting hypnotic which may be given intravenously.

Reference Number 172

Chemical Abstracts, 7 (1913) Page 3789.

Veronal Rashes : With a Note on Luminal is the title of an article in Brit. Med. J. 1913, II : 512, by Bernet.

Reference Number 173

Chemical Abstracts, 20 (1926) Page 1864.

Frensdorf reports in Münch. Med. Wochschr. that Luminal is excreted by the mammary glands and may produce detrimental effects on nursing infants.

Reference Number 174

Chemical Abstracts, 16 (1922) Page 2366.

In the case of luminal poisoning reported in Pharm. Weekblad 59 : 521-2 (1922) no phenobarbital was found in the urine. Veronal can be found in the urine in similar cases. The inference is that luminal, in contrast to veronal, is completely destroyed in the body.

Reference Number 175

Chemical Abstracts, 20 (1926) Page 1851.

Gruber and Baskett in J. Lab. Clin. Med. 10 : 630-41 (1925) report that phenobarbital injected intravenously causes slowing of the heart rate, decrease in force, decrease in volume of spleen and kidney, and has no direct action on the secretion of the urine.

Reference Number 176

Pharmacology and Therapeutics Cushny

Page 570.

Phenobarbital

The action is essentially the same as that of barbital, but for a pure hypnotic action it has not proved as efficient as other members of the barbituric acid group. Its greatest value is in epilepsy, tremors or convulsions due to strychnine or other poisons.

Reference Number 177

Chemical Abstracts, 50, 2 (1956) Page 475

Phenobarbiturate of Papaverine (Pavemal), - by Mossini and Recordati, Boll. Chim. farm. 74 : 658-9 (1955)

A compound, one molecule of each, has been prepared from alcoholic solutions of phenobarbital and papaverine. M.P. 145-6°.

Reference Number 178

Quarterly Journal Pharmacy and Pharmacology, 8, 4 (1935) Page 712.

Arquet (Bull. Sci. Pharm. 42 : 200, 1955) found that the solubility of phenobarbital in ether increased considerably when there was a trace (1-2%) of alcohol present.

Reference Number 179

Quarterly Journal Pharmacy and Pharmacology, 7 (1934) Page 505.

Luminal and Thyroxine to Arrest Lactation, - by Fauvet, through Brit. Med. J. Epit. 2 : 86 (1935).

In cases where stoppage of lactation is desirable, an administration of thyroxine and luminal has been used to bring it about. "Both drugs are effective in antagonising the lactagogue action of the posterior pituitary hormone."

Reference Number 180

Chemical Abstracts, 8 (1914) Page 1156

In doses of .5 grams per day, luminal produced disturbances of the skin and nervous system, these symptoms being due to toxic action which varied in intensity in different individuals.

Reference Number 181

Chemical Abstracts, 28, 5 (1934) Page 6849

Phenobarbital Poisoning, - by Haubrick, New Eng. J. Med. 211 : 264-7 (1934)

A report of a case, with discussion of symptoms and therapy.

Reference Number 182

Journal American Medical Association, Aug. 24, 1935. Page 585

Tetanus, Tetanus Antitoxin or Phenobarbital Deafness, - by Emil Amberg, M.D. and Robert Hewitt, M.D.

"Our patient suffers from almost total deafness in consequence of either tetanus, tetanus antitoxin or possibly phenobarbital."

Reference Number 183

Quarterly Journal Pharmacy, 2 (1929) Page 158

Phenobarbital to Control Pain, - by Gunther and Behneman, California and Western Med. 1928, 29 : 100.

The authors have treated certain cases of severe pain such as tabetic crises and herpes zoster, also withdrawal symptoms of morphine addiction, by hypodermic injections of phenobarbital sodium. Relief of pain occurs in 20-30 minutes.

Reference Number 184

American Journal Pharmacy, June 1934. Page 251

Decomposition of Solutions of Soluble Phenobarbitone

In aqueous solution, sodium phenyl-ethyl barbituric acid slowly hydrolyses with formation of phenyl-ethyl-acetyl-carbamide and carbon dioxide, the latter being determined by barium chloride.

Reference Number 185

Year Book American Pharmaceutical Association, 1933. Page 204

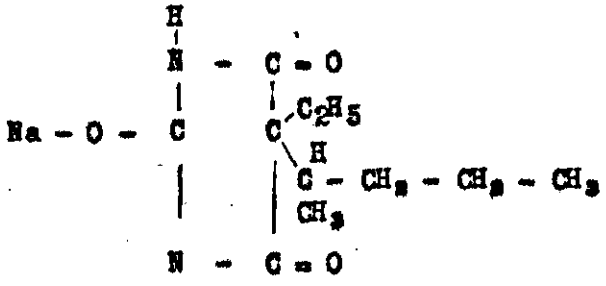
Decomposition of Sodium Phenylethylbarbiturate in Aqueous Solution, - by L. Nielson, Dansk Tido Farm. 7 : 137 (1933).

The author deals with the decomposition of phenobarbital in aqueous solution as he has studied the end products of the decomposition and can give the amount over a period of thirty days.

Reference Number 186

Pentobarbital Sodium N.N.R. p. 106

Sodium ethyl (1 methyl-butyl) barbiturate - sodium ethyl (methyl-propyl carbinyl) barbiturate.



The monosodium salt of ethyl (1 methyl-butyl) barbituric acid, Pentobarbital-sodium, differs from soluble barbital in that one of the ethyl groups of the latter is replaced in the former by a 1-methyl-butyl group.

Actions and Uses :

The actions and uses of pentobarbital sodium are essentially similar to those of barbital, but it is effective in smaller doses. The action is of relatively brief duration which may constitute an advantage, especially when relatively large doses are administered. It is used as a sedative, particularly prior to local, general or special anaesthesia. It can be used safely for such purposes only by those who have had adequate experience and who are familiar with the literature concerning its use. It may be administered by mouth or by rectum ; it may be administered intravenously only in conditions in which oral administration is not feasible either because the patient is unconscious, as in cerebral hemorrhage, eclampsia or status epilepticus, or because he resists as in delirium, or because very prompt action is imperative, as in convulsions from local anaesthetics ; but great caution is necessary when this product is given by vein.

Dosage : Orally, as hypnotic, 1½ grains ; as preanaesthetic sedative 5 grains. Rectally, for analgesia, for infants up to 1 year ½ grain, up to 5 years 1 grain, for adults 5 to 6 grains dissolved in a few cubic centimeters of water.

Caution : Aqueous solutions of pentobarbital-sodium are not stable, but decompose on standing, on boiling a precipitation occurs with the evolution of ammonia.

Pentobarbital-sodium occurs as a white crystalline, odorless powder, with a slightly bitter taste ; very soluble in water, freely soluble in alcohol, practically insoluble in ether. An aqueous solution of pentobarbital-sodium is alkaline to litmus.

Identity tests are given. Tests for purity include sulphates, chlorides, salts of heavy metals, readily carbonizable substances, and uncombined ethyl (1-methyl-butyl) barbituric acid.

Manufactured by Eli Lilly Co.

Reference Number 187

Pharmacology and Therapeutics — Cushny

Page 371

Pentobarbital

Its action is essentially the same as that of barbital, but it is more effective in smaller doses and the depression and sleep come on more rapidly and are of much shorter duration. The destruction of pentobarbital probably takes place mainly in the liver. It is practically entirely destroyed in the body, only small amounts being found in the urine.

Reference Number 188

Quarterly Journal of Pharmacy and Pharmacology 4 (1931) Page 292

Nembutal "844"

This reference is a general one dealing with it as a new proprietary and Nembutal is treated in a manner similar to that given in N.N.R.

Reference Number 189

Manufacturing Chemist, May 1931 — Page 145

Nembutal "844"

The Brit. Med. Journal, 1931, reports as follows :

"Intensive research has been carried on to find one suitable for premedication, in general, spinal or local anaesthesia.

Nembutal is short acting, with recovery in four hours and is therefore particularly suitable for pre-anaesthesia.

It hydrolyses in aqueous solution, therefore should not be boiled to sterilize."

Reference Number 190

Manufacturing Chemist, Sept. 1931. — Page 257

Pentobarbital

Recommended as a basal hypnotic in general anaesthesia, it is put up in capsules for oral and rectal administration and in ampoules for intravenous injection.

Intravenously loss of consciousness occurs within one or two minutes with a dose of 1½ to 5 grains. The maximum dose of 7½ grains should never be exceeded.

Reference Number 190 (Continued)

It would appear that in the case of this hypnotic the toxicity is a matter of some importance.

Reference Number 191

Journal American Medical Association, Feb. 2, 1935. Page 417

Analgesia in Obstetrics

"Pentobarbital sodium has become popular recently for the production of analgesia in labour. The patient may sleep or only doze between pains, but the uterine contractions continue satisfactorily. Although she may not doze continually during the analgesia, often she does not remember what has happened when labour has been completed ; almost complete amnesia may be produced.

Reference Number 192

Chemical Abstracts, 27, 1 (1933) Page 1050

The Use of Intravenous Nembutal during Labor, - by Abbot, Can. Med. Assoc. Jour. 27 ; 620-3 (1932)

Reference Number 193

Chemical Abstracts, 28, 1 (1934) Page 215

The Influence of Morphine on the Premedication Value of Pentobarbital and Amytal, - by Barlow and Duncan, J. Pharmacol. 49 ; 60-66 (1933)

The preanaesthetic values of pentobarbital and amytal differ only quantitatively, the first being approximately twice as active and has a wider margin of safety. Morphine and pentobarbital synergize. Morphine potentiates amytal only within a narrow range of doses.

Reference Number 194

The 1936 Year Book of General Therapeutics Fantus

Page 285

Nembutal Sodium in Propylaxis of Radiation Sickness

Nembutal was given an hour previous to each high voltage X-ray treatment. Many of the patients were freed from vomiting and nausea. Some were enabled to complete the series of treatments otherwise impossible on account of severe radiation sickness.

Reference Number 195

Quarterly Journal Pharmacy and Pharmacology 6 (1933) Page 157

E. Swanson, in a report in J. Pharmac. 46 : 387 (1932), classifies Na amytal and Na pentobarbital as having the same value as basal anaesthetics, this being greater than Na phenobarbital and Na barbital.

Reference Number 196

Chemical Abstracts, 25, 5 (1931) Page 5932

The Action of Pentobarbital Sodium. - by Swanson and Shoule, J. Lab. Clin. Med. 16 : 1056-65 (1931)

Pentobarbital sodium appears to be an efficient hypnotic and anaesthetic. It lowers the blood pressure, diminishes respiration and body temperature when administered to dogs intravenously. Although the toxicity is twice that of Na amytal, its potency is approximately twice as great.

Reference Number 197

Chemical Abstracts, 28, 1 (1934) Page 825

Oxygen Consumption, Respiration, Circulation and Carbohydrate Distribution during Pentobarbital Anaesthesia in Dogs. - by Hall and Sahyun, Arch. intern. Pharmacodynamie, 46 : 160-8 (1933)

Pentobarbital anaesthesia in dogs does not affect the body temperature, oxygen consumption, the glucose or lactate concentration of the blood or glycogen or lactate concentration of the muscle. The respiratory rate and min. vol. increase ; the arterial pressure and liver glycogen decrease. The total carbohydrate content of the body decreases.

Reference Number 198

Chemical Abstracts, 29, 2 (1935) Page 4825

Effect of Nembutal upon Serum Cholesterol of Dogs. - by Bidwell, Shillitto and Turner, Proc. Soc. Exptl. Biol. Med. 32 : 1255-6 (1935)

In seven dogs the concentration of cholesterol in the serum was not affected by deep narcosis with nembutal.

Reference Number 199

Journal American Pharmaceutical Association, Nov. 1935. Page 961

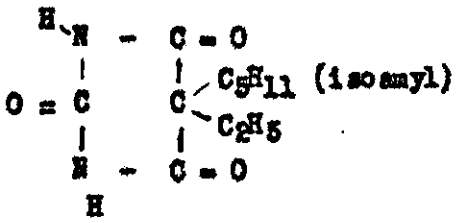
The Detoxification of Strychnine by Pentobarbital Sodium

"In single, equivalent doses pentobarbital sodium is less effective in strychnine poisoning than sodium amytal."

Reference Number 200

Amytal N.N.R. p. 98

Isoamylethylbarbituric acid - Isoamylethylmalonylurea



Amytal differs from barbital in that one of the ethyl groups is replaced by an iso-amyl group in the former.

Action and Uses :

The action and uses of amytal resemble those of Barbital. It is proposed as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anaesthesia.

Dosage : Given orally.

As a sedative : $\frac{1}{3}$ to $\frac{2}{4}$ grains, two or three times daily.

As a hypnotic : $1\frac{1}{2}$ to 5 grains, one half to one hour before sleep is desired.

For use before local or general anaesthesia, the dosage ranges between 5 and 10 grains, being determined by a large number of factors (age, etc.)

As an antispasmodic in tetanus, 6 to 12 grains may be required to control convulsions. Amytal should not be administered to those patients in whom barbital derivatives produce restlessness and excitement.

Amytal occurs as a white crystalline, odorless powder, with a slightly bitter taste ; completely soluble in alcohol and ether ; very slightly soluble in cold water and insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus. It melts at 155-155°C.

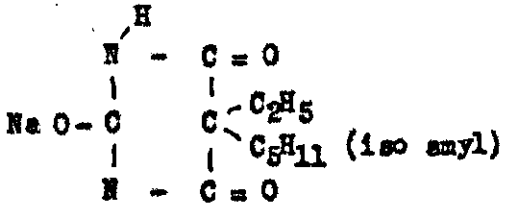
Manufactured by the Eli Lilly Co.

Incineration test, as well as tests for readily carbonisable substances, chlorides and sulphates and salts of heavy metals, are given.

Reference Number 201

Sodium Amytal N.N.R.

Sodium Isoamylethylbarbiturate



Sodium amytal is the sodium salt of isoamylethylbarbituric acid. It differs from soluble barbital in that one of the ethyl groups of the latter is replaced in the former by an isoamyl group.

Actions and Uses :

The actions and uses of sodium amytal resemble those of barbital. The product is proposed as a sedative and hypnotic in the control of insomnia and as a preliminary to surgical anaesthesia.

Dosage : As a potent sedative or hypnotic 5 grains, repeated if necessary at intervals of six hours. For use before local or general anaesthesia, the dosage ranges between 3 to 9 grains, being determined by a large number of factors (age, etc.) As an antispasmodic in tetanus, from 6 to 12 grains may be required to control convulsions. It can be used safely for such purposes only by those who have had much experience and are familiar with the literature concerning such use. In some patients, barbital derivatives produce restlessness and excitement and to these patients sodium amytal should not be administered. It may be administered by mouth, or, if necessary, the same dose may be given rectally, in the form of capsules inserted as suppositories or as powder placed in a little water ; it may be administered intravenously only in conditions in which oral administration is not feasible either because the patient is unconscious, as in cerebral hemorrhage, eclampsia, or status epilepticus, or because he resists, as in delirium, or because a very prompt action is imperative, as in convulsions from local anaesthetics ; but great caution is necessary when this product is given by vein.

Sodium amytal occurs as a white, friable hygroscopic odorless granular powder with a slightly bitter taste ; it is very soluble in water, freely soluble in alcohol, about 1 : 1 ; practically insoluble in ether.

Purity tests include those for chlorides, sulfates, heavy metals, readily carbonizable substances, and uncombined isoamylethylbarbituric acid.

Manufactured by Eli Lilly and Co.

Reference Number 202

Year Book, American Pharmaceutical Association 1930 Page 111

Therapeutic Use of Amytal Sodium, - by L. R. Gorvan, Minn. Med. 15 (1930) page 874, through Squibb Abstr. Bull. 5 A : 1257 (1930).

The author evaluates comparatively the effects of luminal, veronal, bromides and sodium amytal. He goes on further to emphasize the properties of sodium amytal when used for surgical work and intravenously in the control of convulsions. In his opinion it is excellent in controlling convulsions, not satisfactory as a day-time sedative and quite satisfactory as a soporific.

Reference Number 205

Journal of Pharmacology and Experimental Therapeutics, 27, 5 : 189 (1926)

Amytal, Its Use as an Intravenous Anesthetic, - by Page and Coryllos.

Amytal is insoluble, so three methods are described by which it is prepared for intravenous injection.

The first is the preparation of its sodium salt and making an aqueous solution. Care must be taken to avoid excess alkali. The final preparation is stable for 4-5 months.

Secondly, ethylene glycol is used as the solvent for the sodium salt. This solvent has some sterilizing properties and has apparently little effect when injected intravenously.

The third method is that of using gum arabic as a protective colloid for the sodium amytal. The solutions were sterilized by heating on a water bath for the animal injections.

Table I compiles the results of comparative toxicities for increasing dosages. The condition of all animals after anaesthesia was reported as remarkable.

Table II shows that the fatal dose is much higher when the anaesthetic is given in small doses over a considerable interval of time.

Tables II, III and V seem to indicate that there is an optimum dosage at which the blood pressure fall is least.

In general, the respiration is decreased in rate and slightly in amplitude with increasing dosage; just before death the rate increases.

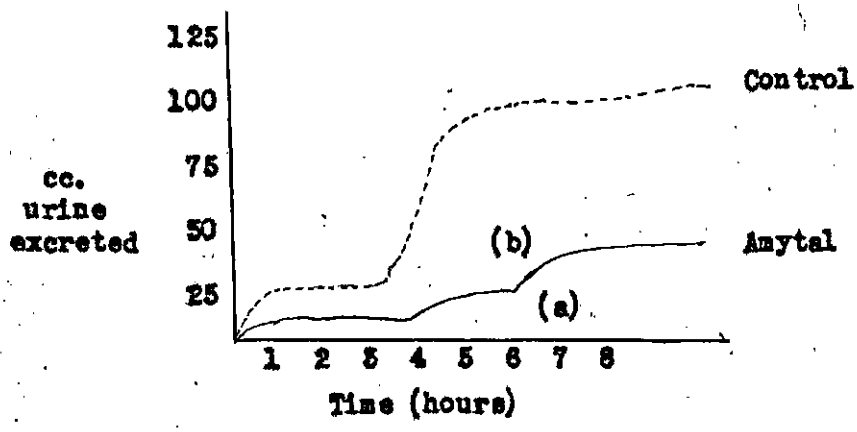
In dogs a dosage of 45 to 60 mgm. has been found most suitable for ordinary experimental procedures.

Reference Number 204

Journal Pharmacology and Experimental Therapeutics, 41 : 485 (1931)

Effect of Amytal on the Excretion of Water, - by Marx.

The author determined the diuretic effect of water administered to dogs by the stomach tube. He gave the same dogs similar amounts of water under amytal anaesthesia, and found a marked decrease in excretion of urine which was roughly proportional to the dosage and occurred irrespective of whether the animal was excited or asleep.



(a) 500 cc. water ; 30 mgm. per K amytal
(b) 500 cc. water ; 15 mgm. per K amytal

He suggests three possible explanations : (1) Impairment of kidney function. (2) The drug may have an effect on cerebral centres regulating water metabolism. This is in line with Molitor and Pick (Arch. f. Exper. Path. u. Pharm. 1923, 107, 180, 185); 1928, 112, 113) who consider hypnotic drugs affect brain centres exclusively. (3) It may effect permeability of endothelium of capillaries, the water going to the tissues instead of to the kidneys. (Magnus, Arch. f. Exper. Path. u. Pharm. 1899, 92, 250).

Reference Number 205

Journal Pharmacology and Experimental Therapeutics, 1930, 39 : 123

Suitability of Amytal as Anesthetic for Laboratory Animals, - by Garry.

Experiments were carried out to test the effect of amytal anaesthesia in cats and rabbits on simple reactions of physiological importance.

Findings : (1) Amytal diminishes or obliterates the inhibitory effect on the heart of stimulation of the peripheral ends of the cut vagus in the cat. (2) In the rabbit the effect of amytal in vagus

Reference Number 205 (Continued)

stimulation is more transient. (3) Amytal lowers blood pressure and has a toxic effect on the heart. (4) Amytal does not have a peripheral paralyzing action on the parasympathetic nerves in general. (5) Phenobarbital does not produce disturbances of vagus action on the heart in anaesthetic dosages.

Reference Number 206

Surg. Gyn. and Ob. 1950, 51 : 855.

Sodium Amytal as Preoperative Medication for Nitrous Oxide Anesthesia, - by Ramsey and Little.

The authors used sodium amytal in doses not exceeding 1 gm. as preoperative medication before 26 subtotal thyroidectomies under N_2O. It renders the patient free from apprehension of the anaesthetic and operation, adequate anaesthesia is obtained with less N_2O and lower concentration, enabling more oxygen to be given, largely obviating cyanosis. Post operatively, the patients were free from nausea, vomiting and laryngeal mucus.

Other clinical studies along similar lines are :

Sodium Amytal as Preanesthetic Medication, - by Mason and Baker, Surg. Gyn. and Ob. 1950, 50 : 828.

Sodium Amytal as Preanesthetic Medication, - by Lundy, Minn. Med. 1950, 15 : 225.

Nembutal for Preanesthetic Medication, - by Lundy, Anesth. and Analg. 1950, 9 : 310.

Reference Number 207

Year Book American Pharmaceutical Association 1951-52. Page 379.

Pharmacological Properties of Amytal, - by Garry, Brit. Med. J. 1 (1953) 421, through Quat. J. Pharm. and Pharmacol. 5 (1952) 726.

In a study of the literature pertaining to amytal for the past ten years, the author has summarized its properties as to dosage and as a basal anaesthetic, effect on the heart, fall in blood pressure due to it, its effect on the nervous system and on the motility of the intestine.

Reference Number 208

Year Book American Pharmaceutical Association 1930. Page 111.

Effect of Amytal upon Uterus and Its Use in Obstetrics, - by Drabkin, Ravdin, Hirst, and Lapham, in Am. J. Med. Sci. 178 (1929), 579 ; through Chem. Abstr. 24 (1930) 428.

Amytal does not affect the rhythmic contractions of the guinea pig uterus, in vivo or in vitro. The response of the uterus to the oxytoxic principle of the pituitary was not disturbed after amytal anaesthesia.

Reference Number 209

Chemical Abstracts, 20, 14 (1936) Page 4929

Behavior of the Blood Sugar in Pigeons under the Influence of Poisons Acting Centrally, - by Rudolf Allers and Josef Brill, Biochem. Z. 285 ; 6-10 (1936).

Amytal causes a rise in glucemia only on repeated administration.

Reference Number 210

Chemical Abstracts, 30, 11 (1936) Page 5879

Effect of Amytal upon Pilocarpine-induced Submaxillary and gastric Secretion, - by Mary F. Montgomery, Proc. Soc. Exptl. Biol. Med., 32 ; 1287-90 (1935)

In the dog, the oral or intravenous administration of Na amytal caused a depression and a shortening of the duration of the secretory response to the intravenous injection of pilocarpine, the effect lasting 6-13 days. This indicates that Na amytal or its decomposition products may remain in the tissues for a considerable length of time.

Reference Number 211

Journal American Medical Association, Aug. 24, 1935. Page 585

Paroxysmal Hyperhidrosis in a Diabetic Patient with Remission under Amytal Therapy, - by Hull, M.D. and Cameron, M.D.

The authors describe a patient who was admitted to the hospital with recurring sweats appearing every 90 to 120 minutes. These were relieved and now greatly diminished by daily dosage (6 grains) of amytal.

Reference Number 212

Chemical Abstracts, 26, 1 (1932) Page 188

The Behavior of Liver Glycogen in Experimental Animals ; The Effect of Ether and Amytal, - by Evans, Tsai and Young. J. Physiol. 75 ; 68-80 (1931)

"Amytal steadily reduces liver glycogen."

Reference Number 213

Chemical Abstracts, 24, 5 (1930) Page 5861

Dilation of the Heart by Amytal, - by Olmstead and Ogden, Proc, Soc. Exptl. Biol. Med. 27 ; 725-8 (1930)

In a heart and lung preparation amytal increases the diastolic volume and decreases useful outflow.

Reference Number 214

The 1936 Year Book of General Therapeutics Fantus

Sodium Amytal in Sleep Treatment of Psychoses

The results of Samuel Broder and M. W. Thorner are considered. Temperature, pulse, respiration and blood pressure readings are taken for a few days prior to treatment with hypnotics to determine the average variation. Sodium amytal is given by mouth in capsule form or by putting powder in orange juice. The dose is regulated by the patient's response.

Reference Number 215

Am. Jour. Surg. 1930, Jan. McCallum and Zerfas

Sodium Amytal as Premedication for Local Anesthesia

The authors gave .5 to .5 gm. sodium amytal with 10-15 mgm. morphine 30 to 60 minutes prior to procaine infiltration. The amytal, like other barbituric acid derivatives, tends to protect the patient from procaine toxidosis.

It gave good results in about 50% of the cases. Patients required greater nursing care postoperatively, usually slept several hours after the operation, and were apt to be restless on awakening.

Reference Number 216

American Journal of Pharmacy, July 1933 Page 369

Sodium Amytal in Strychnine Poisoning. - Stalberg and Davidson, Jour. Am. Med. Assoc., July 8, 1933, page 104.

The modern treatment of strychnine poisoning consists chiefly and pre-eminently in the intravenous administration of sodium amytal, either during the premonitory stage or when the convulsion has begun. The dose is 7½ grains, smaller or larger doses being used and repeated with each convulsion.

To date, eleven cases have been reported of human strychnine poisoning treated successfully with sodium amytal.

Reference Number 217

American Journal of Pharmacy, March 1933. Page 146

Antidote for Strychnine Poisoning

Sodium amytal and sodium pentobarbital are both used effectively in strychnine poisoning.

Reference Number 218

Chemical Abstracts, 28, 3 (1934) Page 6856

A Case of Prolonged Use of a Barbiturate, - by Hoge, Am. Med. 40 : 255-8 (1934)

A patient who had 3-4 amytal tablets daily for a period of 7 years showed a few subjective nervous symptoms, a moderate tachycardia and a slight anaemia.

Reference Number 219

Allobarbitonum B.P. Codex

Synonyms - Diallylbarbituric acid ; Diallylmalonylurea

Allobarbitone is 5 ; 5-diallylbarbituric acid and may be prepared by the condensation of the ethyl ester of diallylmalonic acid with urea. A white crystalline powder, odorless, and has a slightly bitter taste. The saturated aqueous solution is acid to litmus. When fused with caustic alkali it gives off ammonia. The saturated solution im water decolorizes bromine water and potassium permanganate when either reagent is added drop by drop.

Slightly soluble in water, soluble in alcohol and ether, readily soluble in solutions of alkali hydroxides and carbonates. M.P. 171-172°. Ash not more than .1 per cent.

Action and Uses :

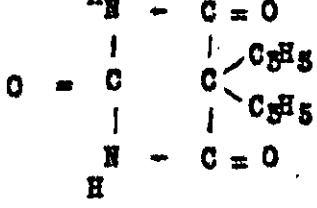
Allobarbitone is a reasonably safe and reliable hypnotic. Its action is similar to that of barbitone, but it is more readily absorbed. Skin rash with fever is a common manifestation of idiosyncracy to the drug. It is administered by cachets or tablets or given subcutaneously.

Dose : .05 to .18 gm., ½ to 3 grains.

Reference Number 220

Dial Ciba N.N.R.

Synonyms - Diallylbarbituric Acid - Diallylmalonylurea



Dial-ciba differs from barbital in that both the ethyl groups of the latter are replaced by allyl groups.

Actions and Uses :

The actions and uses of dial-ciba are essentially similar to those of barbital, but dial-ciba is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses as a hypnotic. Therapeutic doses act on the higher centres of the brain and exert no injurious action on respiration or circulation. The hypnotic action is induced within from one-half to one hour.

Dosage : As a sedative ½ gr. three or four times daily. As a hypnotic 1½ to 4½ grains one half to one hour before sleep is desired.

Reference Number 220 (Continued)

Dial-ciba occurs as a fine, white, crystalline powder, with a slightly bitter taste ; completely soluble in alcohol and ether, very slightly soluble in cold water, insoluble in paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. M.P. 171-175 °C.

Tests for identity (precipitation with mercuric chloride solution, reduction of $AgNO_3$ and $KMnO_4$) and tests for purity (chlorides, sulphates, salts of heavy metals) are given.

Dial-ciba is manufactured by Soc. Chem. Industry, Switzerland.

Reference Number 221

Chemical Abstracts, 25, 2 (1931) Page 5083

"Dial" as an Anesthetic for Surgical Operations on the Nervous System. - by Fulton, Liddell and Rioch, Proc. Physiol. Soc., J. Physiol. XXIII, 70 (1930)

With this anesthetic ("Dial Ciba") the spinal reflexes remain active even in profound anesthesia. In experimental surgery of the nervous system, the drug has two uses :

(1) It appears to constrict small blood vessels of the brain, so that removal of the cerebellum or cerebral hemispheres can be carried out almost bloodlessly without occlusion of any of the great arteries to the head.

(2) Animals remain quiescent for a period of 12-36 hours and thus give opportunity for satisfactory healing of the incision.

Reference Number 222

Year Book American Pharmaceutical Association 1933 Page 205

Combination of Amidopyrine with Barbiturates. - by Pfeiffer and Ochiai, J. prakt. Chem. 136 : 129 (1933), through Squibb Abstr. Bull. 6, A 282 (1933).

The compound of dial and amidopyrine is a true compound, with each in the ratio 1 : 1.

Reference Number 223

American Journal of Pharmacy, Mar. 1934 Page 111

A Molecular Compound of Pyramidon and Diallylbarbituric Acid

Molecular ratio in all drug combinations such as this investigated are 1 : 1. Pyramidon and veronal are cited as an example as well as diallylbarbituric acid and pyramidon.

Reference Number 224

Chemical Abstracts, 9 (1915) Page 2108

Castaldi in Arch. farm. sper. 19 : 289 (1915) reports the pharmacological action of dial.

It acts by exciting the inhibitory centres of the heart and produces narcosis with smaller doses than those required by the other hypnotic derivatives.

Reference Number 225

Journal American Medical Association, Apr. 5, 1957. Page 1172

Evipal : Evipal Soluble

The Winthrop Chemical Co. has been very active in promoting Evipal Soluble in the United States, but has not presented it to the Council on Pharmacy and Chemistry. The Council, however, took it upon itself to investigate the product and reports it as being unacceptable. Evipan was first prepared in the Elberfeld Chemical Laboratory and introduced as a hypnotic in 1932.

Pharmacology :

Weese (Deutsche Med. Wchnschr. 58 : 1205, 1932) determined the hypnotic, narcotic and fatal doses for the cat and mouse orally, for the mouse by subcutaneous injection and for the cat and dog by intravenous injection. He stated it lacks local irritant action and side actions, as well as after-effects.

Weese (Deutsche Med. Wchnschr. 59 : 47, 1933) explained the brief action of evipan, because it is rapidly destroyed in the liver. He described six stages of narcosis.

Parsons (Lancet 2 : 45, July 1, 1933) found that a fall in blood pressure was brought about. His findings did not agree with those of Weese.

Kennedy (J. Pharm. and Exp. Therap. 50 : 347, 1934) reported the therapeutic index of 4 for mice and stated that guinea pigs are more susceptible. Toxic properties predominated when frogs were used.

Kennedy and Narayana (Quart. J. Exp. Physiol. 24 : 69, 1934) found that fatal doses cause death by paralysis of respiration before the heart stopped.

Wright (Proc. Roy. Soc. Med. 29 : 701, 1936) stated the period of recovery in anaesthesia of dogs was associated with frenzied struggling and excitement, and for this reason he had ceased to use it.

Dallemagne (Anesth. & Analg., Mar-Apr. 1936 : 82) reported that Evipan-Sodium caused serious anaemia in dogs, even when the dose was repeated at intervals of several weeks.

Von Brandis (Arch. f. klin. Chir. 177 : 17, 1933) found that in deep narcosis epinephrine, caffeine etc. injure circulation and respiration in the rabbit. He states that these results cannot be transferred directly to man. Then why can Weese's result be transferred directly to man ?

The Therapeutic Use of Evipan as a Hypnotic :

Evipan induces sleep promptly and there are no ill effects from its use. The hypnotic dose is near the narcotic dose in man.

Narcosis :

Holtermann (Deutsche Med. Wchnschr. 59 : 50, 1933) and (München. med. Wchnschr. 80 : 1547, 1933) claimed it could not be used with entire safety for full anaesthesia.

Reference Number 225 (Continued)

Kobel (Deutsche. med. Wchnschr. 59 : 996, 1933) stated that Evipan is not suitable for long operations. He opposed it in obstetrics because of its interference with uterine contractions.

Dosage :

Evipal soluble is sold in ampules, each containing 1 gm. with an ampule which contains 10 cc. of sterile water. The total dose has been lowered from that first suggested by the manufacturer and now depends on the case and whether morphine is given or not. The injection must be slow.

Antidotes :

Observers have reported frequently that lobeline, caffeine, strychnine, coramine, epinephrine, oxygen with CO_2 and artificial respiration have been used without success.

Advantages :

(1) When the dose is calculated with skill, the anaesthesia is well under control; (2) Vomiting occurs less frequently; (3) Evipan sodium does not irritate the respiratory passages ; (4) It does not appear to injure the healthy vital organs ; (5) The absence of a mask is important in operations about the head.

Disadvantages :

(1) First and most important is the uncertainty of the proper dosage; (2) Uncertainty regarding the relative contra-indications ; (3) Evipal sodium depresses the respiration and circulation ; (4) The fall of blood pressure is greater in patients with arteriosclerosis ; (5) Incomplete relaxation of the abdominal muscles; (5) Necessity of a skilled anaesthetic ist, and (6) Prolonged narcosis even after small doses.

Indications and contra-indications, severe accidents, and deaths are reported and summarized.

Summary and Conclusions :

Evipal soluble was introduced as a general anaesthetic to be injected intravenously before adequate studies had been made of it under a great variety of conditions.

Evipal soluble probably has a narrow field of usefulness in which it may be employed with relative safety, provided it is used with skill and with due regard for its limitations. The contra-indications are numerous, but they have not been determined with sufficient precision to permit the use of the substance with absolute safety in many conditions.

It is believed that the anaesthetic is wholly or partly responsible for 43 deaths listed in this report, though several of them would have occurred shortly with any anaesthetic and in the absence of any.

Reference Number 226

Quarterly Journal of Pharmacy and Pharmacology, 8, 2 : 508 (1935)

In an extract from Lancet, Lond. (1934) 227, 508, the statement is made that evipan sodium has proven safe in intravenous injection as an anaesthetic in pulmonary tuberculosis.

Reference Number 227

Quarterly Journal of Pharmacy and Pharmacology, 8, 2 : 508 (1935)

Pharmacology and Therapeutics of Evipan Sodium, - by Slot and Galley, Brit. Med. J. 2, 201 (1934).

The administration of evipan may be repeated without ill effects. It is advisable to follow the injection with chloroform, gas and oxygen, or ether.

The use of evipan is contra-indicated in cases of liver embarrassment or when there is any depression of the respiratory centre.

Reference Number 228

Quarterly Journal of Pharmacy and Pharmacology, 8, 3 : 590 (1935)

Jarman, in Proc. Roy. Soc. Med. 28 : 341 (1935), claims that evipan has a very large scope in the field of safe and useful anaesthesia, provided it is administered only to patients in prone position, not to old or feeble patients, and if an adequate airway is maintained.

Reference Number 229

Chemical Abstracts, 28, 1 (1934) Page 2410

Evipan, A New General Anesthetic for Dental Surgery, - by Bunyan, Brit. Dental J. 56 : 23-4 (1934)

The drug is contra-indicated in liver and gall bladder disorders. Its use may entail respiratory embarrassment which can be overcome by administration of lobeline or CO_2. The period of recovery varies from one half to one hour.

Reference Number 230

Chemical Abstracts, 28, 2 (1934) Page 5789

Sodium Evipan, Intravenous Anesthesia in Gynecology, - by Albert Sharman, Glasgow Med. J. 5 ; 104-7 (1934)

This article gives a note on 157 cases.

Reference Number 251

Chemical Abstracts, 29, 5 (1935) Page 8128

Evipal Anesthesia for Radium Therapy, - by Twombly and Pack, Radiology 25 ; 295-9 (1935)

The intra-cavitary and interstitial use of radium usually requires some form of anesthesia. Evipal is found to be ideally suited for the purpose when used as the soluble sodium salt. Numerous experiments with animals and clinical results are reported.

Reference Number 252

Chemical Abstracts, 29, 5 (1935) Page 8137

Evipal as an Adjunct to Regional Anesthesia, - by H. Lieber, Anesthesia & Analgesia, 14 ; 159-61 (1935)

A review.

Reference Number 255

Chemical Abstracts, 30, 5 (1936) Page 8391

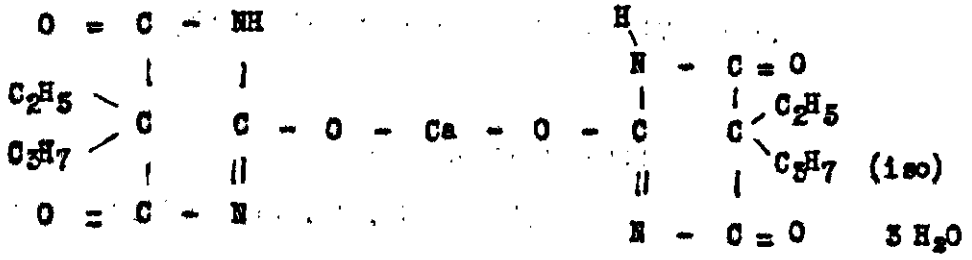
Evipan and Evipan Sodium, - by Bennett, Med. J. Australia 25, II ; 266-8 (1936)

Evipan is recommended as a pre-anesthetic in short anesthesia, especially useful for nervous individuals, and has little or no toxic effect on the heart.

Reference Number 254

Ipral Calcium N.N.R. Page 102

Calcium ethylisopropylbarbiturate



The calcium salt of ethylisopropylmalonylurea.

Action and Uses :

Ipral calcium has the therapeutic properties of barbituric acid. It is soluble in water and absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours. In therapeutic doses it affects the higher cerebral centers almost exclusively, and such doses exert no perceptible effect on the heart or circulation directly.

Ipral calcium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral calcium is not readily developed, but that its action is so persistent that a patient frequently sleeps the night succeeding that when the hypnotic was administered.

Dosage :

2 to 4 grains, followed by a cupful of hot water, tea or milk.

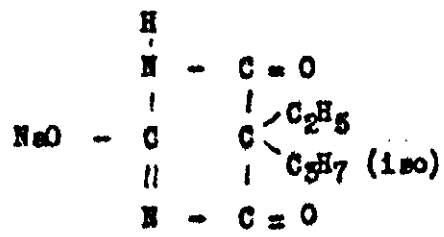
Ipral calcium occurs as a white crystalline, odorless powder, with a slightly bitter taste. It is soluble in about 40 parts of water at 25°C., insoluble in alcohol. An aqueous solution is alkaline to litmus. Tests for identity, limit of carbonate and limit of uncombined ethylisopropylbarbituric acid are given.

Manufactured by E. R. Squibb & Sons.

Reference Number 255

Ipral Sodium N.N.R.

Sodium ethylisopropylbarbiturate



Sodium salt of ethylisopropylmalonylurea

Action and Uses :

Ipral sodium has the therapeutic properties of barbituric acid. It is soluble in water and is absorbed promptly. It is claimed that it is excreted rapidly, but some action commonly persists for twenty-four hours. In therapeutic doses it affects the higher cerebral centres almost exclusively, and such doses exert no perceptible effect on the heart or circulation directly.

Ipral sodium is used as a hypnotic to combat restlessness, irritability and sleeplessness. It is claimed that tolerance to ipral sodium is not developed readily and that its action is persistent.

Dosage :

2 to 4 grains, followed by a cupful of hot water, tea or milk.

Caution : Aqueous solutions of ipral sodium are not stable, but decompose on standing ; on boiling, a precipitation occurs.

Reference Number 256

Chemical Abstracts, 12 (1918) Page 977

Ethylisopropyl barbituric acid (ipral), patented May 12, is said to possess hypnotic and sedative properties. Its preparation is given.

Reference Number 257

Chemical Abstracts, 20 (1926) Page 1852

Jackson and Laurie, in J. Lab. Clin. Med. 11 : 116-22 (1925), claim ipral to be effective, having a great margin of safety, producing sleep approaching closely normal sleep, without lassitude next day. It has no ill effects on heart, lungs or kidneys.

Reference Number 258

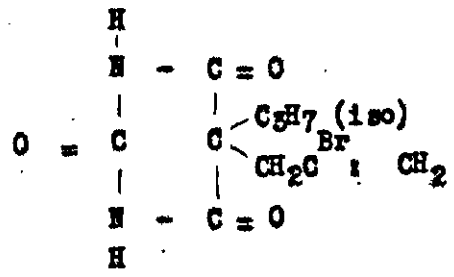
Quarterly Journal of Pharmacy and Pharmacology, 1 (1928) Page 501

Ipral (Pharm. Monatsh. 9 : 9, 1928), a hypnotic, is the calcium salt of ethylisopropyl barbituric acid. It is soluble in water, possesses the therapeutic properties of veronal, and is sold as powder and in tablets.

Reference Number 259

Nostal N.N.R.

Isopropyl bromallyl barbituric acid - 5-iso-propyl-5- -bromallyl barbituric acid



Nostal differs from barbital in that both the ethyl groups are replaced, one by an isopropyl group and the other by a substituted brominated allyl group.

Action and Uses :

The actions and uses of nostal are essentially similar to those of barbital, but nostal is more active than barbital and is used in correspondingly smaller doses. Fractional doses are used as a sedative and larger doses an a hypnotic. Therapeutic doses act on the higher centres of the brain and are claimed not to exert any apparent injurious effect on the heart, circulation or kidneys.

Dosage :

As a sedative : $\frac{3}{4}$ to $\frac{1}{2}$ grains.

As a hypnotic : $1\frac{1}{2}$ to $4\frac{1}{2}$ grains ; for children $\frac{3}{4}$ to $1\frac{1}{2}$ grains according to age. Nostal should be administered preferably with a hot drink.

Nostal occurs as a colorless crystalline odorless powder, with a slightly bitter taste ; it is readily soluble in alcohol, glacial acetic acid and acetone, sparingly soluble in ether, chloroform, benzene and water. A saturated aqueous solution is acid to litmus. Nostal melts at 177-179°C.

Tests are listed for identity. Tests for purity include soluble halides, sulphates and salts of heavy metals.

Manufactured by J. D. Riedel - E. de Haen, Berlin.

Reference Number 240

Chemical Abstracts, 19 (1925) Page 1511

Boedecker and Ludwig, in Klin. Wochschr. 5 : 2055-5 (1924), describe noctal as the most effective narcotic of the barbituric acid series yet prepared. The corresponding chloro derivative is only slightly less effective.

Reference Number 241

Chemical Abstracts, 30, 20 (1936) Page 7222

The Cause of the Delayed Death in the Rat by Nostal and Related Barbiturates, - by Holck and Cannon, J. Pharmacol. 1936, 289-309.

Several of the halogen compounds of nostal and of alurate were studied as to the time of delayed death.

Reference Number 242

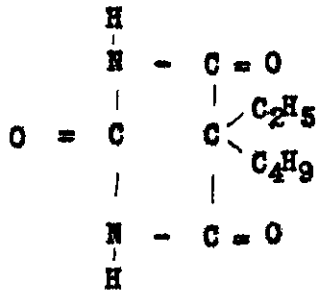
Year Book of the American Pharmaceutical Association 1925 Page 157

Noctal is -brompropenylisopropylbarbituric acid and it has in doses of .1 gm. the same effect as .5 gm. of veronal.

Reference Number 245

Neonal N.N.R.

n-Butylethylbarbituric acid - n-Butylethylmalonyl urea - 2, 4, 6-trioxy-5-n-Butylethylpyrimidin, SONERYL,



Neonal differs from barbital in that one of the ethyl groups is replaced by a normal butyl group.

Actions and Uses :

The actions and uses of neonal are essentially similar to those of barbital, but it is about three times as active as the latter, hence it is used in correspondingly smaller doses. It is claimed that it exerts a sedative action to an exceptional degree, and that it is useful therefore in high nervous tension, neurosis and other conditions in which a sedative is required.

Dosage :

From $\frac{3}{4}$ to 6 grains. For mild insomnia $\frac{3}{4}$ to $1\frac{1}{2}$ grains is stated ordinarily to produce sleep. A dose of 6 grains is the maximum dose which should be required in the course of 24 hours, administered in divided doses.

Neonal occurs in white, crystalline, odorless powder, with a slightly bitter taste. It is readily soluble in alcohol, about 1-5, and ether about 1 in 10 ; very slightly soluble in cold water, insoluble in paraffin hydrocarbons. A saturated aqueous solution is acid to litmus. Melts at 124-127°C.

Tests for readily carbonizable substances, chlorides, sulphates, and salts of heavy metals are listed.

Manufactured by Abbott Laboratories.

Reference Number 244

Chemical Abstracts, 23, 5 (1929) Page 4950

Les Etablissements Poulenc. Freres. Ger. 481, 129, Feb. 5, 1922, reports the preparation of butylethylbarbituric acid (Neonal, soneryl (Fr.) from the condensation of esters of butylethylmalonic or butylethylcyano acetic acid with urea.

Reference Number 245

Journal of the Chemical Society, London. Sept. 1922, Vole 121-22 (i) 900.

Carnot and Tiffeneau in Compt. rend. 1922, 175 : 241-244, report ethylbutylbarbituric acid (neonal) as a new hypnotic, the best of the series containing barbital and amytal.

C. A. 17 (1923), page 3408, says of this same report : "It (neonal) was found in their study of unsymmetrical disubstituted malonylureas. It was found to be three times as hypnotic in its effect as veronal.

Reference Number 246

Chemical Abstracts 18 (1924) Page 1878

Tiffeneau and Layrand report in Bull. Sci. pharmacol. 31, 129-135 (1924), the preparation of butylethylbarbituric acid (neonal) and its patent under the trade name of soneryl. It was prepared by the condensation of butylethylmalonic ester with urea in the presence of sodium ethoxide.

Reference Number 247

Chemical Abstracts, 21, 1 (1927) Page 1522

Volwiler, March 15, patented butylethylbarbituric acid (neonal). It is obtained by the reaction of butylethylmakonic ester with urea. It is hypnotic in action.

Reference Number 248

Chemical Abstracts, 28, 1 (1934) Page 533

Action of Butylethylmalonylurea (Neonal) on the Excitability of the Nervous Centres of Selachians, - by Obre, Compt. rend. soc. biol. 114 : 455-5 (1933) and 114 : 667-9 (1933)

Reference Number 249

Quarterly Journal of Pharmacy and Pharmacology, 6 (1933) Page 741

Sodium Soneryl as a Basal Hypnotic, - by Birdsall, Brit. Med. J. 1933, 1 : 871.

Sodium soneryl was found to be a reliable basal narcotic, producing sleep or drowsiness in 95% of the cases when administered one hour before the induction of general anaesthesia. Respiration is depressed in fewer cases than with nembutal. The author has not administered sodium soneryl in cases of senility, pulmonary disease, renal impairment or arteriosclerosis.

Reference Number 250

Chemical Abstracts, 30, 6 (1936) Page 1872

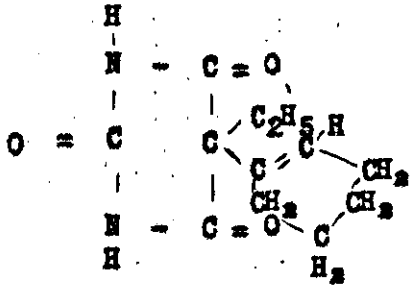
A Quantitative Study of the Phenomena of Synergism, - by Olszycka, Compt. rend. 20 : 796-7 (1935).

By injecting together inactive doses of alcohol and neonal sleep was produced, depending on the proportions used. A mixture of effective doses of the two hypnotics produced sleep of only slightly longer duration than that produced by each separately.

Reference Number 251

Phanodorm N.N.R. p. 109.

Cyclobarbital, Cyclohexenyl ethyl barbituric acid, 2, 4, 6-trioxy-5-cyclo-hexenyl-ethyl-pyrimidin



Phanodorm differs from barbital in that one of the ethyl radicals is replaced by a cyclo-hexenyl group.

Actions and Uses :

The actions and uses of phanodorm resemble those of barbital. It is eliminated more rapidly than barbital, hence the action is not so lasting. This is an advantage when it is used to put one to sleep, and sleep will then continue without its further action. It is used mainly for its sedative action in nervous insomnia, neurasthenia, psychoses and various types of insomnia.

Dosage :

For the mildest type of simple insomnia 1½ grains. In intractable or obstinate insomnia from 5 to 6 grains. The larger dose should not be repeated within less than twelve hours. The average dose is 5 grains.

Phanodorm occurs as a white, crystalline powder, with a bitter taste ; it is readily soluble in alcohol, about 1 in 5, and ether, about 1 in 10, very slightly soluble in benzene and cold water. A saturated aqueous solution is acid to litmus. It melts at 171-174°C.

Tests for identity, for purity (including sulphates, chlorides, salts of heavy metals) are also given.

Manufactured by the Winthrop Chemical Co.

Reference Number 252

Chemical Abstracts, 19 (1925) Page 3566

Bayer and Co. describe the preparation of Phanodrom (Patent).

Reference Number 253

Chemical Abstracts, 23, 1 (1929) Page 483

Schulemann and Mersemberg, Nov. 6, 1929, announced the U. S. patent on Phanodorm. Details are given as to the preparation.

Reference Number 254

Chemical Abstracts, 29, 5 (1935) Page 8159

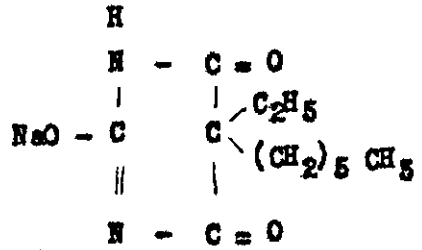
Case of Fatal Phanodorm Poisoning (Suicide), - by K. Huchzermeyer, Med. Klin. 31 : 549-51 (1935)

Poisoning from swallowing 40 tablets of Phanodorm dissolved in cider resulted in death in 20 hours, because of respiratory failure and lung edema. Respiratory stimulants were of no avail.

Reference Number 255

Ortal-Sodium. N.N.R. Page 107

Sodium n-hexylethyl barbiturate - Sodium n-hexylethyl malonyl urea



Ortal-Sodium is the monosodium salt of n-hexylethyl barbituric acid. It differs from soluble barbital in that one of the ethyl groups of the latter is replaced in the former by a n-hexyl group.

Action and Uses :

The actions and uses of ortal sodium are essentially similar to those of barbital, but ortal-sodium is more active than barbital and it is used in correspondingly smaller doses.

Dosage :

From 5 to 6 grains, followed by a glass of water. It is rarely necessary to give more than 15 grains in twenty-four hours. When oral administration is contra indicated, ortal-sodium may be administered rectally.

Manufactured by Parke Davis & Co.

Caution : Aqueous solutions of ortal-sodium are not stable, but decompose on standing ; on boiling a precipitation occurs with the evolution of ammonia.

Ortal-sodium is an odorless, white or slightly yellowish powder, with a bitter taste ; it is very soluble in water, soluble in alcohol, practically insoluble in ether and benzene. An aqueous solution of ortal-sodium has an alkaline reaction to litmus.

Tests for purity (sulphates, chlorides, salts of heavy metals, carbonizable substances, and uncombined acid) are indicated.

Reference Number 256

Journal of the American Chemical Society, 46 : 1707-11 (1924)

Dox, in an attempt to extend the results of Carnot and Tiffeneau, reports the discovery of ethylhexyl barbituric acid (Ortal) and classifies it as more effective than veronal, more rapid in its action, and less toxic, but the effect was shorter. Of two other derivatives, 5 hexyl-1-methyl and 5 hexyl-1-phenyl-barbituric acid prepared at the same time, the first was inert and the second toxic without preliminary hypnotic effect.

Reference Number 257

Chemical Abstracts, 21, 2 (1927) Page 1871

Dox, April 12, patented ethyl-hexyl-barbituric acid (Ortal) which possesses hypnotic properties. It can be prepared by the reaction of sodium ethoxide, ethyl hexylmalonate and urea, treating the product with HCl and recrystallisation.

Reference Number 258

Therapeutic Notes, Parke-Davis, May 1935. Page 165

Dosage of Ortal-Sodium

This drug has a wide dosage range, from $\frac{3}{4}$ grains for waking hours sedation to 9 to 10 grains for amnesia in second stage labour. Ortal-sodium is put out in 5 grain capsules, so that all dosages may be treated conveniently.

Reference Number 259

Chemical Abstracts, 30, 15 (1936) Page 4568

The Effects of Ortal Sodium and Sodium Amytal upon Excised Smooth Muscles, - by Gruber, Scholten, De Note and Wilson, J. Pharmacol. 54 : 541-550 (1936)

Ortal-sodium is far more active than sodium amytal in depressing excised smooth muscles.

Pernocton

Reference Number 260

Chemical Abstracts, 26, 1 (1932) Page 1558

Relation between Narcosis and Diuresis, - by Bonsmann, Arch. exptl. Path. Pharmakol. 161 : 76-87 (1931)

Pernocton, whether in hypnotic or anaesthetic doses, causes transitory inhibition of diuresis. Sodium luminal also inhibits diuresis ; this inhibition is not due to diminished intestinal absorption, for it is not overcome by intravenous injection of Ringer solution.

Reference Number 261

Chemical Abstracts, 50, 14 (1956) Page 4950

Relief of Pain in Obstetrics with Pernocton, - by Jerome Long, J. Tenn. State Med. Assoc. 29 : 155-8 (1936)

The use of pernocton in obstetrics is reviewed. Case reports are presented on 62 patients on whom pernocton was successfully employed.

Reference Number 262

Chemical Abstracts, 25, 5 (1927) Page 5508

This is a reference on Noctal and Pernocton taken from Arch. exptl. Path. Pharmakol. 139.

Noctal and pernocton are converted in the animal organism to non-toxic acetonyl compounds.

The bromalkyl group is not alone important in the preparation of such hypnotics. Barbituric acids having an asymmetric C atom in a branched alkyl substituent (Pernocton) are the most active of all previously known hypnotics with respect to dosage and rapidity of narcosis. Pernocton was investigated fully.

Reference Number 265

Quarterly Journal of Pharmacology. 1 (1928) Page 480

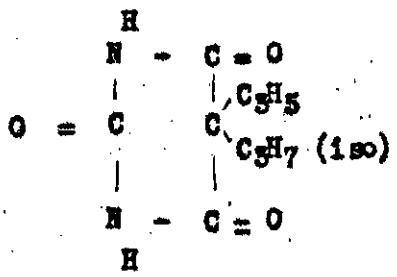
Pernocton for the Production of Painless Labour, - Vogt. Med. Klinik 1928, 24 ; through Brit. Med. J. Epit. 1928, 1 : 56.

The author has used pernocton without ill effect to mother or infant. The preparation did not interfere with uterine contractions. The analgesic effect lasts for two or three hours.

Reference Number 264

Alurate N.N.R. Page 98

Allylisopropylbarbituric acid - Allylisopropyl malonyl urea



It differs from barbital in that both of the ethyl groups are replaced, one by an allyl group and one by an isopropyl group.

Actions and Uses :

The action and uses of alurate are essentially similar to those of barbital, but alurate is more active and is used in correspondingly smaller doses.

Fractional doses are used as a sedative and larger doses as an hypnotic. Therapeutic doses act on the higher centres of the brain and are claimed not to exert any apparent injurious effect on the heart, circulation or kidneys.

Dosage :

For mild cases of insomnia 1 grain may be administered at bedtime. In obstinate cases 2 grains.

Identification :

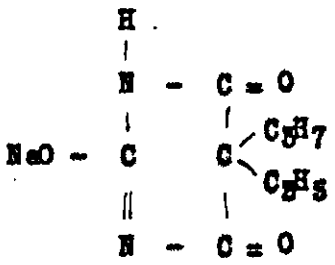
Alurate occurs as a fine, white, odorless, crystalline powder, with a slightly bitter taste. It is completely soluble in alcohol, chloroform and ether ; very slightly soluble in cold water, insoluble in the paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. Alurate melts at 140 to 141.5°C.

Tests are listed to show the presence of the Purine ring and nitrogen. Purity tests for the presence of chlorides, sulfates, and salts of heavy metals.

Reference Number 265

Sodium Alurate N.N.R.

Sodium allylisopropyl barbiturate



The monosodium salt of allyl isopropyl barbituric acid, sodium alurate differs from soluble barbital in that both the ethyl groups of the latter are replaced, one by an allyl group and the other by an isopropyl group.

Action and Uses :

These are the same as those of alurate. The soluble sodium salt is intended for oral or rectal administration, particularly as preanaesthetic medication. Sodium alurate may also be used in other cases in which large individual doses are required.

Dosage :

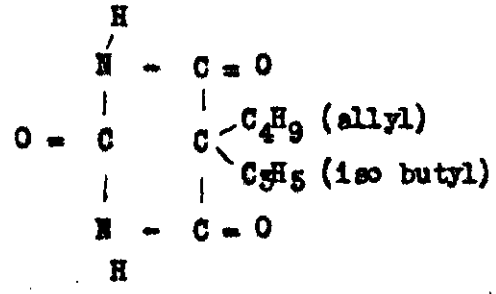
The average preoperative dose is 1 grain for each 15 pounds of body weight. One third of the calculated dose is given ten or twelve hours prior to operation (usually the evening before) ; the remainder two hours before operation. Experience is necessary in the use of these large dosages, as the amount of the drug must be adjusted to the individual patient in order to avoid undesirable reactions.

Sodium alurate is a white, microcrystalline, hydroscopic, odorless powder, with a slightly bitter taste ; it is very soluble in water, very slightly soluble in alcohol, practically insoluble in ether. An aqueous solution of sodium alurate is alkaline to litmus.

Reference Number 266

Sandoptal N.N.R.

Isobutylallyl barbituric acid - Isobutylallylmalonylurea
2, 4, 6, trioxy-5-isobutylallyl
pyrimidin



Sandoptal differs from barbital in that both of the ethyl groups of the latter are replaced, one by an iso-butyl group and the other by an allyl group.

Actions and Uses :

The same as those of barbital and its therapeutically useful derivatives.

Dosage : For mild insomnia 5 grains.
For use in obstinate cases of insomnia 6 to 12 grains.

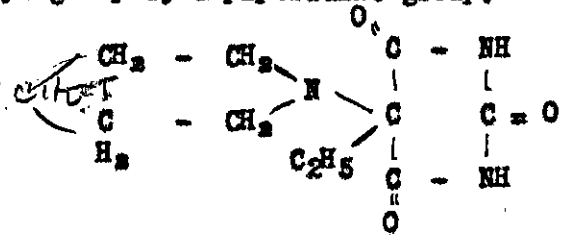
Sandoptal occurs as a white, crystalline, odorless powder, with a slightly bitter taste ; completely soluble in ethyl alcohol, acetone, chloroform, ether, ethyl acetate, and glacial acetic acid, slightly soluble in cold water, sparingly soluble in boiling water and petroleum ether, insoluble in paraffin hydrocarbons. A saturated aqueous solution is acid to litmus paper. It melts at 158-159°C. It is stable in air.

Reference Number 267

Manufacturing Chemist, July 1936 Page 232

Eldoral

A new sedative and hypnotic is Eldoral (Heyden, Radebeul-Dresden), the chemical composition of which is given as ethyl pentamethyleme uramil, and it is thus closely related to diethyl barbituric acid, only differing from the latter by the replacement of one ethyl group by a piperidine group.



Eldoral differs, however, from diethyl barbituric acid in not inducing sleep, but in producing the preliminary condition for prevention of nervous insomnia, and it should be administered with this object in view. The usual dose is half a tablet of .25 gm. in the morning on an empty stomach and before the mid-day meal, and 1 tablet half an hour before sleep is desired.

Reference Number 268

Chemical Abstracts, 29, 5 (1935) Page 8139

"Rectidon" in Obstetrical Practice. - by Heyrowsky, Med. Klin. 31 : 886-9 (1935)

Rectidon, the next higher homolog to pernocton, administered rectally has been used with success in obstetrics. It has no toxic action on mother or child.

Reference Number 269

Chemical Abstracts, 28, 5 (1934) Page 6845

Painless Childbirth with Rectidon, - by Schoenes, Deut. Med. Wochschr. 60 : 1054-5 (1934)

Rectidon is a compound preparation of sec. amyl -bromallyl malonylurea, which administered rectally eliminates the pain of parturition.

Reference Number 270

Quarterly Journal of Pharmacy and Pharmacology, 7 (1934) Page 766

Rectidon (Pharm. Ztg. Berlin 1934, 79 : 568)

It is the sodium salt of sec.-amyl- -bromallyl-malonylurea. By rectal administration it produces sleep in 15-20 minutes. It does not affect the heart, circulation or blood pressure.

Reference Number 271

Quarterly Journal of Pharmacy and Pharmacology, 7 (1934) Page 159

Rutonal

This is phenylmethylbarbituric acid and is suggested for use when phenobarbital or others can not be tolerated, since it has a lower toxicity than these compounds. It is indicated for the treatment of epilepsy, chorea, migraine and whooping-cough.

Reference Number 272

Phenobarbital U.S.P.

Essentially the same standards are given as those in the B.P. Tests for identity, purity and dosage are also the same. Official title, though, is Phenobarbital.

Phenobarbital solubile U.S.P. is essentially the same as that for Phenobarbitum solubile B.P.

Reference Number 273

Barbital U.S.P.

Essentially the same standards are given as those in the B.P. Tests for identity, purity, and dosage are also the same. The official title, though, is Barbital.

Barbital solubile U.S.P. is treated the same as Barbitonum solubile B.P.

Reference Number 274

Elix Phenobarbitali N.F. VI

Contains in each 100 ccs. not less than .38 gm. and not more than .42 gm. of phenobarbital. Tr. Sweet Orange Peal, Tr. Cudbear, alcohol, glycerin, syrup and distilled water are the other components of the elixir.

Tabellae Phenobarbitali N.F. VI
Tabellae Phenobarbitali solubilis N.F. VI

Reference Number 275

Elixir Barbitali N.F. VI

Contains in each 100 ccs. not less than 3.2 gm. and not more than 3.8 gm. of Barbital. Caramel, Compound Spirit of Vanillin, Alcohol and glycerin are the other ingredients.

Tabellae Barbitali N.F. VI
Tabellae Barbitali Solubilis N.F. VI