Pharmaceutical Chemistry

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Synthesis of Essential Drugs

By *R.S. Vardanyan* and *V.J. Hruby*, Elsevier, 2006

1. General Anesthetics

In surgical practice: general anesthesia (narcosis) refers to the condition of an organism with a reversible loss of consciousness at a controlled level of nervous system suppression.

It includes the components: analgesia (absence of pain), amnesia (absence of memory), suppression of reflexes such as bradycardia, laryngospasm, and loss of skeletal muscle tonicity.

General anesthesia: a complex procedure involving preanesthetic assessment, administration of general anesthetic drugs, cardiorespiratory monitoring, analgesia, airway management, and fluid management.

General anesthetics: a drugs provide relief of pain, weaken the reflex and muscle activity, and ultimately result in loss of consciousness.

Ideal anesthetic: have a wide range of therapeutic index and no significant side effects.

Drugs used in anesthesiology: block or suppress neurological impulses mediated by the central nervous system, and permit surgical, obstetric, and diagnostic procedures to be completed painlessly.

General anesthetics:

1. Inhalation (e.g. halothane, enflurane, isoflurane, methoxyflurane, and nitrous oxide)

2. Non-inhalation; intravenous (e.g. barbiturates, ketamine, and etomidate)

Inhalation anesthetics

The object of inhalation anesthetics: obtain a concentration (partial pressure) of the drug in the brain sufficient to reach the desired level of anesthesia.

Anesthetic molecules must pass through the lungs into the brain through various biological phases. Therefore, inhalation anesthetics must be **soluble in blood and interstitial tissue**.

Wide variation in structure: ranging from complex steroids to the inert monatomic gas xenon

Mechanism by inhalation anesthetics is not exactly known.

Interaction of inhalation anesthetics with cellular structures: van der Waals

Action of general anesthetics:

blockage of ion channels and/or

specific changes in mechanisms of the release of neurotransmitters.

Proposed mechanisms:

1. ***Hydrate hypothesis****:* Anesthetic molecules can form hydrates with structured water, which can stop brain function in corresponding areas.

2. ***Ion channel hypothesis****:* Anesthetics block ion channels by interacting with cellular membranes and reducing the flow of Na^+ ions and increasing the flow of K^+ ions into the cell, which leads to the development of anesthesia.

3. ***Fluid membrane hypothesis****:* Anesthetics stabilize, or rather immobilize the cell membrane, hampering membrane fluidity, which produces changes in the ion channel action.

Selection of a specific anesthetic or combination of anesthetics is made depending on the type of medical intervention.

Old drugs: ether, chloroform, tricholoroethylene, ethyl chloride or chloretane, and also cyclopropane.

New drugs: halothane, enflurane, isoflurane, metoxyflurane, and nitrous oxide.

Halothane

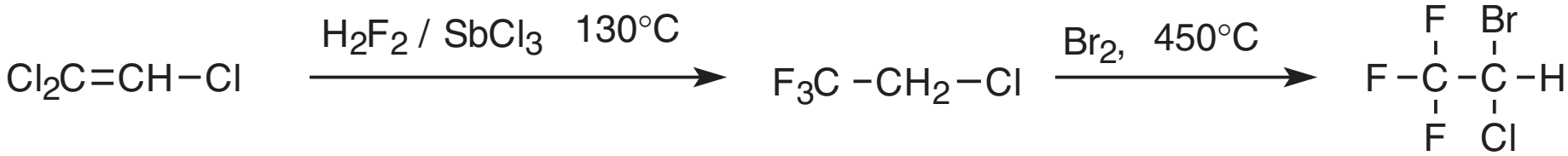
Halothane is a modern and widely used inhalation anesthetic.

It begins to act very quickly, which is pleasing to patients, and it is very safe.

The only drawback to using it is its hepatotoxicity.

It is used in both short and long-lasting surgical operations.

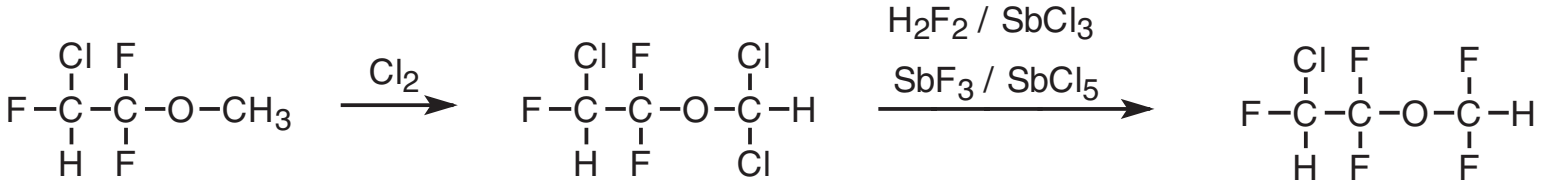
Synonym: fluothane



Enflurane

Enflurane has practically all the same characteristics as halothane and is used in the same situations. It is poorly absorbed.

Synonym: ethrane

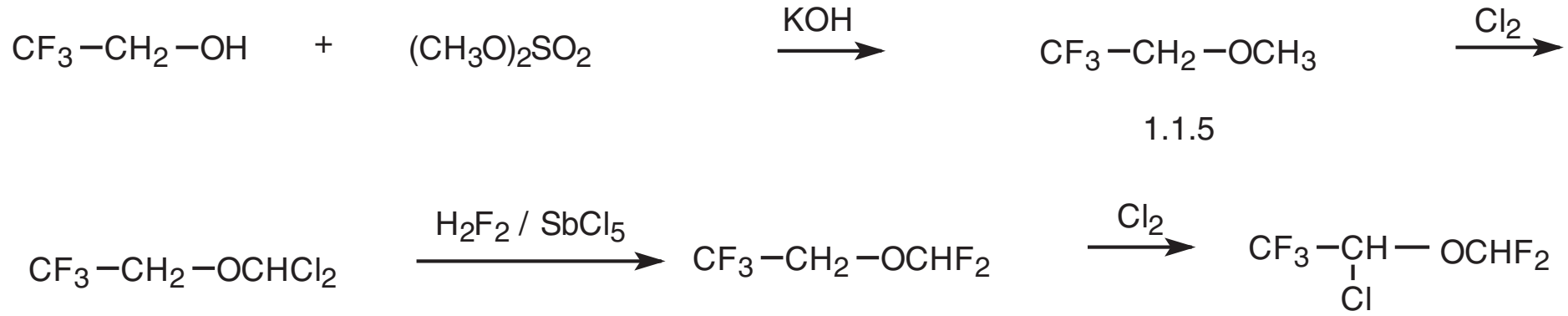


Isoflurane

Isoflurane is analogous to enflurane.

It has a somewhat pungent odor which sometimes causes difficulties.

Synonym: Forane



Metoxyflurane

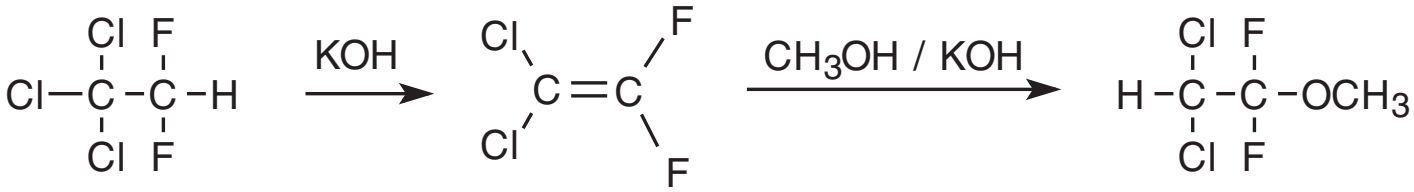
Methoxyflurane is an extremely powerful inhalation anesthetic that is an excellent skeletal muscle relaxant.

Disadvantage: 1) its relatively high solubility, which causes the patient to make a slow transition back into consciousness.

2) fluorine ions are the product of its biotransformation, which may lead to the development of **renal failure**.

It is recommended to use methoxyflurane for anesthesia during interventions of no more than 2 h.

Synonym: penthrane



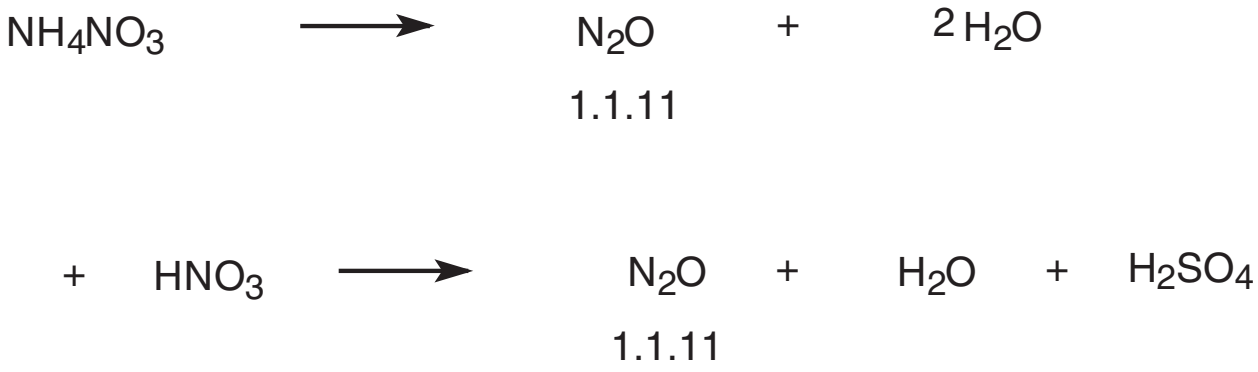
Nitrous oxide

Nitrous oxide is also called laughing gas, and is a weak anesthetic.

It is usually used together with hypnotics, analgesics, and muscle relaxants.

It is sometimes called an ideal anesthetic because of the absence of any kind of suppressive influence on respiration.

Use of nitrous oxide for more than 2 h is counterproductive since it causes a severe reduction of methionine synthesis, which in turn can cause a severe decrease in the level of vitamin B12 with all its subsequent consequences.



Non-inhalation anesthetics

To place a patient under narcosis in modern anesthesiology, multiple drugs are used both prior to using inhalation anesthetics and during the procedure.

During noninhalation anesthesia, control and regulation during the procedure is significantly harder than inhalation anesthesia.

Simplicity of intravenous anesthesia equipment and various combinations (neuroleptanalgesia, ataragesia, tranquilizeresia) are beneficial in clinical use.

Drugs:

ketamine and ethomidate as short-lasting drugs

short-lasting barbiturates (thiopental, methohexital)

opioid analgesics (morphine, fentanyl)

benzodiazepine tranquilizers (diazepam, lorazepam, and midazolam),

Ketamine

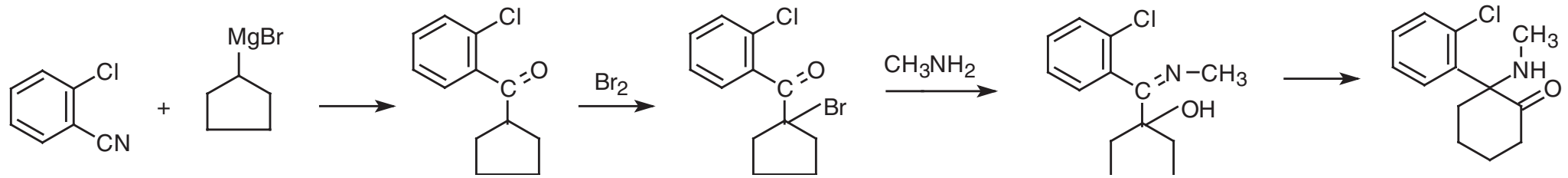
used in brief surgical procedures.

It causes a condition known as dissociative anesthesia, which ensures amnesia and analgesia, and preserves normal respiration and muscle tonicity in the patient.

Ketamine is practically void of muscle relaxant capabilities.

Preanesthetic medications such as morphine, scopolamine, benzodiazepine, and butyrophenones **lower** dysphoric effects of ketamine.

Synonyms: ketanest and ketalar



Etomidate

Derivative of imidazole.

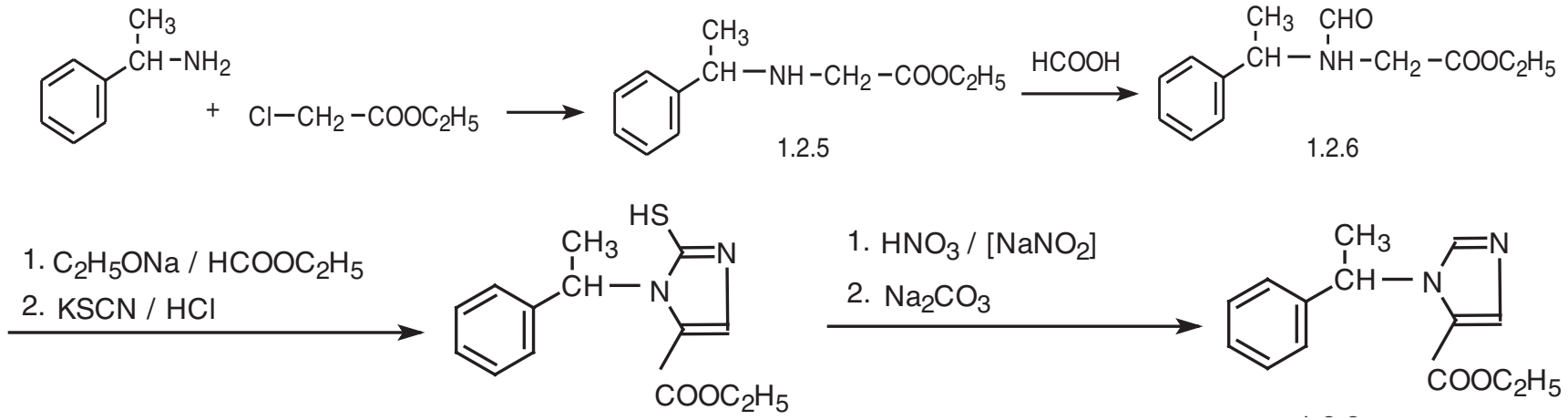
Duration of its action depends on the administered dose.

It can be classified as a sedative hypnotic drug because of the quick loss of consciousness upon intravenous administration.

Due to its poor solubility in water at pH values higher than 3, it is used in clinical situations in a solution of propylene glycol, which causes pain during injection.

Disadvantage: causes post-operative nausea and vomiting

Synonym: hypnomidate



Thiopental

Barbiturates are hypnotics, and at therapeutic doses has a very weak analgesic and muscle relaxant effect.

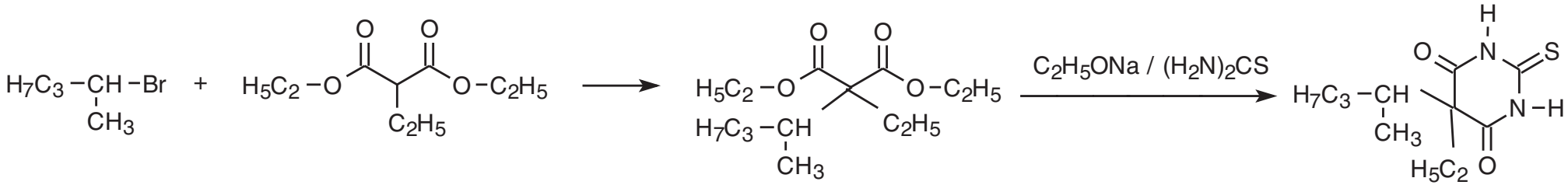
Thiopental is an extremely **short-lasting** barbiturate that makes anesthesia pleasant and smooth for the patient. Coming back into consciousness happens 15 min after administration.

Oppressive effect on the myocardium and central nervous system

Lesser effect acts on the smooth muscle of blood vessels

Barbiturates change into soluble form on treatment with bases, appears in the market under the name sodium thiopental. The formation of a salt occurs due to the sulfur atom in an enethiolate form.

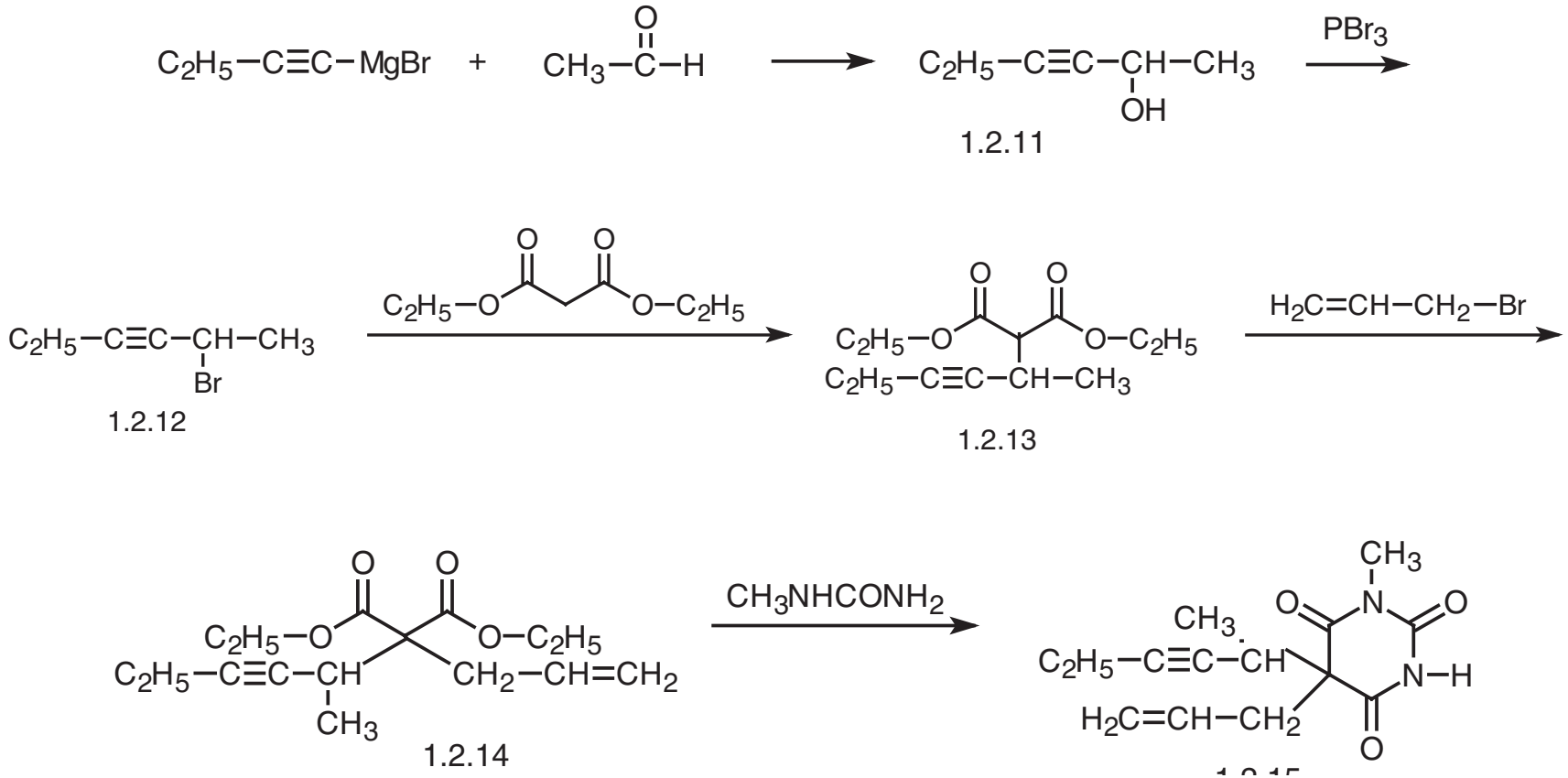
Synonym: pentothal, trapanal, farmotal, and intraval



Methohexital

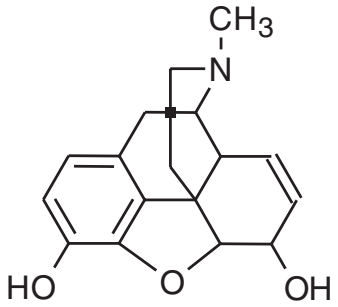
An extremely short-lasting barbiturate, slightly shorter active time than thiopental.

Synonym: pentothal, intraval, farmotal, and ravonal



Opioid analgesics

Opioid analgesics, in particular morphine, fentanyl, alfentanil, and sufentanyl are widely used in the practice of anesthesiology as adjuncts.



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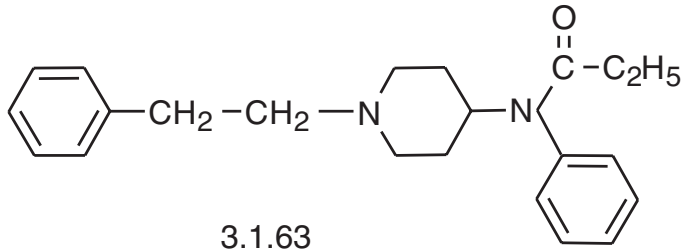
morphine



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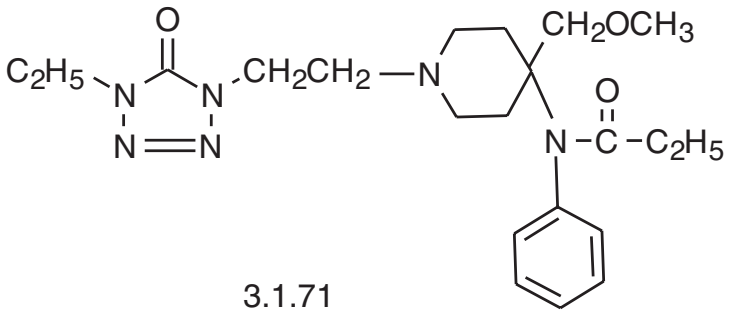
fentanyl



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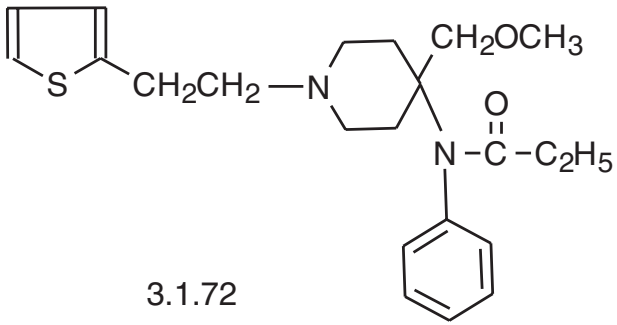
alfentanil



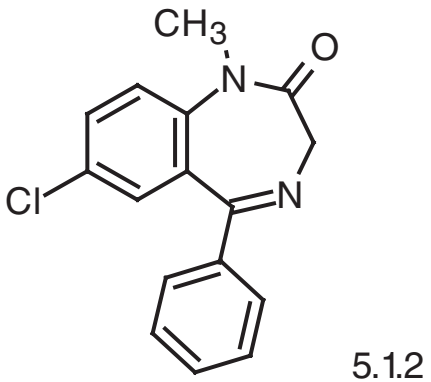
3.1.72

sufentanyl

Benzodiazepines

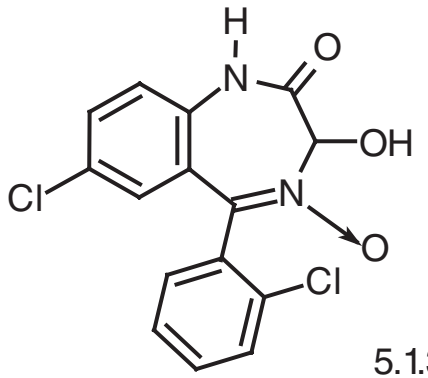
Benzodiazepines: diazepam, lorazepam, and midazolam

Have anxiolytic, sedative, and anticonvulsant effects, that cause amnesia and muscle relaxation, are frequently used to relieve patients' anxiety during anesthesia.



5.1.2

diazepam



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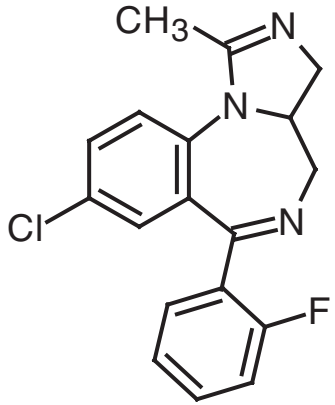
lorazepam



midazolam