*Third Edition—Second Printing*

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

## A SYLLABUS FOR STUDENTS AND CLINICIANS

*By*

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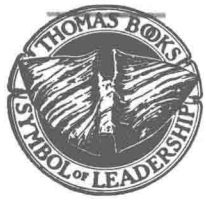


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# THE PHARMACOLOGY OF ANESTHETIC DRUGS

*To*

**E. A. ROVENSTINE, M.D.**

*who, with his emphasis upon the basic sciences*
*in the teaching of anesthesiology,*
*prompted the preparation*
*of this syllabus.*

# PREFACE TO THIRD EDITION

NEARLY A DECADE has passed since the first edition of this book was prepared. During this period anesthesiology has grown into a well-defined medical specialty. At the time of preparation of the original text, knowledge of certain aspects of anesthesiology was meagre.

Although much still remains to be learned concerning basic principles and fundamentals, considerable data has been added to our fund of knowledge over the ten year period. These advances in our knowledge have been in all aspects of anesthesiology. The greatest advances, however, have been in the pharmacological aspects of the science. Most of the recently acquired pharmacological data has been obtained in the operating room on surgical patients. Information not available from patients has been supplied by the laboratory. This newer clinical experience, coupled with the recently added laboratory investigations have made possible a re-evaluation of earlier reported subject matter. In many instances, modification of the existing subject matter has been necessary; in others the previous observations are still acceptable. As a result, certain gaps have appeared in the text which need to be filled if the book is to continue to serve the purposes for which it was intended and which it seems to have filled, as evidenced by five printings of the second edition. The author feels that before any further publication is made, the original text should be completely rewritten and brought as nearly up-to-date as possible.

The purpose and general plan remains the same. Likewise, there has been no departure from the original form save for the inclusion of tables of the less common drugs used only occasionally by the anesthesiologist. Some of the more pertinent subjects of clinical importance have been elaborated upon and presented in greater detail. This has resulted in a larger volume. The properties and actions of non-narcotic drugs used in conjunction with anesthesia, such as curare, the central nervous system stimulants, and drugs acting upon the autonomic nervous system have also been summarized. In describing these substances emphasis has been placed on their relationship to anesthesiology.

The writer is indebted to Mr. William Branks Stewart of the Department of Visual Education, Louisiana State University, School of Medicine, for the preparation of the diagrams used throughout the text.

JOHN ADRIANI, M.D.

*New Orleans, Louisiana*

# PREFACE TO FIRST AND SECOND EDITIONS

THIS OUTLINE is limited to fundamentals. It was presented originally to acquaint the student anesthetist at New York University College of Medicine and Bellevue Hospital with pharmacological facts relating to drugs in current use. The subject matter has been arranged in diagrammatic fashion to focus attention on physiological and pathological changes occurring in various organs and systems so that further study and interest in the fundamental sciences associated with anesthesiology may be stimulated. It is hoped that this outline will be helpful to the clinician who, although his major interest may be in another field, frequently employs the drugs reviewed.

The material presented is a compilation of data from periodicals, textbooks, and other sources in medical and scientific literature. The data will of necessity appear dogmatic in this type of arrangement. The reader should not be misled by the undeserved air of finality the syllabus assumes. There are many highly controversial issues. In these controversial matters, the data selected are those which have fallen in line with the clinical experiences of the writer. The reader should realize that the accumulated data are those of numerous observers who have utilized a variety of experimental methods and subjects and that interpretations may vary with the individual observer. Furthermore, in completing studies in anesthesia, variations in techniques of drug administration may alter experimental results, even though the studies were made under identical experimental conditions. Much of the included data is taken from observations on subjects other than man. Unfortunately, many results cannot be applied unreservedly to man since variations in species do occur. In many instances, the facts presented are the only ones available and must serve as a guide until human investigations are obtained.

Data on newer drugs, particularly the barbiturates and local anesthetics, are incomplete. These drugs are too numerous for individual treatment. Facts pertaining to the group as a whole have, therefore, been selected and a few important individual variations have been mentioned. Items of importance and interest to the clinician, with a direct bearing on clinical anesthesia or surgery, have been selected from less relevant material which are of major interest to the pharmacologist. A brief bibliography is provided. References to older experiments, frequently quoted in standard textbooks, are omitted. More recent periodicals are listed. Manuscripts describing several drugs are listed with the group of general articles. For the sake of brevity, the subject of the report is mentioned rather than its complete title.

The writer wishes to express his appreciation of the numerous suggestions and criticisms offered by Dr. E. A. Rovenstine, Director of the Division of Anesthesia at Bellevue Hospital, and to Dr. Bert B. Hershenson, a colleague and former member of the Division of Anesthesia.

JOHN ADRIANI, M.D.

*New York, New York*

# CONTENTS

# THE PHARMACOLOGY OF ANESTHETIC DRUGS

# SECTION I. EFFECTS OF PHYSICAL AND CHEMICAL PROPERTIES ON PHARMACOLOGICAL ACTIVITY

## CENTRAL NERVOUS SYSTEM DEPRESSANT DRUGS

Drugs acting upon the central nervous system either stimulate or depress the various cells and structures. Depressant drugs are classed according to the type of action or responses they produce. The following types are recognized:

*Types*

*Analgesic*—Agent causing relief of pain. Usually accomplished without loss of consciousness or stupor—Acetyl salicylic acid, aminopyrine and low concentrations of nitrous oxide are analgesics.

*General Anesthetic*—Agent causing loss of sensation. Also accompanied by loss of consciousness—Ether, chloroform, cyclopropane are anesthetics.

*Narcotic*—An agent producing analgesia followed by or accompanied by sleep or stupor—Morphine, dilaudid, codeine are narcotics.

*Soporific, Somnifacient, Hypnotic*—An agent causing deep sleep with little or no analgesia—Barbiturates, chloral, paraldehyde, avertin, sulphonmethanes all come under this classification. Depth or intensity of hypnosis varies with dosage.

*Sedative*—An agent which causes mild depression. Quiets nervous excitement or calms without causing sleep—Bromides, barbital, phenobarbital and small doses of hypnotics are sedatives.

*Local Anesthetic*—An agent capable of blocking nerve conduction when applied locally to any type of nerve tissue in any portion of the nervous system—Procaine, pontocaine, benzyl alcohol are local anesthetics.

No absolutely well-defined classification of nervous system depressant drugs can be made because some overlapping exists between the various types. Large doses of hypnotics may produce anesthesia. Minimal concentration of anesthetics (nitrous oxide, ethylene, ether, etc.) produces analgesia without loss of consciousness or reflexes.

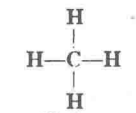
## THE CHEMICAL NATURE OF CENTRAL NERVOUS SYSTEM DEPRESSANT DRUGS

All the available agents fall into two chemical groups—the inorganic and the organic.

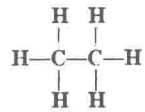
1. *Inorganic*—With the exception of nitrous oxide and carbon dioxide, and salts of bromine and magnesium, inorganic compounds play little if any part in depression of the central nervous system.
2. *Organic*—The majority of anesthetic, analgesic, hypnotic, and narcotic drugs are organic compounds containing carbon, hydrogen, oxygen, and in some cases halogens, nitrogen and sulphur. Some are gases or highly volatile liquids—others non-volatile or solid. Volatile and gaseous agents are administered by inhalation; the non-volatile by other routes. The chemical nature of central nervous system depressants is best understood by studying the various classes of organic compounds from which they are derived.

HYDROCARBONS—Compounds composed entirely of carbon and hydrogen. Three major groups exist—the aliphatic or open chain, the alicyclic or closed ring structures and the aromatic. The aliphatic and alicyclic groups contribute important inhalation agents; the aromatic does not. Aliphatic hydrocarbons are subdivided into saturated and unsaturated derivatives.

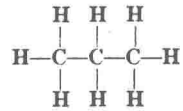
*Saturated Hydrocarbons*—Saturated straight chain hydrocarbons possess feeble anesthetic properties. They are of no clinical value because the effective concentration is high and the margin of safety is narrow. Potency increases as molecular weight increases. Methane has been tried but is not potent. Others likewise are not suitable.



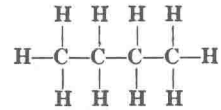
*Methane*
BP −160.0°C



*Ethane*
−85.4°

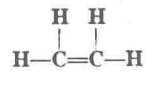


*Propane*
−37.0°

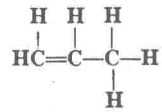


*Butane*
10.0°

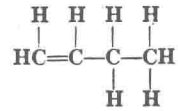
*Unsaturated Hydrocarbons (double bonded)*—Ethylene is the most widely employed derivative in this group. Propylene has been tried but possesses undesirable effects on the circulation. Higher members of the series are unsatisfactory.



*Ethylene*
−81.0°

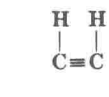


*Propylene*
−23.0°

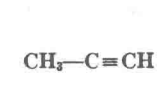


*Butylene*
−5.0°

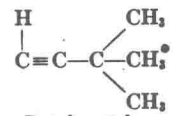
*Unsaturated Hydrocarbons (triple bonded)*—Acetylene is the only satisfactory compound in this group. Methyl acetylene and higher molecular weight derivatives are toxic and unsatisfactory.



*Acetylene*
−81.0°

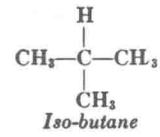


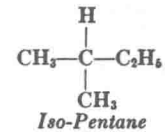
*Methyl acetylene*
−23.0°

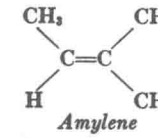


*Butyl acetylene*
27.5°

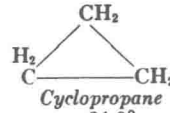
*Branched Chain Derivatives*—Both saturated and unsaturated derivatives have been tried and found to be limited in usefulness. *Amylene* has been used intravenously but possesses undesirable side actions.

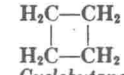

*Iso-butane*

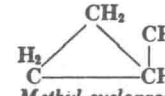

*Iso-Pentane*


*Amylene*

*Cyclic*—Lower members of this series are useful. Methyl-substituted derivatives have been tried and found toxic. *Cyclopropane* and *cyclobutane* have been used clinically.


*Cyclopropane*
−34.0°

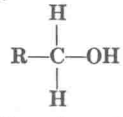

*Cyclobutane*
−15.0°

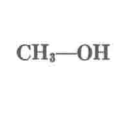

*Methyl-cyclopropane*
5.0°

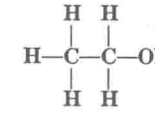
Lower molecular weight members are gases or volatile liquids which are poorly soluble in water but soluble in lipoids. Specific gravity is less than that of water. Narcotic potency increases as molecular weight increases. Narcotic potency increases as unsaturation increases (acetylene-ethylene-ethane). Hydrocarbons are chemically inert in vivo. Margin of safety varies but as a rule decreases as molecular weight increases. Some hydrocarbons cause deleterious effects upon cardiac tissues or induce undesirable neuro-muscular responses such as convulsions, twitchings, etc. Volatility and water solubility increase as molecular weight increases.

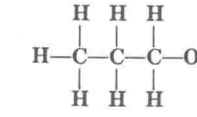
ALCOHOLS—The substitution of one hydrogen atom of a hydrocarbon by a hydroxyl (OH) group yields an alcohol. Alcohols containing one hydroxyl group are known as monohydric alcohols, two dihydric, three trihydric, and so on. Alcohols are either aliphatic, alicyclic, aromatic, or heterocyclic. Aliphatic alcohols produce hypnosis and general anesthesia; aromatic and heterocyclic alcohols are important in local anesthesia (see local anesthetics). Alcohols are classed as primary, secondary, or tertiary, depending upon the position of the hydroxyl group.

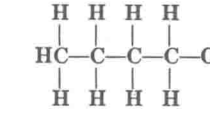
*Primary Alcohols*—Primary alcohols have two hydrogen atoms on the hydroxyl bearing carbon. *Ethyl alcohol* is the most important primary aliphatic alcohol with anesthetic activity.



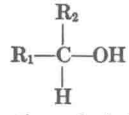

*Methyl*
BP 66.0°

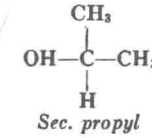

*Ethyl*
78.5°

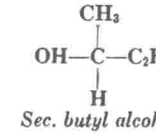

*Propyl*
97.0°


*Butyl*
117.0°

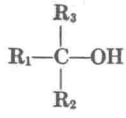
*Secondary Alcohols*—Secondary alcohols have one hydrogen and two radicals on the hydroxyl bearing carbon. No important secondary aliphatic alcohol is used for anesthesia or hypnosis.

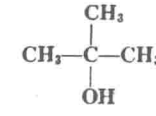


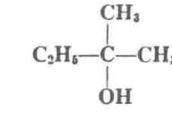

*Sec. propyl*


*Sec. butyl alcohol*

*Tertiary Alcohols*—Tertiary alcohols have three radicals on the hydroxyl bearing atom. *Amylene hydrate* is the only currently employed drug in this group.




*Ter. butyl*


*Ter. amyl*
(amylene hydrate)
BP 102.0°

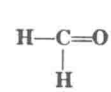
The substitution of the hydroxyl group for a hydrogen atom in an aliphatic hydrocarbon decreases its narcotic potency. Likewise, water solubility increases, lipoid solubility decreases. The compound loses its inertness in vivo and becomes more reactive. Narcotic potency is decreased, and decreases still more with additional hydroxylation. Volatility and flammability are also decreased.

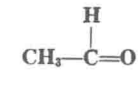
ALDEHYDES—Oxidation of primary alcohols yields compounds containing the aldehyde (CHO) group. The substitution of a hydrogen atom of an alicyclic, aromatic and heterocyclic compound converts it into an aldehyde. Aldehydes polymerize to form metaldehydes and paraldehydes. Alcohol and aldehydes condense to form products known as acetals. Paraldehydes and acetals depress the central nervous system.

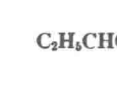
*Aliphatic Aldehydes*—No important aliphatic compounds are nervous system depressants. Acetaldehyde is the least toxic of this group, but is irritating and feeble in its action.

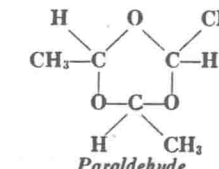
*Alicyclic Aromatic and Heterocyclic Aldehydes*—No important nervous system depressants exist in these groups.

*Paraldehydes*—Higher molecular weight paraldehydes have been studied but are toxic. Paraldehyde, the simplest member of the series, is useful as a sedative and hypnotic. Paraldehyde is derived from acetaldehyde.


*Formaldehyde*
BP −21.0°


*Acetaldehyde*
21.0°


*Propionaldehyde*
49.0°


*Paraldehyde*
121.0°

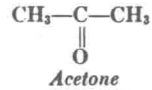
The conversion of an alcohol into an aldehyde causes an increase in irritating properties and a weakening of narcotic potency (ethyl alcohol is more useful and less irritating than acetaldehyde its corresponding aldehyde). Potency increases as molecular weight increases. Water solubility and volatility decrease as molecular weight increases.

Polymerization to paraldehydes forms an entirely new series of compounds distinctly unlike aldehydes. Paraldehydes are more potent than the aldehydes from which they are derived. They are also less soluble, less volatile and less irritating. Potency and toxicity increase as molecular weight increases. Volatility decreases as molecular weight increases. Halogenation of aldehydes enhances their potency (see halogenated derivatives).

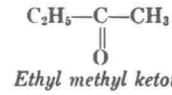
ACETALS—The interaction of alcohols with aldehydes produces acetals. Acetal is the most useful member of this group.

KETONES—Oxidation of secondary alcohols yields ketones—compounds containing the carbonyl (C=O) group. Ketones are of relatively little importance as central nervous system depressants. Halogenated ketones unlike the aldehydes are not useful as nervous system depressants.

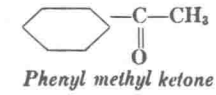
Phenyl methyl ketone or *hypnone* has been used as a hypnotic and sedative. Potency of ketones increases as molecular weight increases.



*Acetone*
BP 61.0°



*Ethyl methyl ketone*



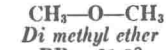
*Phenyl methyl ketone*

ACIDS—Organic acids are compounds containing the carboxyl (COOH) group. The replacement of a hydrogen atom of a hydrocarbon by a carboxyl group nullifies its action as a nervous system depressant. The carboxylic acids therefore are of no importance as anesthetic agents.

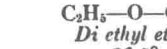
ESTERS—The interaction of an organic acid with an alcohol results in an ester. Esters may be derived from aliphatic, alicyclic, aromatic and heterocyclic acids and alcohols. Esters derived from aliphatic alcohols and carboxylic acids are mild hypnotic and sedative substances. None are clinically important. Such esters are less potent than the alcohols from which they are derived. The majority of local anesthetic drugs are complex esters of aromatic or heterocyclic acids and complex alcohols (see local anesthetic drugs).

ETHERS—Compounds formed by attaching two organic radicals to an oxygen atom are known as ethers. They may also be termed organic oxides. Ethers may be classed as aliphatic, alicyclic, aromatic or heterocyclic. Aliphatic and alicyclic ethers are potent and useful for general anesthesia. Aromatic and heterocyclic ethers play no role in general anesthesia but appear in local anesthetics. Ethers may be symmetrical if both radicals attached to the carbon atom are similar or unsymmetrical if they are dissimilar. Unsaturated linkages may appear on one or both radicals of ethers.

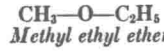
*Saturated Aliphatic Ethers—Di ethyl ether* is the most useful and potent of this group. Ethyl propyl ether has been used clinically also but is not generally accepted. Di methyl ether has been used clinically but is not satisfactory.



*Di methyl ether*
BP −21.0°



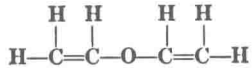
*Di ethyl ether*
36.5°
"Ether"



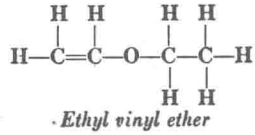
*Methyl ethyl ether*

*Ethyl propyl ether*

*Unsaturated Aliphatic Ethers—Di vinyl oxide* is the most important compound of this group. Higher molecular weight compounds are not satisfactory.



*Dirinyl ether*
BP 28.0°



*Ethyl vinyl ether*

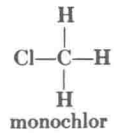
*Mixed Ethers*—Various alicylic and aliphatic ethers have been prepared and tried clinically. None has yet attained any widespread clinical use. Cyclopropyl methyl ether, or cyprome, cyclopropyl ethyl ether or cypreth have been tried, but discarded.

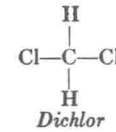
Aliphatic and alicyclic ethers are more volatile than the alcohols to which they are related or from which they are derived. They are miscible with lipoids and hydrocarbons, highly flammable, and slightly soluble in water. The presence of unsaturated linkages and the presence of the alicyclic radicals increases their potency.

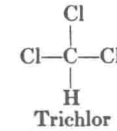
Low molecular weight ethers are very volatile, irritating and require low concentrations for surgical anesthesia. Toxicity increases with increase in molecular weight. Halogenated ethers are not generally useful. Unsaturation causes an increase in secretory activity of ethers.

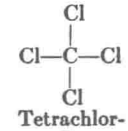
HALOGENATED DERIVATIVES—Compounds derived from chlorine and bromine are useful central nervous system depressants. Fluorine and iodine yield toxic or non-anesthetic derivatives. The most useful compounds are aliphatic hydrocarbons, alcohols, and aldehydes. Alicyclic compounds are of no importance; aromatic derivatives are toxic. The following aliphatic halogenated compounds are important:

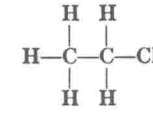
*Halogenated Hydrocarbons (saturated)*—Many derivatives of bromine and chlorine have been prepared which possess a depressant action on the nervous system. *Chloroform* and *ethyl chloride* are currently used. The majority of derivatives in this group are administered by inhalation.


monochlor methane *Methyl chloride* BP 39.0°

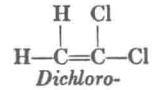

*Dichlor methane* 41.0°

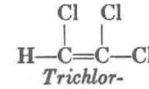

Trichlor methane *chloroform* 61.2°


Tetrachlor-methane *carbon tetrachloride* 76.2°

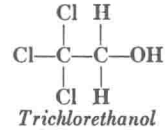

ethyl chloride BP 12.5°

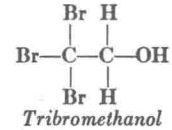
*Halogenated Hydrocarbons (unsaturated)*—*Trichlorethylene* is the only member of this group employed clinically for inhalation; other derivatives are irritating, toxic, or not easily volatilized.

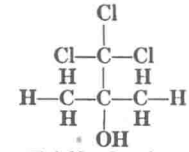

*Dichloro-ethene* 37.0°


*Trichlor-ethylene* 87.0°

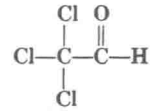
*Halogenated Alcohols*—*Trichlorethanol* and *tribromethanol* are potent hypnotics used for basal anesthesia. Drugs in this group are non-volatile and cannot be administered by inhalation. They are formed by reduction of aldehydes. Halogenation increases the potency of aliphatic alcohols.

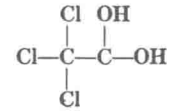

*Trichlorethanol* BP 156.0°

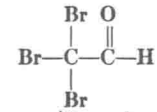

*Tribromethanol* "Avertin" Melting point 81.0°


*Trichlor butyl alcohol* "Chloretone"

*Halogenated Aldehydes*—*Chloral* and *bromal* are used clinically. These derivatives are more volatile than the corresponding halogenated alcohols. Halogenation diminishes irritating qualities and improves the potency of aliphatic aldehydes. Hydrates form when they interact with water. Halogenated aldehydes, like the alcohols, are not sufficiently volatile to be used for inhalation.


*Chloral*

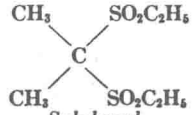

*Chloral hydrate*

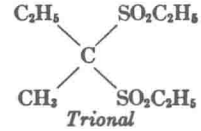

*Bromal*

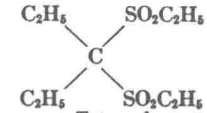
Halogenation enhances narcotic potency and causes a decrease in volatility of aliphatic substances. Inflammability decreases as the number of halogen atoms increases. Chlorinated derivatives are more volatile and less potent than brominated compounds. Many halogenated hydrocarbons are of limited usefulness because they are toxic to the heart and liver.

SULPHONATED COMPOUNDS—Sulphur containing compounds are of little clinical importance with the exception of the thio-barbiturates (see barbiturates) and the sulphonated aliphatic compounds derived from sulphonic acid. The sulphone methanes, derived from ethyl sulphonic acid, possess hypnotic properties. Aromatic sulphonic acid derivatives do not.

*Sulphone Methanes*—Three important compounds exist in this group. *Sulphonal*, *trional*, and *tetronal*.


*Sulphonal*

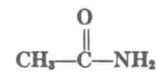

*Trional*

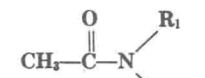

*Tetronal*

The sulphone methanes are little used clinically because they are feeble hypnotics. They dissolve in water with difficulty and possess cumulative properties.

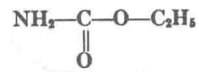
AMIDES—Amides may be considered as ammonia with one of its hydrogen atoms replaced by an acyl radical. They may also be considered as carboxylic acids with the hydroxyl group replaced by an animo group. Certain amides possess hypnotic and sedative actions. Amides are non-volatile drugs.

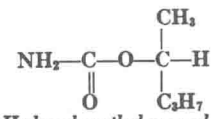
*Substituted Aliphatic Amides*—The amides have no depressant effects unless the hydrogen atoms are substituted by aliphatic, aromatic and other groups. None of this group is employed clinically.

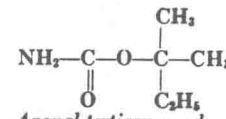

*Acetamide*


*Aliphatic and aromatic groups*

*Urethanes*—Carbamic acid, the monamide of carbonic acid, forms esters with various aliphatic alcohols. This group of esters is known as *urethanes*. Ethyl carbamate or *ethyl urethane*, *hedonal*, and *aponal* have been used clinically. Potency of urethanes increases as molecular weight increases. Urethanes formed from primary alcohols are less potent than those formed from secondary, those from secondary less potent than those from tertiary. Ethyl urethane, hedonal and aponal are important urethanes.


*Ethyl urethane*


*Hedonal methyl propyl carbonyl carbamate*


*Aponal tertiary amyl carbamate*