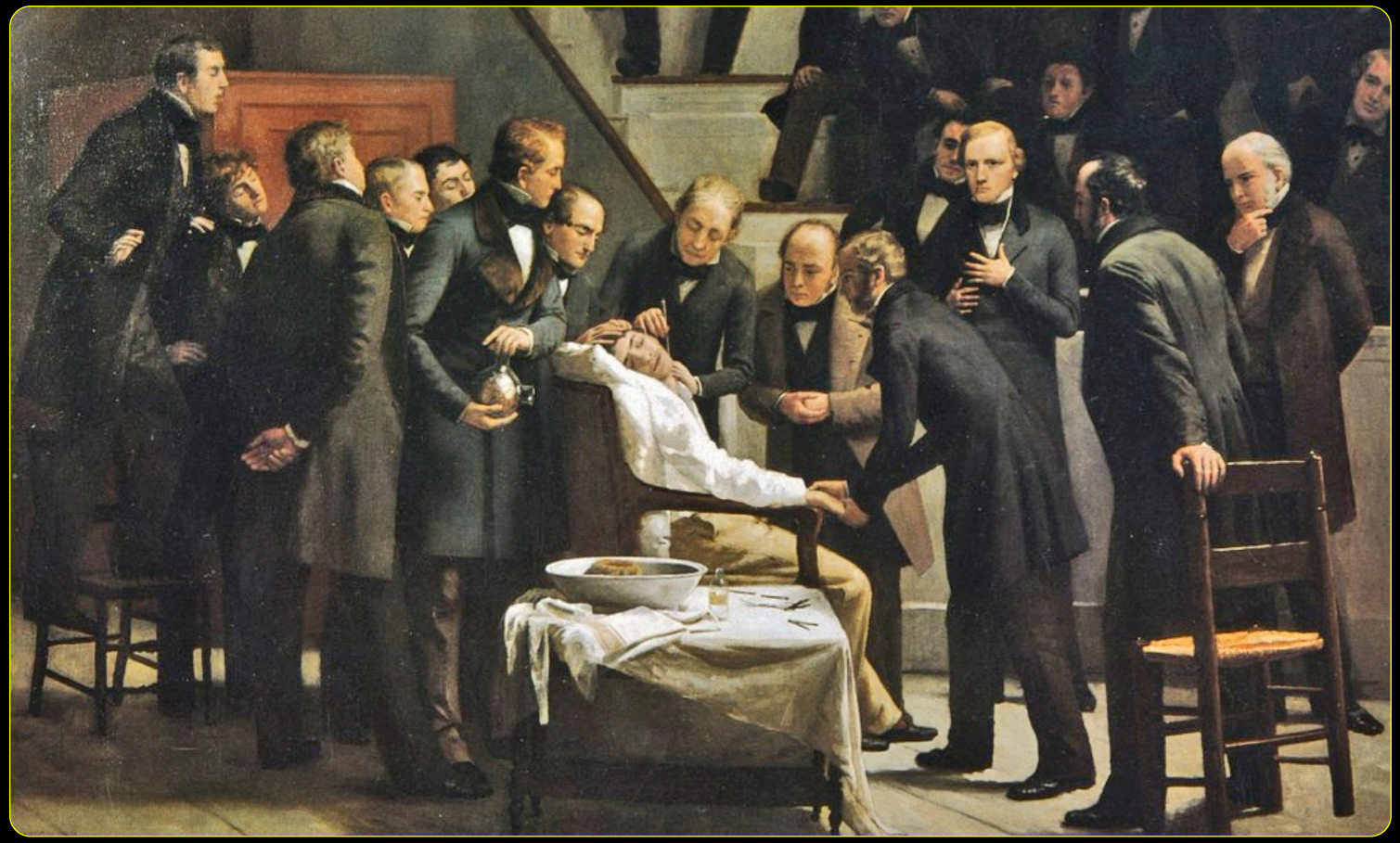
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

Massachusetts General Hospital, SAD, 16. X 1846.

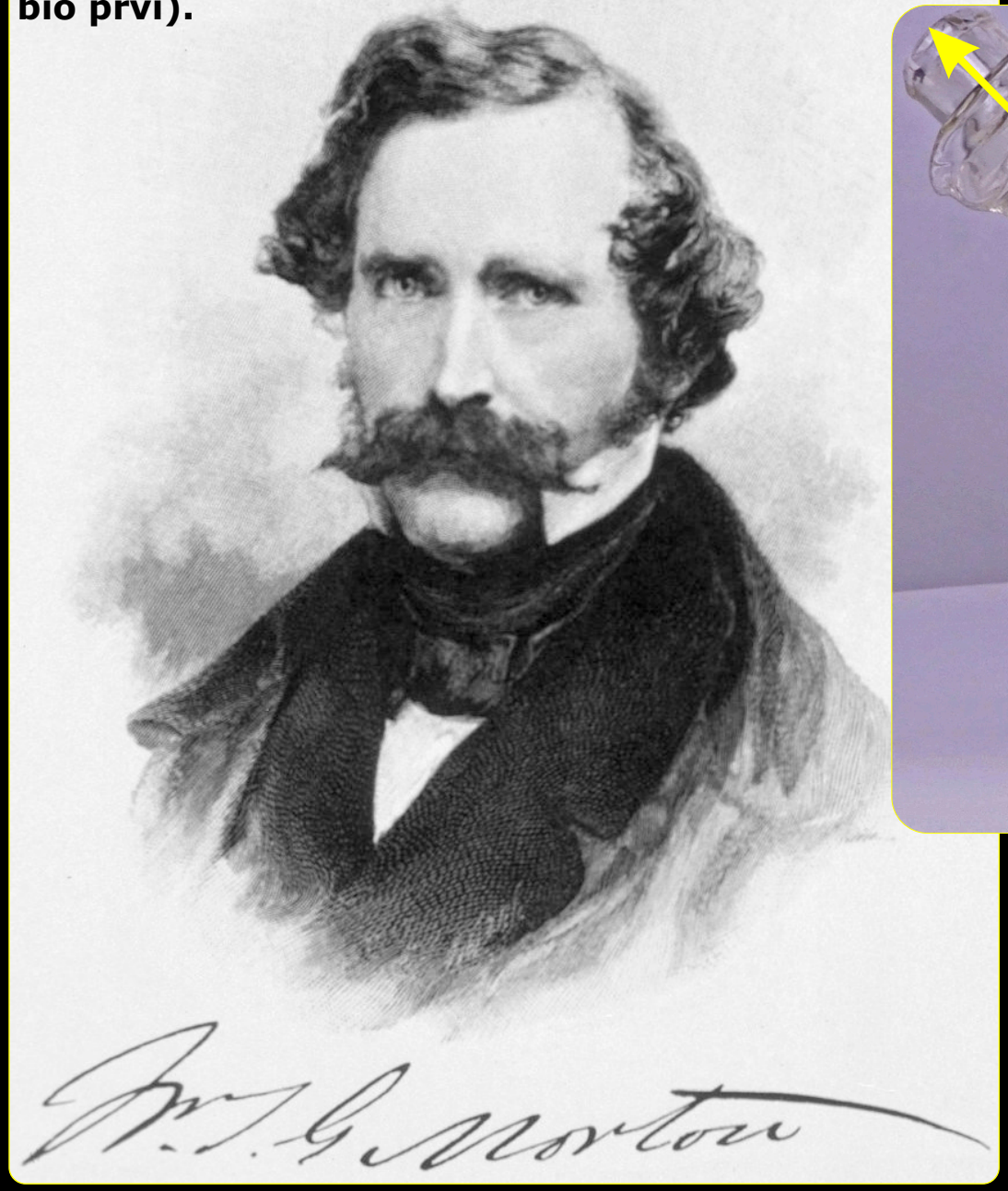


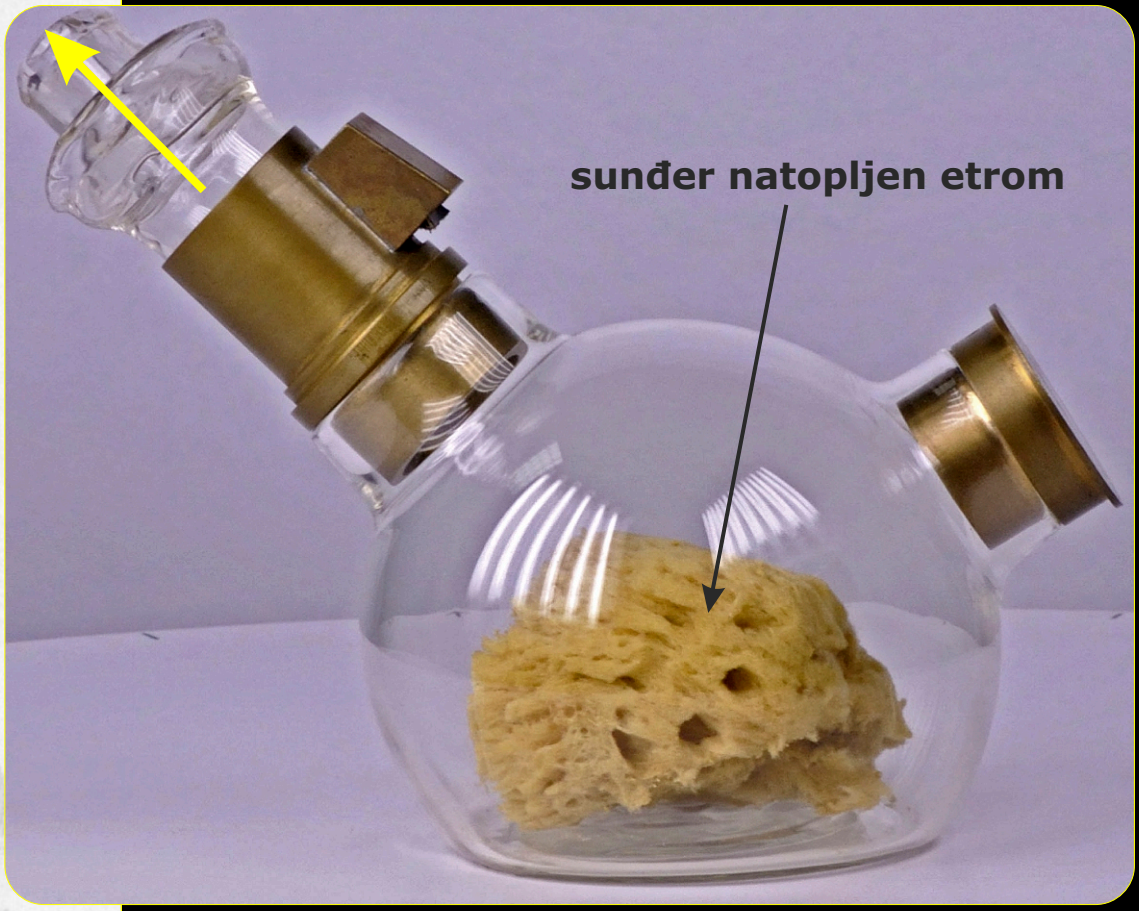
Slika Robert C. Hinckley-a. "The First Operation Under Ether"
(smatra se da nije faktografski potpuno tačna)

PRVI ANESTETICI ODN. ANALGETICI BILI SU ALKOHOL I OPIJUM. PRIMENJIVANI SU, POVREMENO, TOKOM HIRURŠKIH INTERVENCIJA, OD ANTIČKIH VREMENA.

PRVI PRAVI ANESTETICI POČELI SU DA SE PRIMENJUJU POLOVINOM 19. VEKA I BILI SU INHALACIONI: DIETILETAR I HLOROFORM;
DANAS SE VIŠE NE KORISTE JER DIETILETAR NIJE DOVOLJNO EFIKASAN, A HLOROFORM JE IZRAZITO TOKSIČAN, AKUTNO I HRONIČNO.

**William Thomas Green Morton (09. VIII 1819 – 15.VII 1868). Američki stomatolog i pronalazač etarske anestezije (istorijski je sporno da li je bio prvi).**

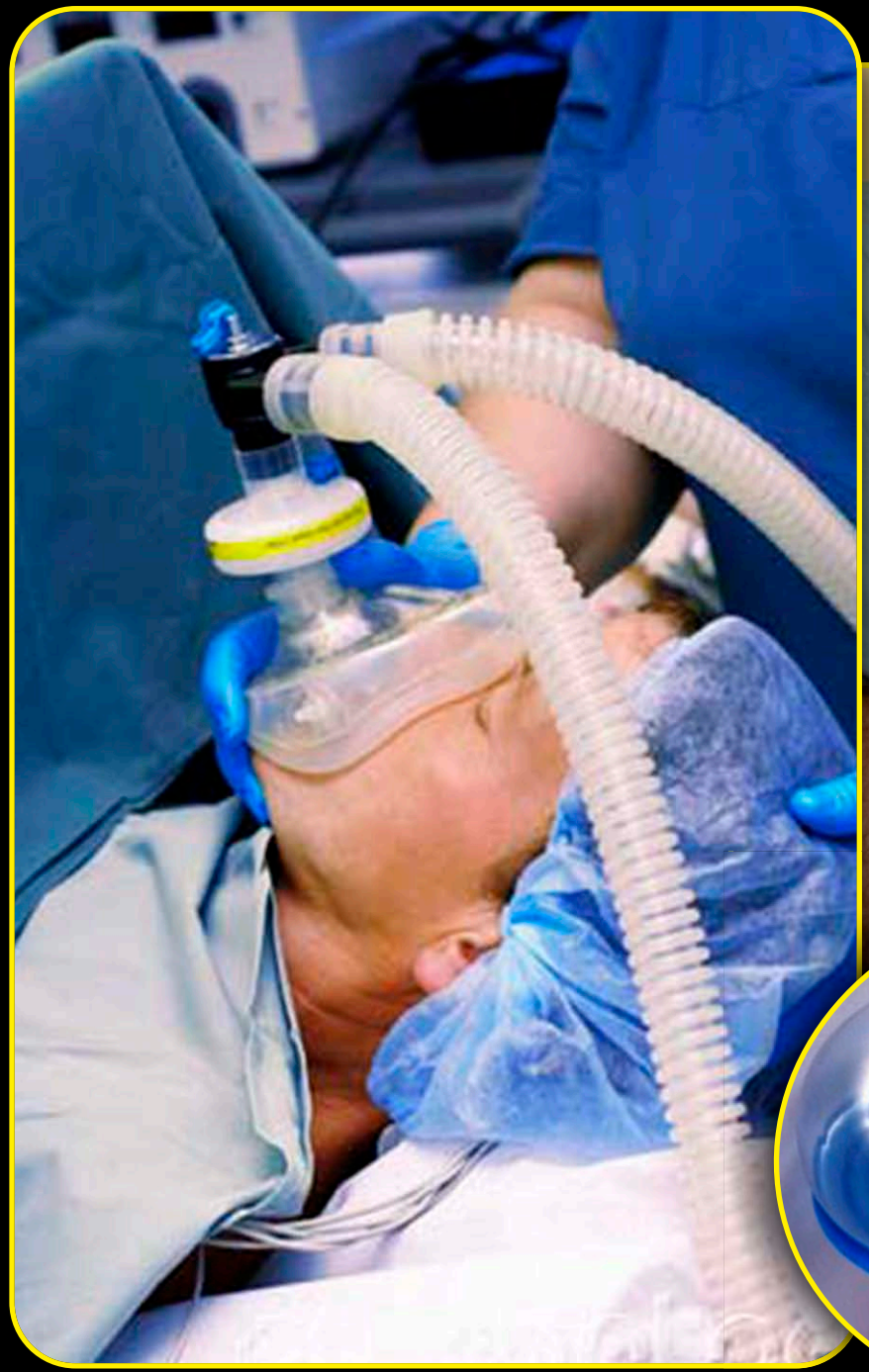


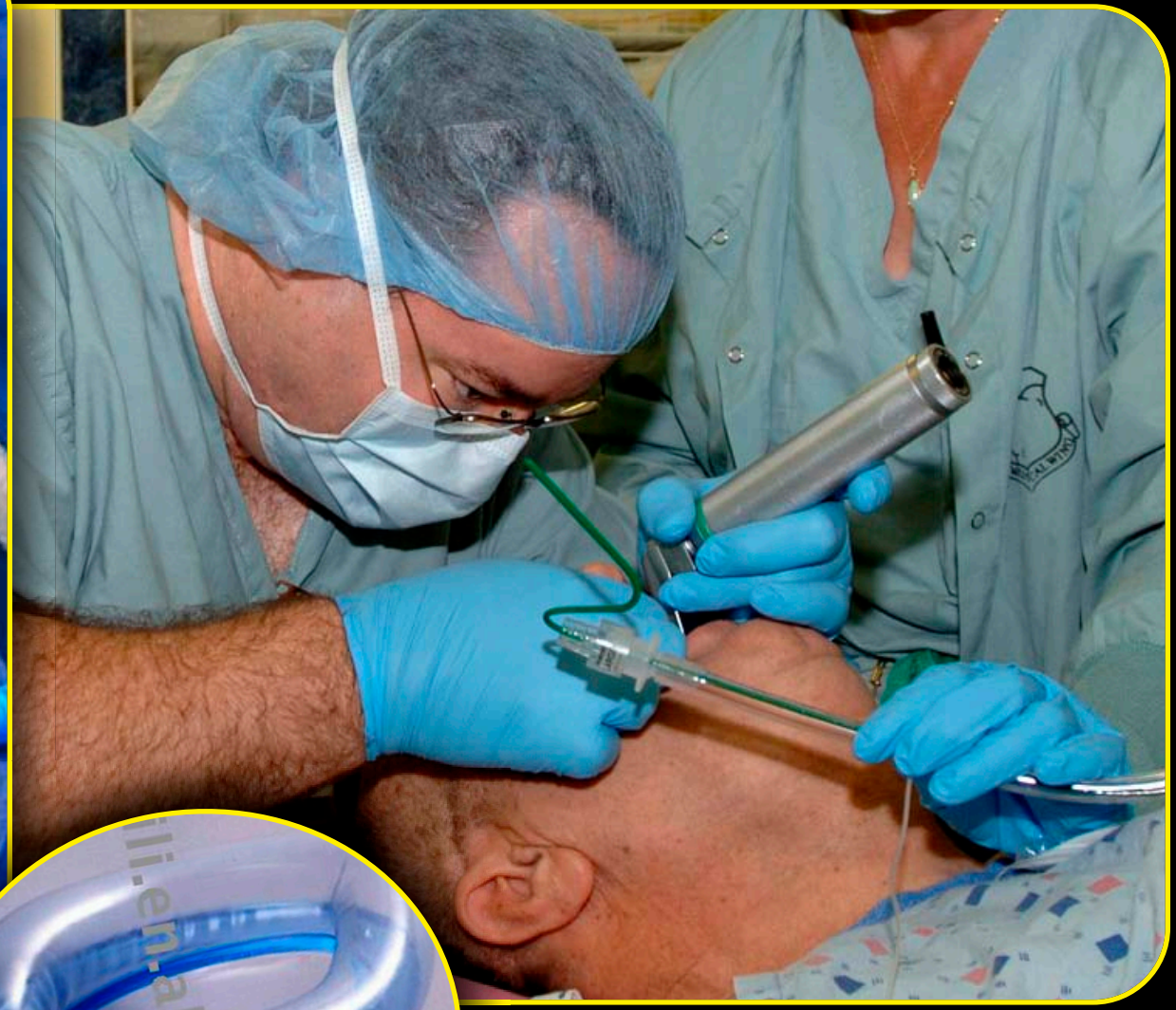


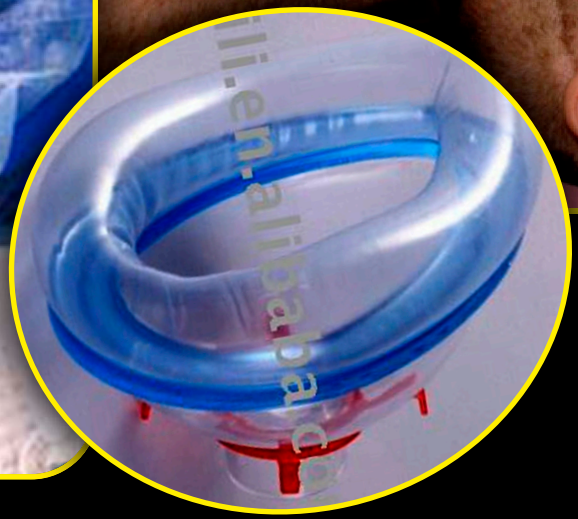

**Kopija ranih inhalatora za etarsku anesteziju**

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI





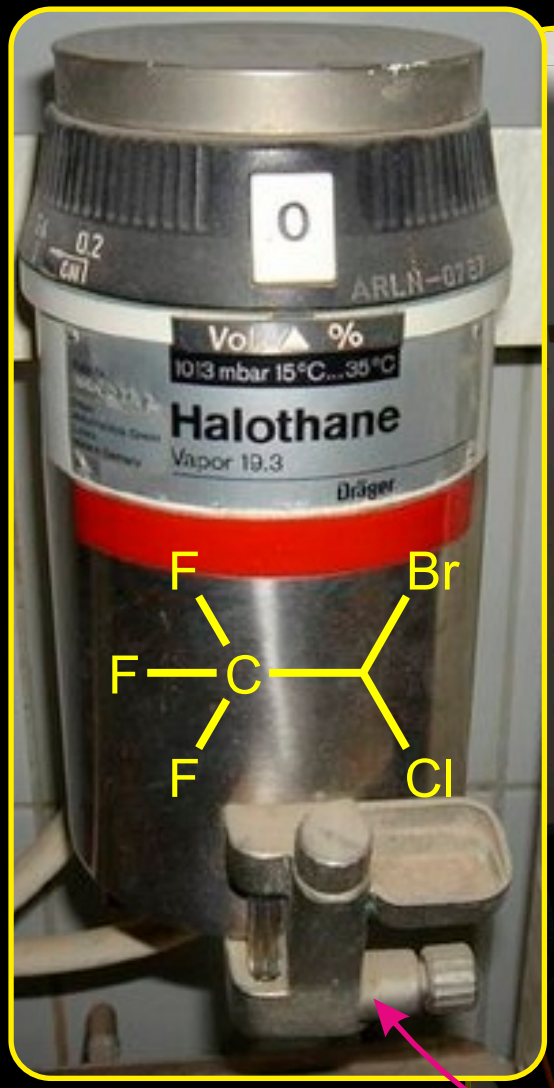


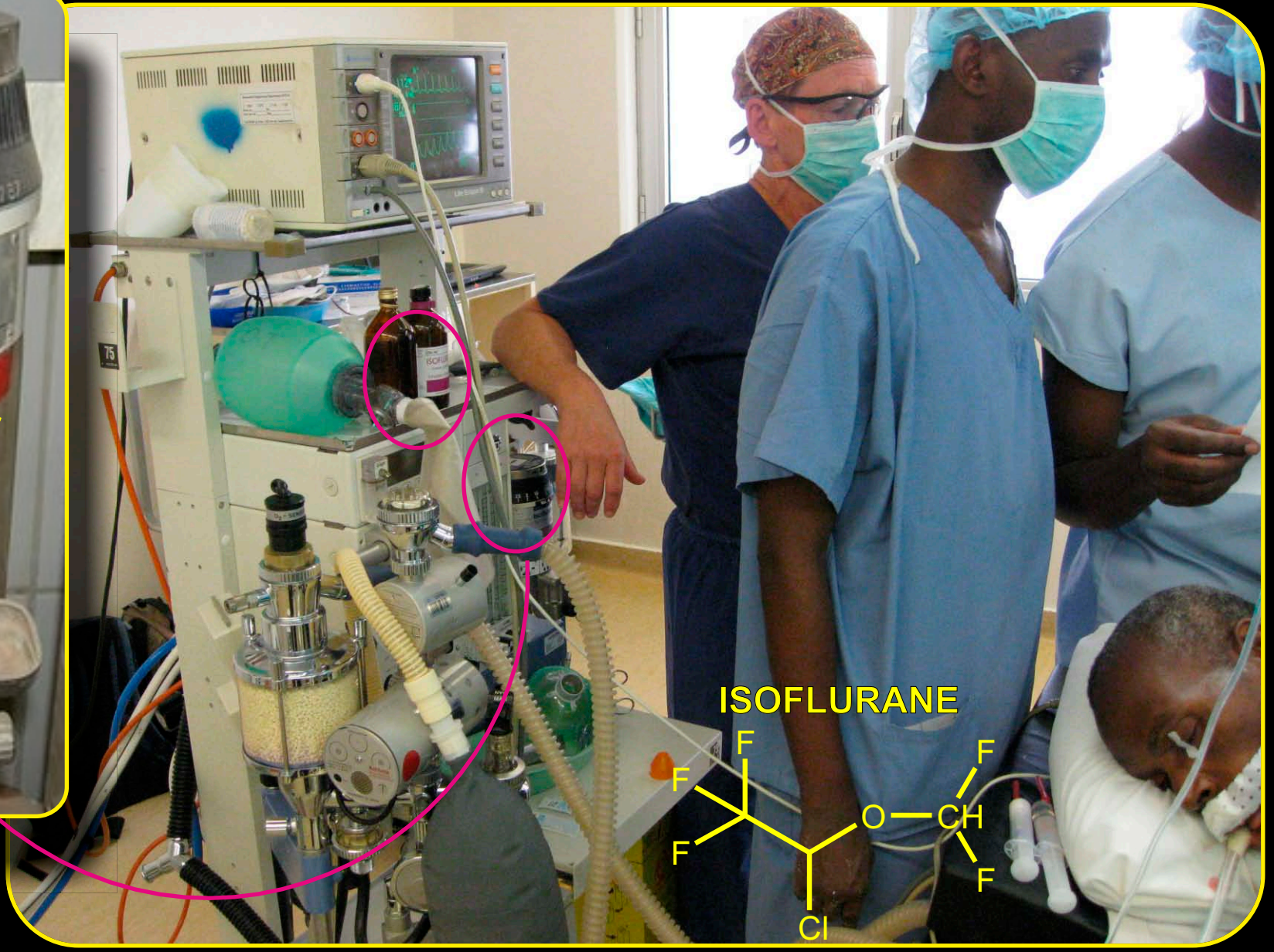
SAVREMENI INHALATORI ZA ANESTEZIJU (ETAR SE VIŠE NE KORISTI KAO ANESTETIK)

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI



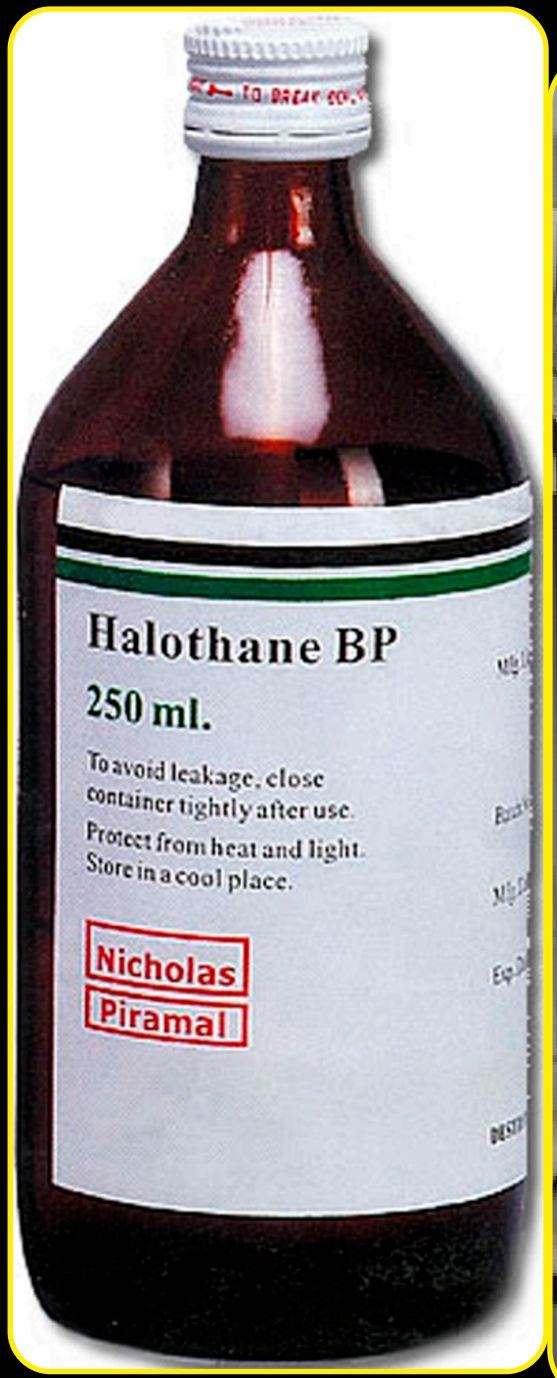



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI





# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

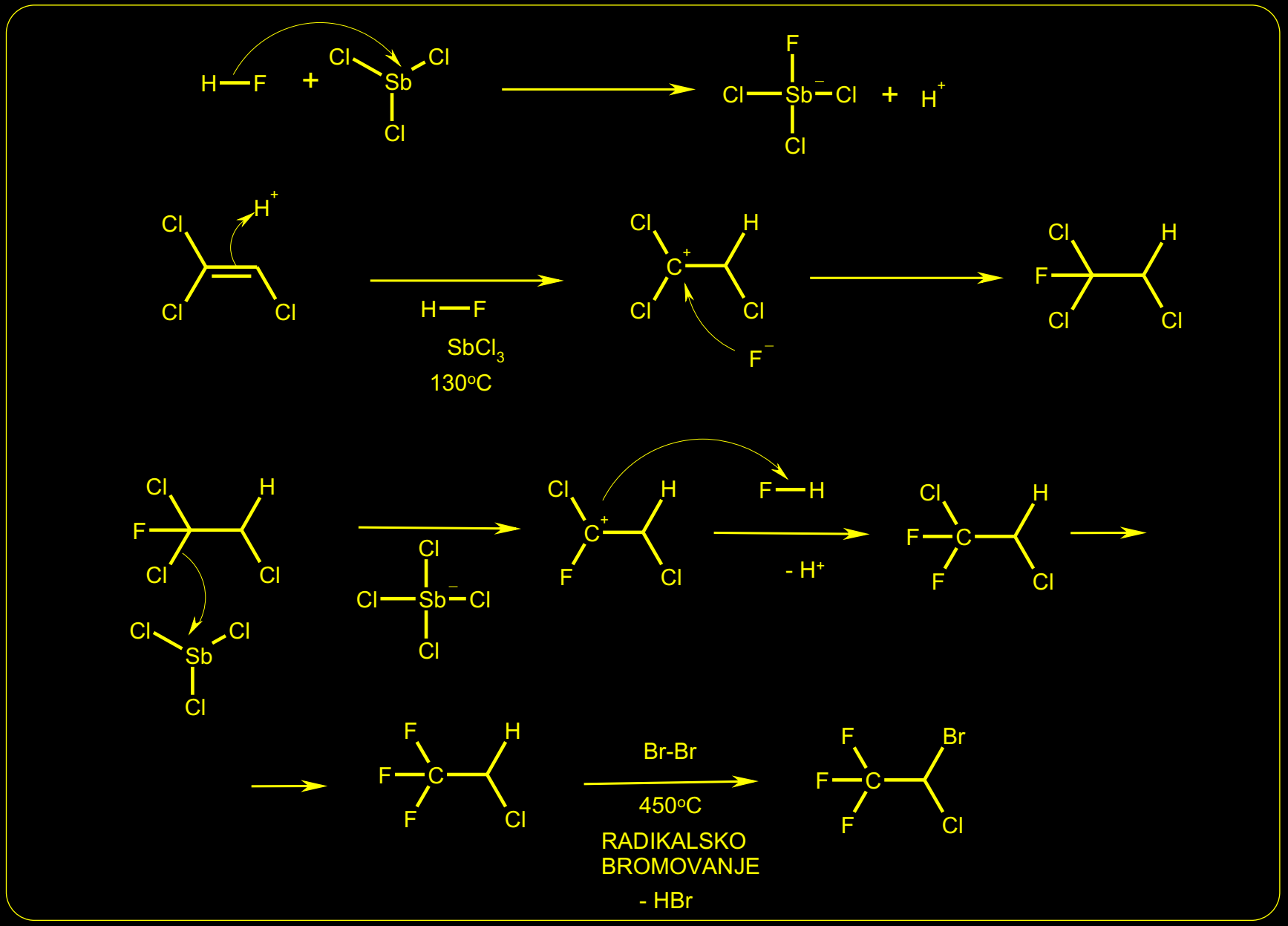
## 1. OPŠTI ANESTETICI

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

### -HALOTHANE (HALOTAN)



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

**THE MERCK INDEX**

**AN ENCYCLOPEDIA OF**

**CHEMICALS, DRUGS, AND BIOLOGICALS**

THIRTEENTH EDITION

Editorial Staff

Maryadele J. O'Neil, Senior Editor
Ann Smith, Senior Associate Editor
Patricia E. Heckelman, Associate Editor
John R. Obenchain Jr., Editorial Assistant
Jo Ann R. Gallipeau, Technical Assistant
Mary Ann D'Arecca, Administrative Associate
Susan Budavari, Editor Emeritus

Published by
Merck Research Laboratories

Division of
MERCK & CO., INC.
Whitehouse Station, NJ
2001

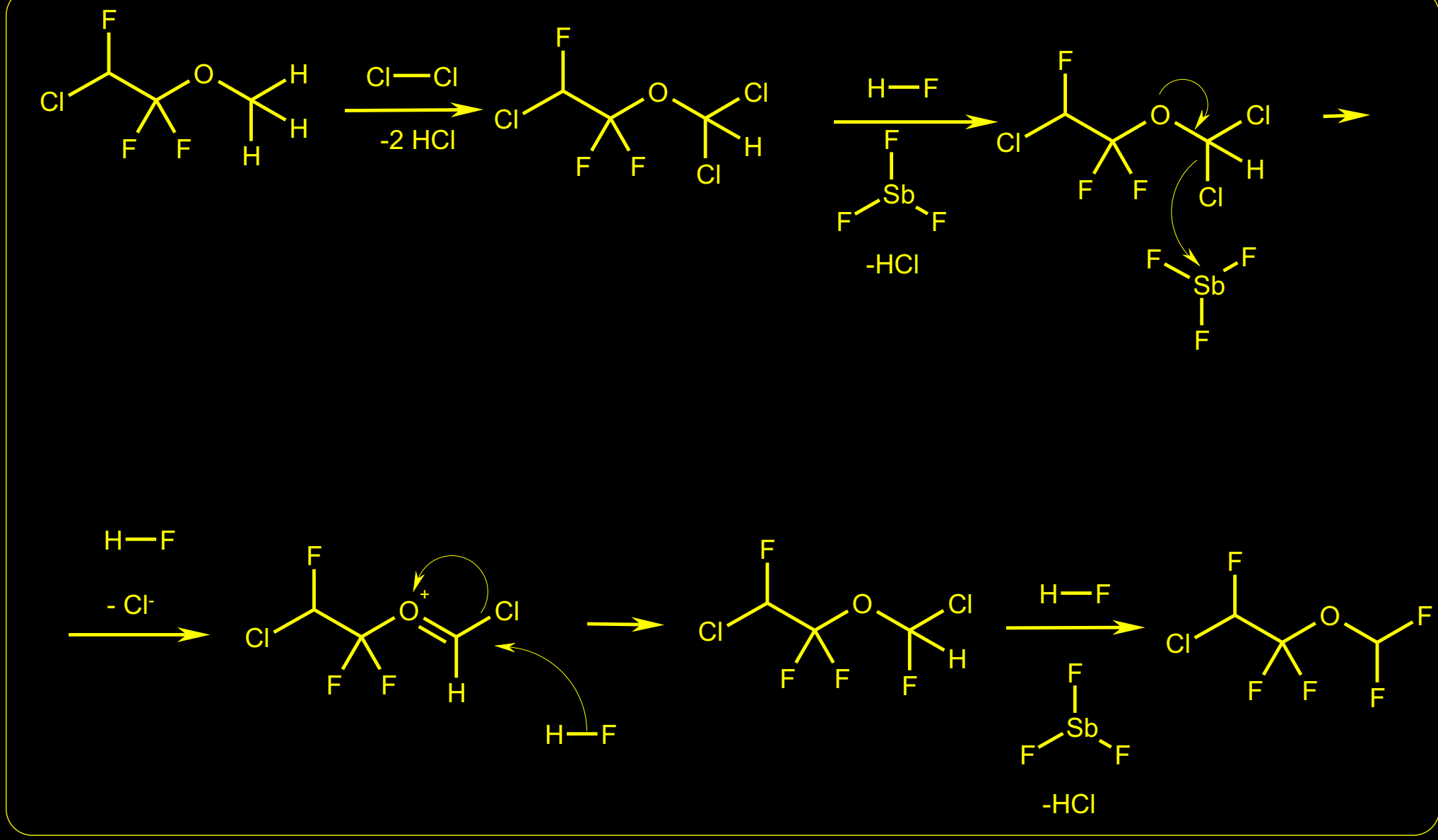
Monograph Number: 4619
Title: **HALOTHANE**
CAS Registry Number: 151-67-7
CAS Name: 2-Bromo-2-chloro-1,1,1-trifluoroethane
Additional Names: bromochlorotrifluoroethane; 1,1,1-trifluoro-2,2-chlorobromoethane
Trademarks: Fluothane (Ayerst); Rhodialothan (Nattermann)
Molecular Formula: C2HBrClF3
Molecular Weight: 197.38.
Percent Composition: C 12.17%, H 0.51%, Br 40.48%, Cl 17.96%, F 28.88%
Line Formula: CF3CHClBr
Literature References: Prepn from a mixt of F3CCH2Cl and F3CCBr2Cl: Suckling, Raventos, US 2921098 (1960 to I.C.I.); by rearrangement of F2BrCCHFCl: Scherer, Kühn, US 2959624 (1960 to Hoechst); from BrClCHCBrCl2: Chapman, McGinty, GB 805764 (1958 to I.C.I.); from Br2ClCCF3: McGinty, US 3082263 (1963 to I.C.I.); Madai, Muller, J. Prakt. Chem. 19, 83 (1963). Enantiomeric resolution: J. Meinwald et al., Science 251, 560 (1991). Comprehensive description: R. D. Daley, Anal. Profiles Drug Subs. 1, 119-147 (1972).
Properties: Non-flammable, highly volatile liquid. Characteristic, sweetish, not unpleasant odor. d 1.871. bp 50.2°; $bp_{243}$ 20°. nD0 1.3697. Sensitive to light, may be stabilized with 0.01% thymol. Soly in water 0.345%. Miscible with petr ether, other fat solvents.
Boiling point: bp 50.2°C; $bp_{243}$ 20°C
Index of refraction: nD0 1.3697
Density: d420 1.871
CAUTION: Potential symptoms of overexposure are irritation of eyes, skin, respiratory system; confusion, drowsiness, dizziness, nausea, analgesia, anesthesia; cardiac arrhythmia; liver and kidney damage; decreased audio visual performance. See NIOSH Pocket Guide to Chemical Hazards (DHHS/NIOSH 97-140, 1997) p 156.
Therap-Cat: Anesthetic (inhalation).
Therap-Cat-Vet: Anesthetic (inhalation).

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

#### -ENFLURANE (ENFLURAN)



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

**THE MERCK INDEX** Monograph Number: 3615

***Title***: **ENFLURANE**

***CAS Registry Number***: 13838-16-9 ***CAS Name***: 2-Chloro-1-(difluoromethoxy)-1,1,2-trifluoroethane

***Additional Names***: 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether; methylflurether

***Manufacturers' Codes***: compd 347; NSC-115944

***Trademarks***: Alyrane (Pharmacia & Upjohn); Efrane (Abbott); Ethrane (Ohmeda)

***Molecular Formula***: C3H2ClF5O ***Molecular Weight***: 184.49.

***Percent Composition***: C 19.53%, H 1.09%, Cl 19.22%, F 51.49%, O 8.67% Line Formula: $CHF_2OCF_2CHClF$

***Literature References***: Prepn by fluorination of the corresp dichloromethyl ether: R. C. Terrell, GB 1138406; idem, US 3469011; US 3527813 (1969, 1969, 1970 all to Air Reduction). ***Synthesis and anesthetic properties:*** R. C. Terrell et al., J. Med. Chem. 14, 517 (1971); 15, 604 (1972). Enantiomeric resolution: J. Meinwald et al., Science 251, 560 (1991).

***Properties***: Stable, volatile, non-flammable liq. bp 56.5°. nD20 1.3025. d2525 1.5167. Does not degrade in the presence of alkali or light. Miscible with other organic liquids incl. fats and oils.

***Boiling point:*** bp 56.5° ***Index of refraction:*** nD20 1.3025 ***Density:*** d2525 1.5167

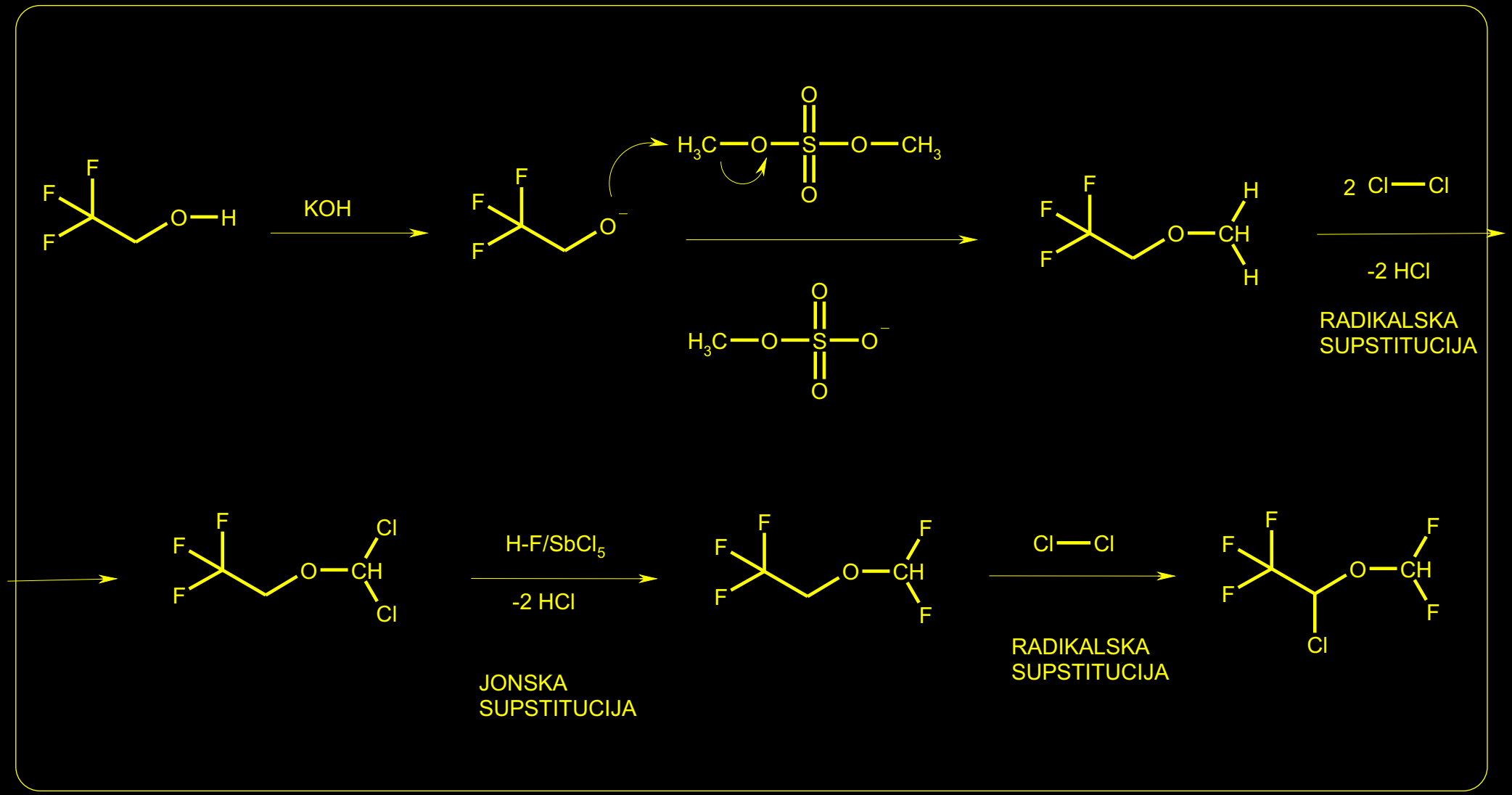
CAUTION: Potential symptoms of overexposure are eye irritation; CNS depression, analgesia, anesthesia, seizures, respiratory depression. See NIOSH Pocket Guide to Chemical Hazards (DHHS/NIOSH 97-140, 1997) p 128. Therap-Cat: Anesthetic (inhalation).

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

### -ISOFLURANE (ISOFLURANE)



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

THE MERCK INDEX *Monograph Number: 5193*

*Title*: Isoflurane *CAS Registry Number*: 26675-46-7

*CAS Name*: 2-Chloro-2-(difluoromethoxy)-1,1,1-trifluoroethane

*Additional Names*: 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether

*Manufacturers' Codes*: compd 469 *Trademarks*: Aerrane (Ohmeda); Forane (Ohmeda); Forene (Abbott)

*Molecular Formula*: $C_3H_2ClF_5O$ *Molecular Weight*: 184.49.

*Percent Composition*: C 19.53%, H 1.09%, Cl 19.22%, F 51.49%, O 8.67%

Line Formula: $CF_3CHClOCHF_2$

*Literature References*: Prepn: Croix, Terrell, DE 1814962 (1969); Terrell, US 3535388; US 3535425 (both 1970 to Air Reduction); Terrell et al., J. Med. Chem. 14, 517 (1971). Series of articles on pharmacology: Anesthesiology 35, 8-53 (1971); Byles et al., Can. Anaesth. Soc. J. 18, 376-407 (1971).

*Enantiomeric resolution*: J. Meinwald et al., Science 251, 560 (1991).

*Properties*: Clear, colorless liquid having a slight odor. bp 48.5°. Vapor pressure at 25°: 330 mm. sp gr 1.45. nD20 1.3002. Nonflammable; soda lime stable. Easily miscible with organic liquids including fats and oils.

*Boiling point*: bp 48.5° *Index of refraction*: nD20 1.3002

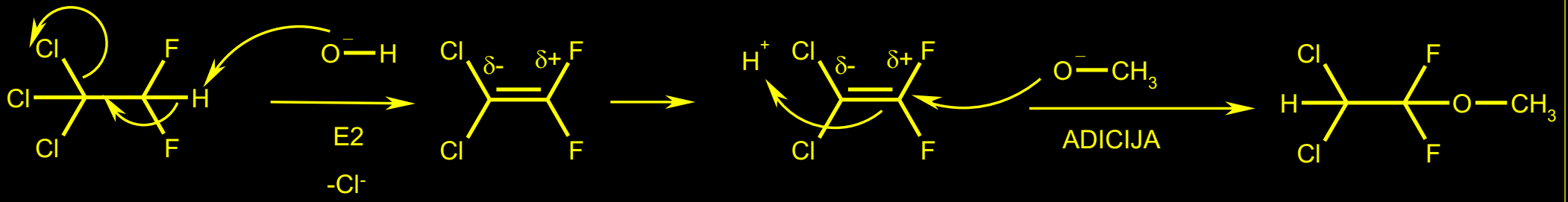
Use: Solvent and dispersant for fluorinated materials. Therap-Cat: Anesthetic (inhalation). Therap-Cat-Vet: Anesthetic (inhalation).

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

#### -METHOXYFLURANE (METHOKSIFLURAN)




#### -AZOT-SUBOKSID (NITROUS OXIDE)

$$NH_4NO_3 \longrightarrow N_2O + 2H_2O$$

#### -KSENON (Xe) I CIKLOPROPAN

**Xe** $\triangle$

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

**THE MERCK INDEX** Monograph Number: 2777
Title: Cyclopropane
CAS Registry Number: 75-19-4
Additional Names: Trimethylene
Molecular Formula: C3H6
Molecular Weight: 42.08.
Percent Composition: C 85.63%, H 14.37%
Literature References: Prepd by reduction of 1,2-dibromocyclopropane with zinc and alcohol: Lott, Christiansen, J. Am. Pharm. Assoc. 19, 341 (1930); Schlatter, J. Am. Chem. Soc. 63, 1733 (1941); from 1,3-dibromopropane with zinc and alcohol in absence of water: Ashdown et al., ibid. 58, 850 (1936); by the action of sodium vapor on 1,3-dibromopropane: Bawn, Hunter, Trans. Faraday Soc. 34, 608 (1938); from 1,3-dichloropropane heated with an excess of zinc dust, iodine and ethanol in 80% yield: Hass et al., Ind. Eng. Chem. 28, 1178 (1936); from 1,3-dichloropropane with zinc in presence of sodium iodide: US 2102556 (1937); cf. US 2098239; GB 498225; US 2211787; US 2235679; US 2235762; US 2240513; US 2240514; US 2242235. From ethylene by the reaction with methylene iodide and a zinc-copper couple in 29% yield: Simmons, Smith, J. Am. Chem. Soc. 80, 5323 (1958); Chem. & Eng. News 36, 40 (Dec 8, 1958).
Properties: Flammable gas. Characteristic odor resembling that of petr ether. mp -127°. bp -33°. Liquefies at 4-6 atms. One liter of cyclopropane (at 1 atm, 0°) weighs 1.879 g. One vol of cyclopropane dissolves in about 2.7 vols of water at 15°. Freely sol in alcohol, ether. Sol in fixed oils. Concd H2SO4 absorbs the gas readily.
Melting point: mp -127°
Boiling point: bp -33°
CAUTION: Mixture of cyclopropane with oxygen or air may explode when brought in contact with a flame or other causes of ignition. Explosive limits (% by vol in air), lower: 2.41; upper: 10.3. The explosibility is greater than that of other anesthetic-oxygen mixtures because of the comparatively larger amounts of oxygen that are compatible with cyclopropane anesthesia. Rich oxygen mixtures are therefore to be avoided.
Therap-Cat: Anesthetic (inhalation).
Therap-Cat-Vet: Anesthetic (inhalation).

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

Monograph Number: 6687 Title: Nitrous Oxide CAS Registry Number: 10024-97-2
Additional Names: Dinitrogen monoxide; laughing gas; hyponitrous acid anhydride; factitious air
Molecular Formula: $N_2O$ Molecular Weight: 44.01. Percent Composition: N 63.65%, O 36.35%
Literature References: Constituent of the earth's atm, about 0.00005% by volume: Slobod, Krogh, J. Am. Chem. Soc. 72, 1175 (1950). Prepd by thermal decompn of ammonium nitrate: E. H. Archibald, The Preparation of Pure Inorganic Substances (Wiley, New York, 1932) p 246; Castner, Kirst, US 2111276 (1938 to du Pont). Preparation and purification: Schenk in Handbook of Preparative Inorganic Chemistry vol. 1, G. Brauer, Ed. (Academic Press, New York, 2nd ed., 1963) pp 484-485. The chief impurity of the commercial product is N2, although NO2, N, O2, and CO2 may also be present. Teratogenicity study: G. A. Lane et al., Science 210, 899 (1980). Reviews: Beattie, "Nitrous Oxide" in Mellor's Vol. VIII, suppl II, Nitrogen (part 2) 189-215 (1967); Jones in Comprehensive Inorganic Chemistry vol. 2, J. C. Bailar, Jr. et al., Eds. (Pergamon Press, Oxford, 1973) pp 316-323.
*Properties*: Colorless gas. Asphyxiant. Slightly sweetish odor and taste. Supports combustion. Very stable and rather inert chemically at room temperatures. Dissociation begins above 300° when the gas becomes a strong oxidizing agent. mp -90.81°; bp760 -88.46°; Trouton constant 21.4: Hoge, J. Res. Nat. Bur. Stand. 34, 281 (1945). Dipole moment 0.166. d-89 (liq) 1.226; d(S.T.P.) 1.967; d(gas) 1.53 (air = 1). Critical temp 36.5°; crit press. 71.7 atm. Heat of vaporization (bp): 3.956 kcal/mole. While in the steel cylinder nitrous oxide is compressed to the form of gas over liq and has a pressure of ~800 lbs/sq. in. at room temp. At 20° and 2 atm one liter of the gas dissolves in 1.5 liters of water. Freely sol in sulfuric acid. Sol in alcohol, ether, oils.
Melting point: mp -90.81° Boiling point: bp(760) -88.46°
Density: d(-89°C) (liq) 1.226; d(S.T.P.) 1.967; d(gas) 1.53 (air = 1)
CAUTION: Potential symptoms of overexposure are dyspnea; drowsiness, headache; asphyxia; reproductive effects; direct contact with liquid may cause frostbite. See NIOSH Pocket Guide to Chemical Hazards (DHHS/NIOSH 97-140, 1997) p 234.
Use: To oxidize organic compds at temps >300°; to make nitrites from alkali metals at their boiling points; in rocket fuel formulations (with carbon disulfide); in the prepn of whipped cream.
Therap-Cat: Anesthetic (inhalation); analgesic.

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.1 INHALACIONI ANESTETICI

### -METHOXYFLURANE (METHOKSIFLURAN)

**THE MERCK INDEX** Monograph Number: 6023 Title: Methoxyflurane CAS Registry Number: 76-38-0
CAS Name: 2,2-Dichloro-1,1-difluoro-1-methoxyethane
Additional Names: 2,2-dichloro-1,1-difluoroethyl methyl ether; 1,1-difluoro-2,2-dichloroethyl methyl ether
Manufacturers' Codes: DA-759
Trademarks: Metofane (Vericore); Penthrane (Abbott); Pentrane (Abbott)
Molecular Formula: $C_3H_4Cl_2F_2O$ Molecular Weight: 164.97.
Percent Composition: C 21.84%, H 2.44%, Cl 42.98%, F 23.03%, O 9.70%
Line Formula: $CH_3OCF_2CHCl_2$
Literature References: Prepn and properties: Miller et al., J. Am. Chem. Soc. 70, 431 (1948); Park et al., ibid. 73, 861 (1951); GB 754976 (1956 to Standard Tele. & Cable).
Properties: Liquid, bp 105°; $bp_{100}$ 51°. mp -35°. nD20 1.3861; nD25 1.3839. d 1.4262 (Miller); d 1.4226 (Park).
Melting point: mp -35° Boiling point: bp 105°; $bp_{100}$ 51°
Index of refraction: nD25 1.3839
Density: d 1.4262 (Miller); d420 1.4226 (Park)
CAUTION: Potential symptoms of overexposure are eye irritation; CNS depression, analgesia; anesthesia, seizures, respiratory depression; liver and kidney injury. See NIOSH Pocket Guide to Chemical Hazards (DHHS/NIOSH 97-140, 1997) p 196.

Therap-Cat: Anesthetic (inhalation).

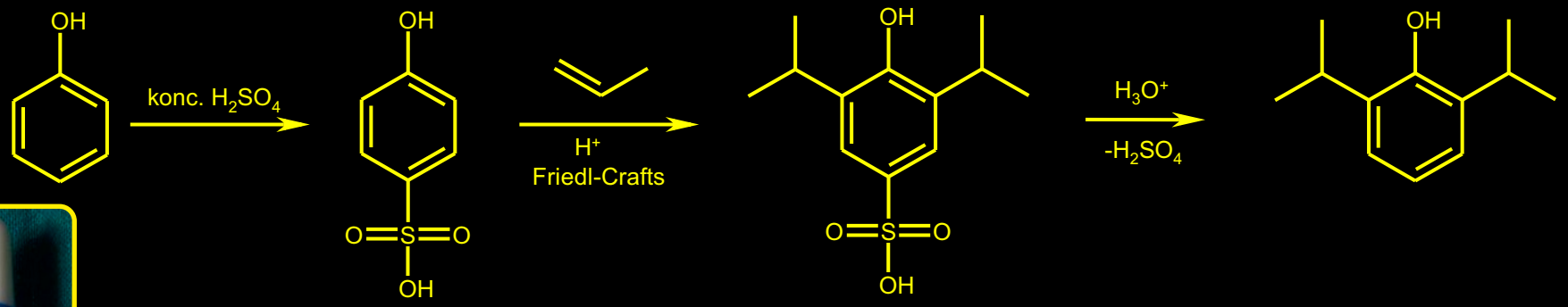
Therap-Cat-Vet: Anesthetic.

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

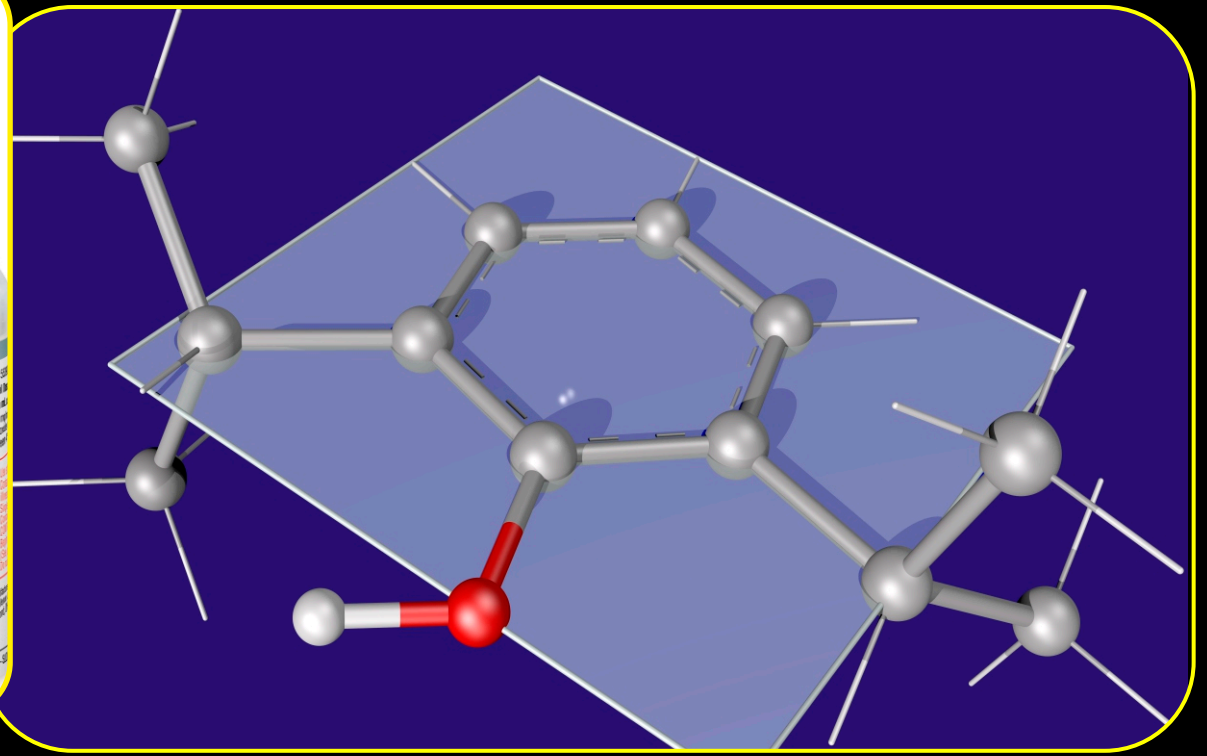
## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

**-PROPOFOL (2,6-DIISOPROPYLPHENOL)**





# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

### -PROPOFOL (2,6-DIISOPROPYLPHENOL)

**THE MERCK INDEX** Monograph Number: 7927 Title: Propofol CAS Registry Number: 2078-54-8 CAS Name: 2,6-Bis(1-methylethyl)phenol Additional Names: 2,6-diisopropylphenol; disoprofol Manufacturers' Codes: ICI-35868 Trademarks: Ansiven (Abbott); Diprivan (Zeneca); Disoprivan (Zeneca); Rapinovet (Mallinckrodt) Molecular Formula: $C_{12}H_{18}O$ Molecular Weight: 178.27.

Percent Composition: C 80.85%, H 10.18%, O 8.97%

Literature References: Prepn: A. J. Kolka et al., J. Org. Chem. 21, 712 (1956); 22, 642 (1957); G. G. Ecke, A. J. Kolka, US 2831898 (1958 to Ethyl Corp.); T. J. Kealy, D. D. Coffman, J. Org. Chem. 26, 987 (1961); B. E. Firth, T. J. Rosen, US 4447657 (1984 to Universal Oil Products). Chromatographic study: J. K. Carlton, W. C. Bradbury, J. Am. Chem. Soc. 78, 1069 (1956). Animal studies: J. B. Glen, Brit. J. Anaesth. 52, 731 (1980). Pharmacokinetics: H. K. Adam et al., ibid. 743; idem, ibid. 55, 97 (1983). Determn in blood: eidem, J. Chromatog. 223, 232 (1981). Comparative studies vs other injectable anesthetics: B. Kay, D. K. Stephenson, Anaesthesia 35, 1182 (1980); D. V. Rutter et al., ibid. 1188. Use in i.v. anesthesia: E. Major et al., ibid. 37, 541 (1982). Cardiovascular effects: D. Al-Khudhairi et al., ibid. 1007. Pharmacology of emulsion formulation: J. B. Glen, S. C. Hunter, Brit. J. Anaesth. 56, 617 (1984). Series of articles on pharmacology and clinical experience: Postgrad. Med. J. 61, Suppl. 3, 1-169 (1985).

Properties: $bp_{30}$ 136°. $bp_{17}$ 126°. mp 19°. nD20 1.5134. nD25 1.5111. $d_{20}$ 0.955.

Melting point: mp 19° Boiling point: $bp_{30}$ 136°; $bp_{17}$ 126° Index of refraction: nD20 1.5134; nD25 1.5111 Density: $d_{20}$ 0.955 Therap-Cat: Anesthetic (intravenous).

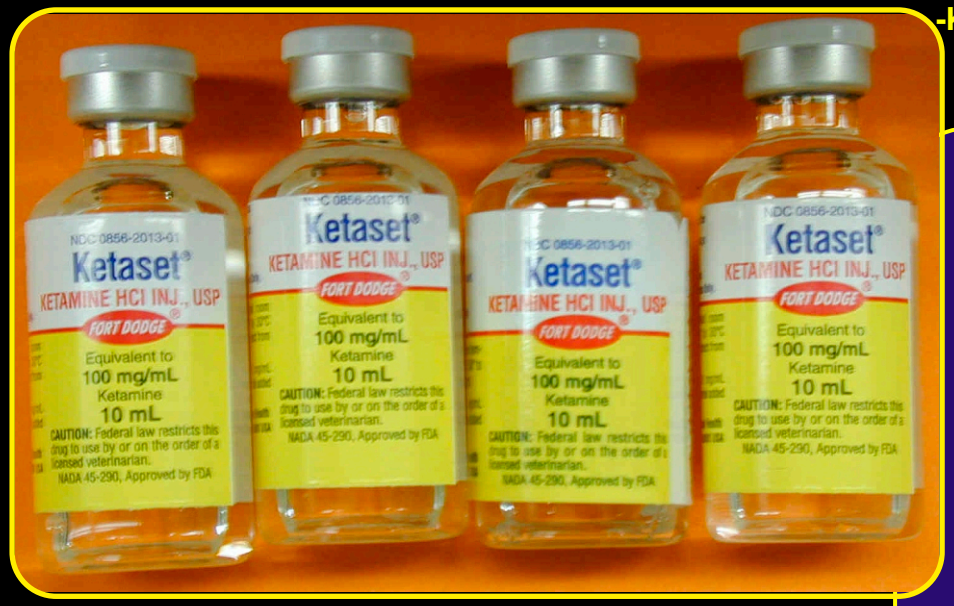
Therap-Cat-Vet: Intravenous anesthetic (dogs and cats).

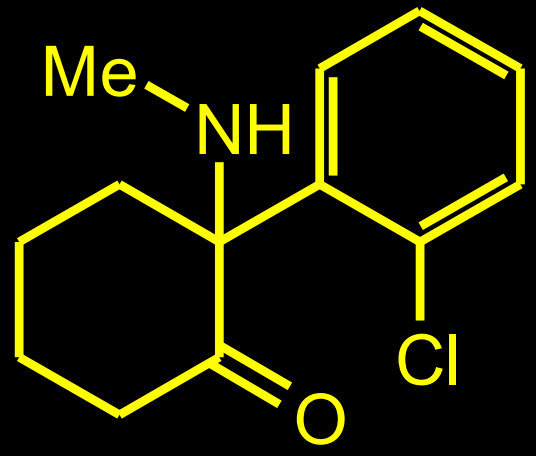
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

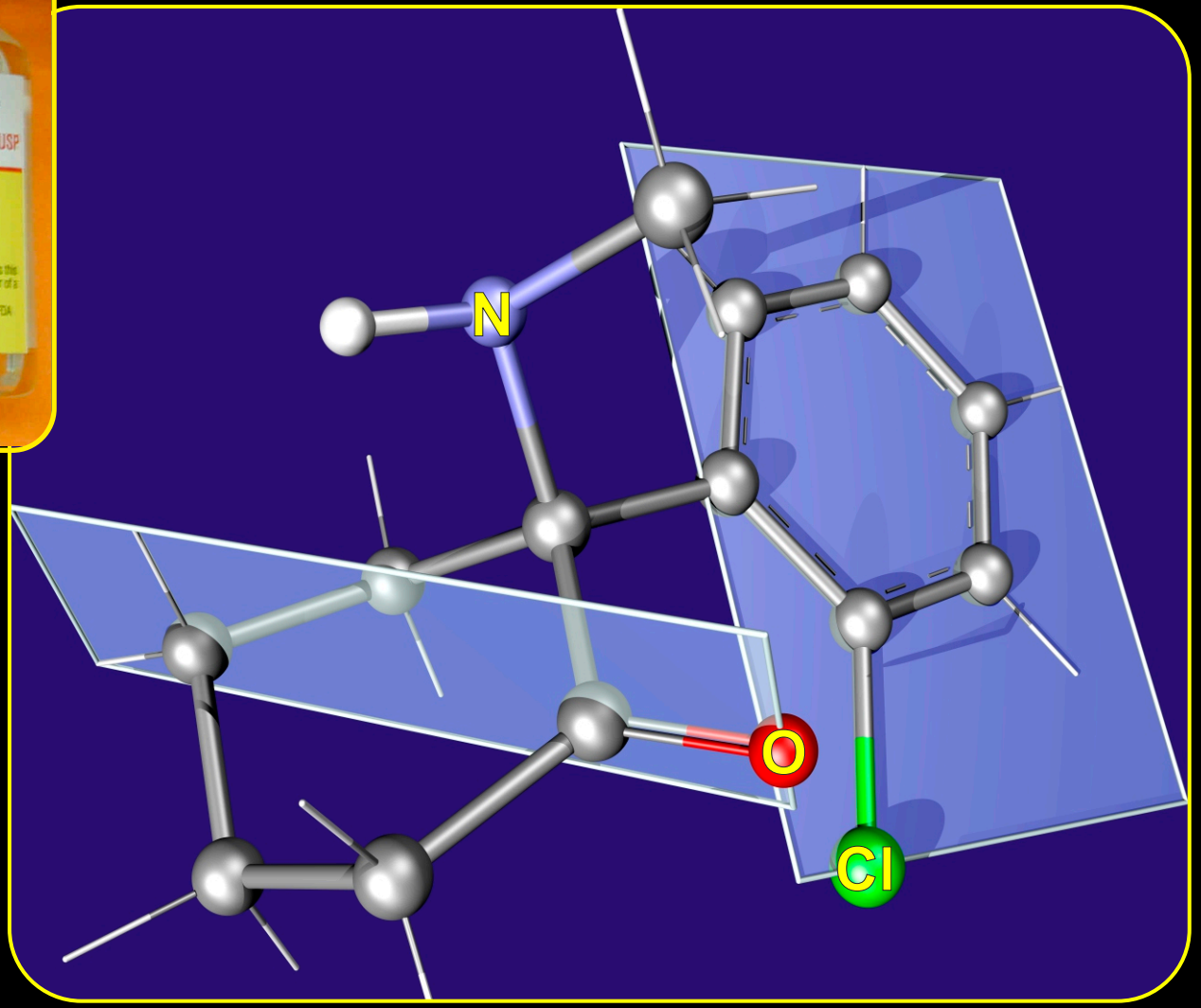
## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

-KETAMINE (KETAMIN)



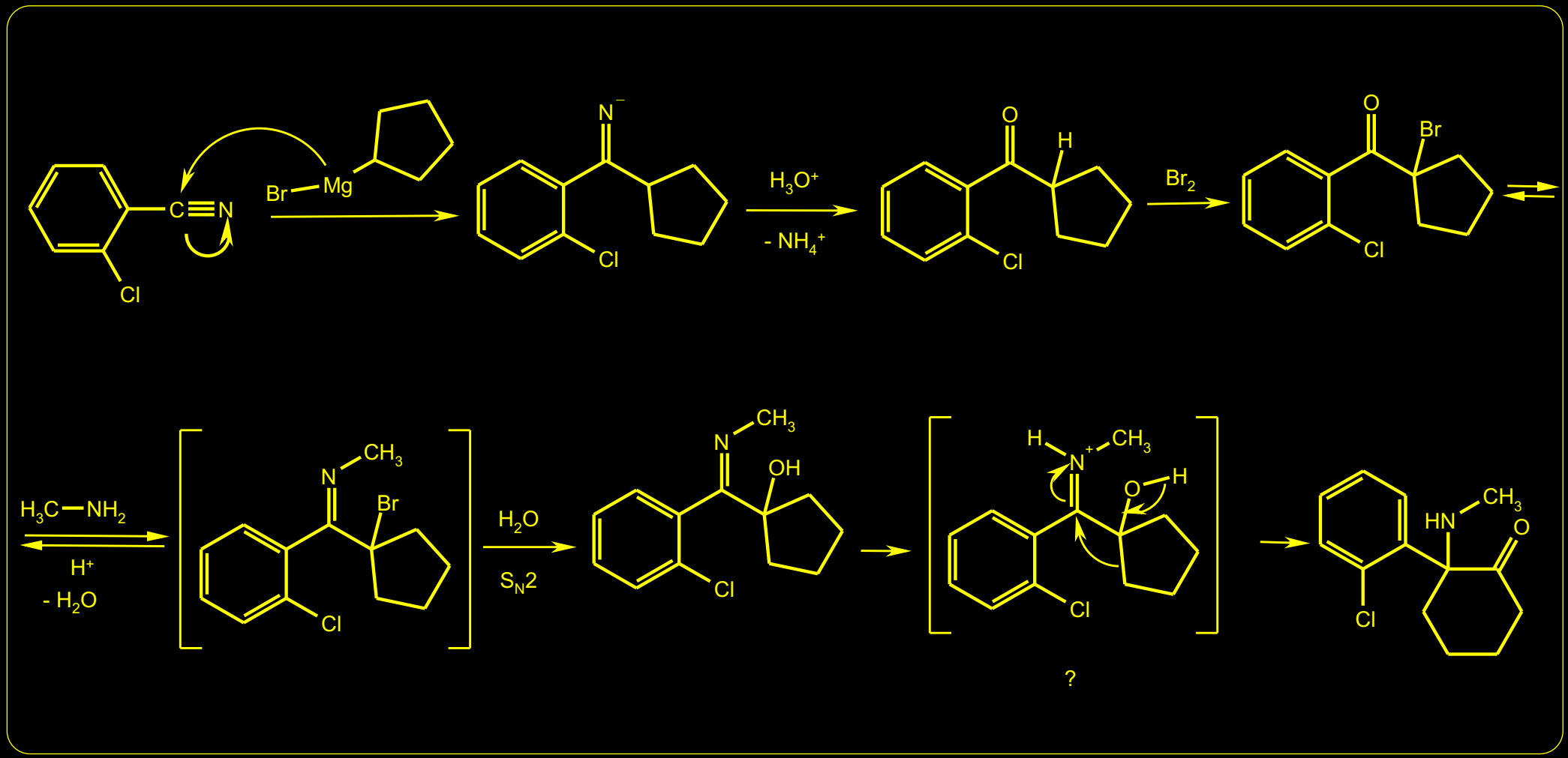



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

### -KETAMINE (KETAMIN)



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

**THE MERCK INDEX** Monograph Number: 5312 Title: Ketamine CAS Registry Number: 6740-88-1
CAS Name: 2-(2-Chlorophenyl)-2-(methylamino)cyclohexanone
Molecular Formula: C13H16ClNO Molecular Weight: 237.73. Percent Composition: C 65.68%, H 6.78%, Cl 14.91%, N 5.89%, O 6.73%
Literature References: Prepn: C. L. Stevens, BE 634208; idem, US 3254124 (1963, 1966 both to Parke, Davis). Isoln of optical isomers: T. W. Hudyma et al., DE 2062620 (1971 to Bristol-Myers), C.A. 75, 118119x (1971). Clinical pharmacology of racemate and enantiomers: P. F. White et al., Anesthesiology 52, 231 (1980). Toxicity: E. J. Goldenthal, Toxicol. Appl. Pharmacol. 18, 185 (1971). Enantioselective HPLC determn in plasma: G. Geisslinger et al., J. Chromatog. 568, 165 (1991). Comprehensive description: W. C. Sass, S. A. Fusari, Anal. Profiles Drug Subs. 6, 297-322 (1977). Review of pharmacology and use in veterinary medicine: M. Wright, J. Am. Vet. Med. Assoc. 180, 1462-1471 (1982). Review of pharmacology and clinical experience: D. L. Reich, G. Silvay, Can. J. Anaesth. 36, 186-197 (1989); in pediatric procedures: S. M. Green, N. E. Johnson, Ann. Emerg. Med. 19, 1033-1046 (1990).
Properties: Crystals from pentane-ether, mp 92-93°. uv max (0.01N NaOH in 95% methanol): 301, 276, 268, 261 nm (A1%1cm 5.0, 7.0, 9.8, 10.5). pKa 7.5. pH of 10% aq soln 3.5. Melting point: mp 92-93° pKa: pKa 7.5
Absorption maximum: uv max (0.01N NaOH in 95% methanol): 301, 276, 268, 261 nm (A1%1cm 5.0, 7.0, 9.8, 10.5)

Derivative Type: Hydrochloride CAS Registry Number: 1867-66-9 Manufacturers' Codes: CI-581
Trademarks: Ketaject (Bristol-Myers Squibb); Ketalar (Parke-Davis); Ketanarkon (Streuli); Ketanest (Parke-Davis); Ketaset (Am. Home); Ketavet (Gellini); Vetalar (Am. Home)
Molecular Formula: C13H16ClNO.HCl Molecular Weight: 274.19. Percent Composition: C 56.95%, H 6.25%, Cl 25.86%, N 5.11%, O 5.84% Properties: White crystals, mp 262-263°. Soly in water: 20 g/100 ml. LD50 in adult mice, rats (mg/kg): 224 ±4, 229 ±5 i.p. (Goldenthal). Melting point: mp 262-263° Toxicity data: LD50 in adult mice, rats (mg/kg): 224 ±4, 229 ±5 i.p. (Goldenthal)

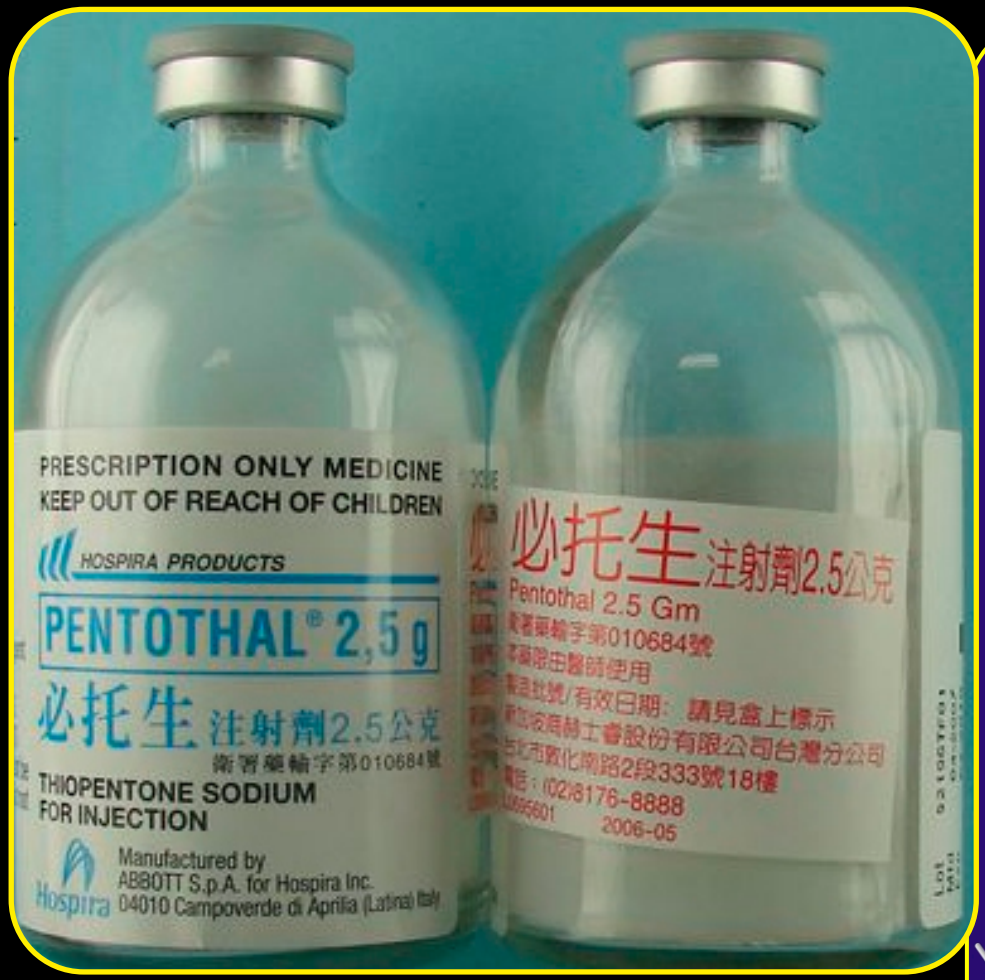
NOTE: This is a controlled substance (depressant): 21 CFR, 1308.13.
Therap-Cat: Anesthetic (intravenous).
Therap-Cat-Vet: Anesthetic (intravenous).

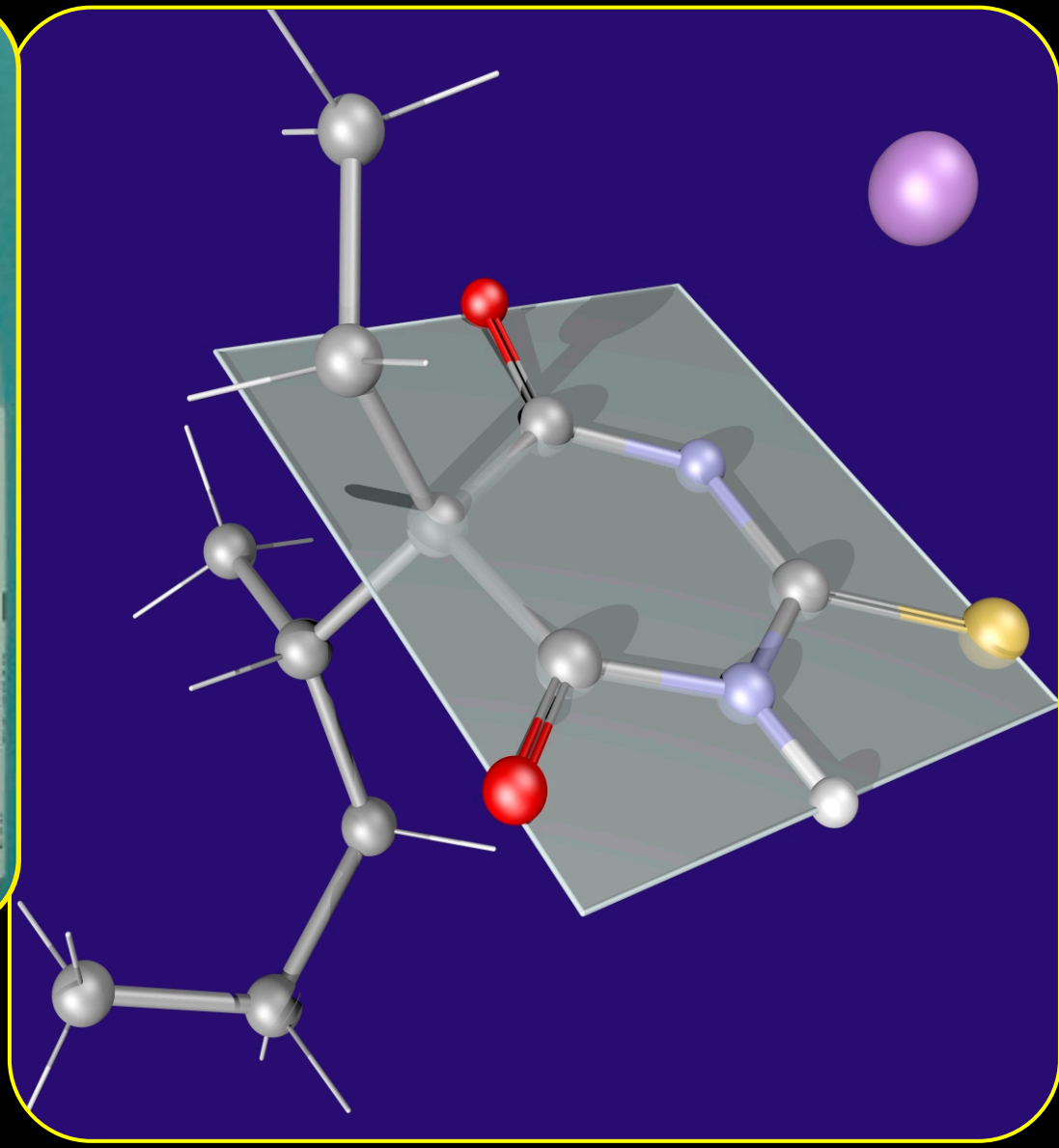
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

THIOPENTAL SODIUM(TIOPENTAL NATRIJUMOVA SO)



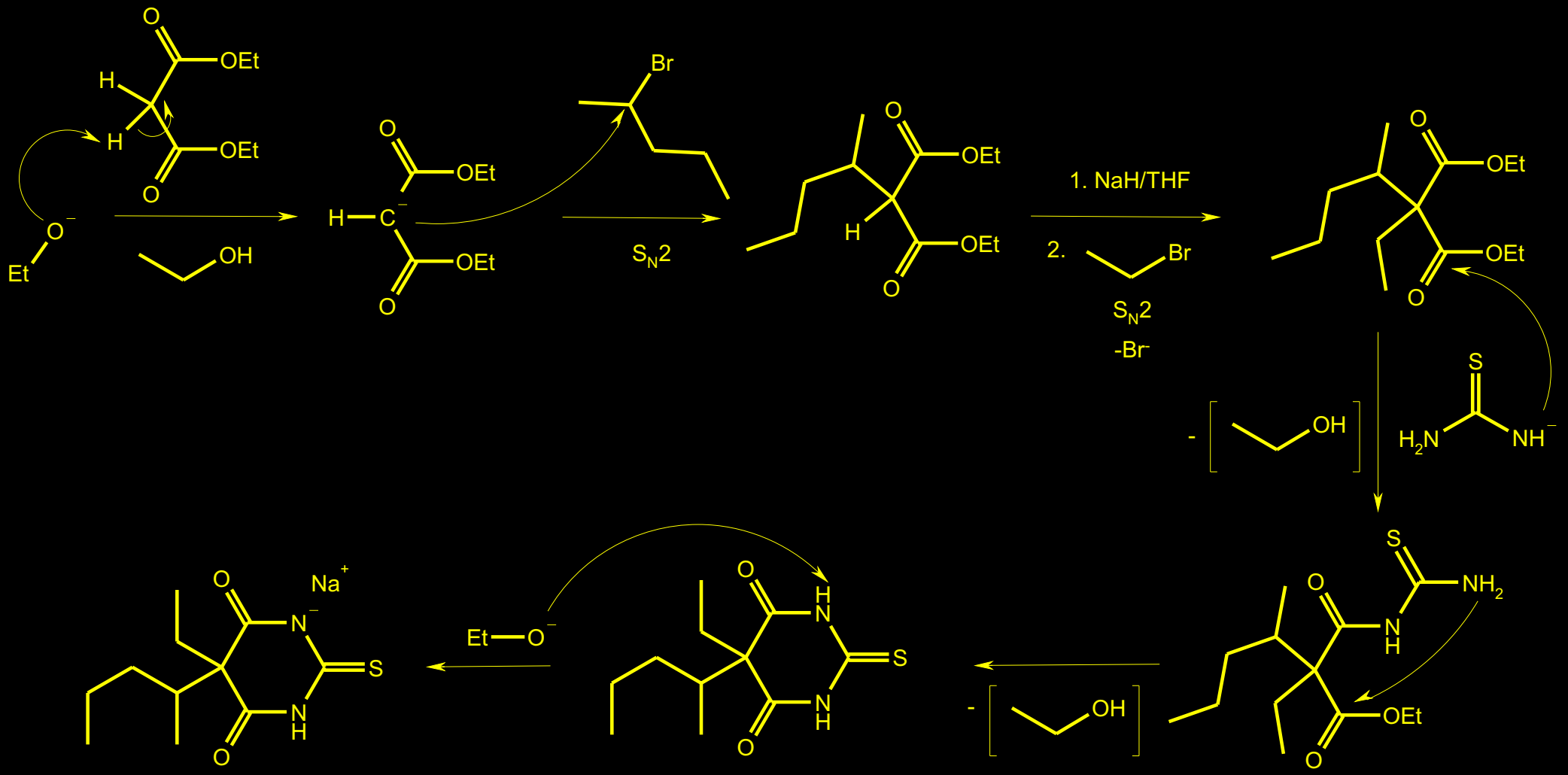



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

THIOPENTAL SODIUM(TIOPENTAL NATRIJUMOVA SO)



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

**THE MERCK INDEX** Monograph Number: 9425 Title: Thiopental Sodium CAS Registry Number: 71-73-8

CAS Name: 5-Ethyldihydro-5-(1-methylbutyl)-2-thioxo-4,6(1H,5H)-pyrimidinedione monosodium salt

Additional Names: 5-ethyl-5-(1-methylbutyl)-2-thiobarbituric acid sodium salt; thiomebumal sodium; penthiobarbital sodium; thiopentone sodium; thionembutal

Trademarks: Intraval Sodium (RPR); Nesdonal Sodium (RPR); Pentothal Sodium (Abbott); Trapanal (Byk-Gulden)

Molecular Formula: $C_{11}H_{17}N_2NaO_2S$ Molecular Weight: 264.32.

Percent Composition: C 49.99%, H 6.48%, N 10.60%, Na 8.70%, O 12.11%, S 12.13%

Literature References: Prepn: US 2153729 (1939); US 2876225 (1959). Prepn of nonhygroscopic crystals: Hartop, US 3109001 (1963 to Abbott). Acute toxicity: Christensen, Lee, Toxicol. Appl. Pharmacol. 26, 495 (1973). Comprehensive description: M. J. McLeish, Anal. Profiles Drug Subs. Excip. 21, 535-572 (1992).

Properties: Yellowish-white, hygroscopic powder. Alliaceous, garlic-like odor. Sol in water, alcohol. Insol in ether, benzene, petr ether. Aq solns are alkaline to litmus. Solns dec on standing; on boiling precipitation occurs. LD50 in mice (mg/kg): 149 i.p.; 78 i.v. (Christensen, Lee).

Toxicity data: LD50 in mice (mg/kg): 149 i.p.; 78 i.v. (Christensen, Lee)

CAUTION: May be habit forming: 21 CFR, 329.1 and is a controlled substance (depressant): 21 CFR, 1308.13.

Therap-Cat: Anesthetic (intravenous).

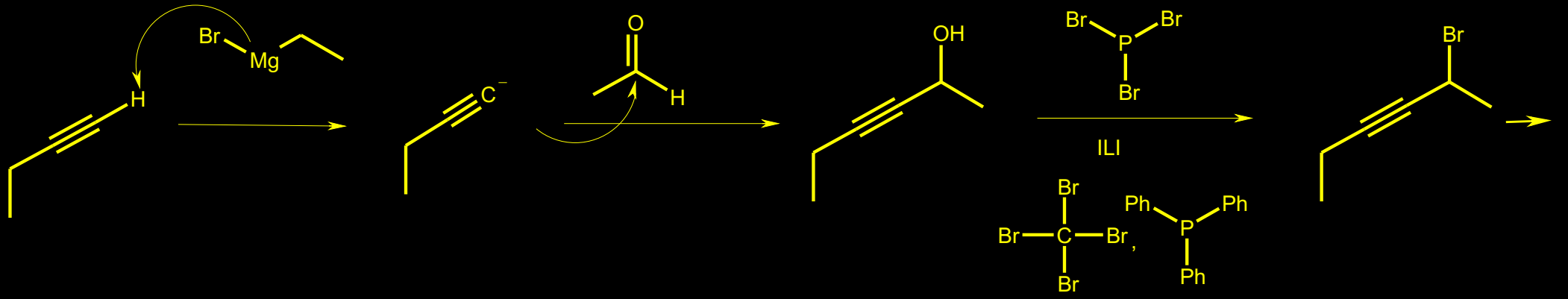
Therap-Cat-Vet: Short-acting anesthetic.

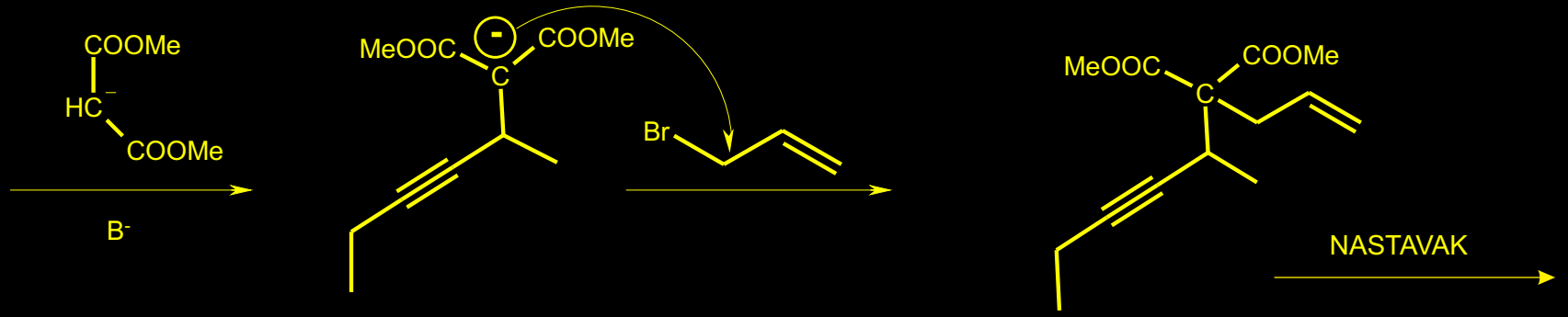
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

METHOHEXITAL (METOHEKSITAL)



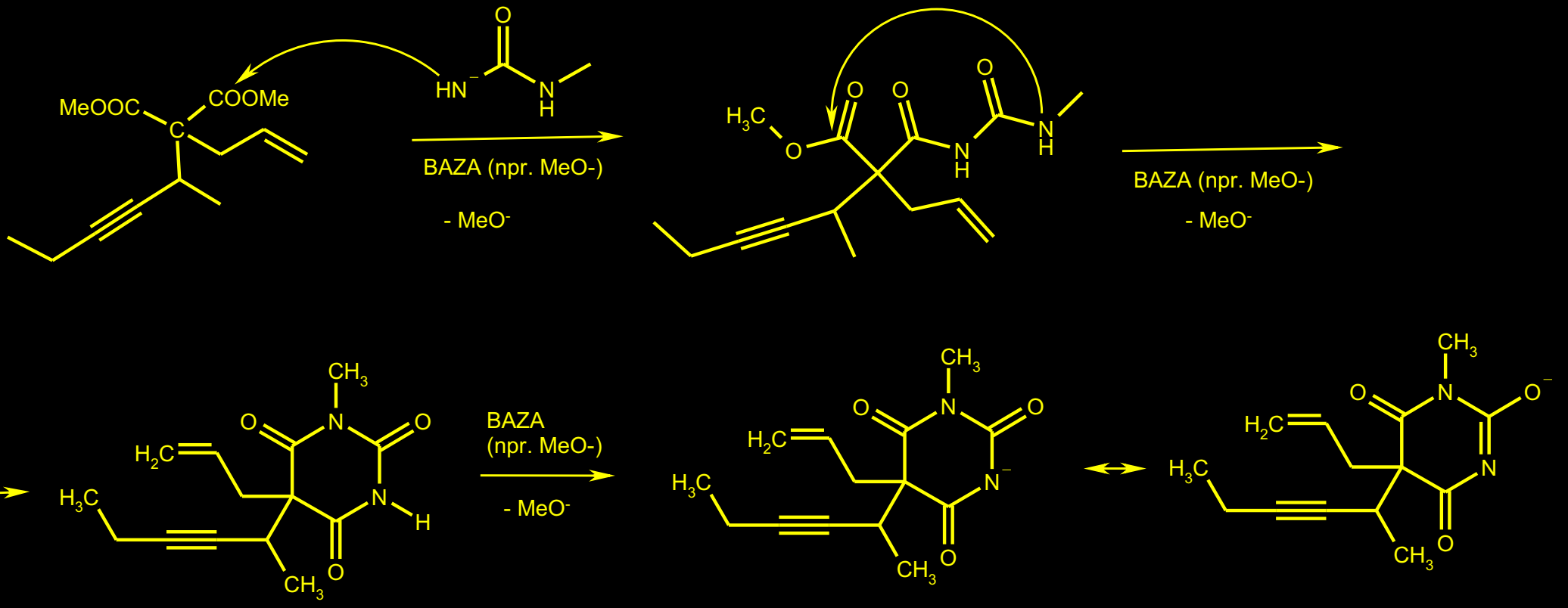



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

METHOHEXITAL (METOHEKSITAL) - NASTAVAK



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 1. OPŠTI ANESTETICI

### 1.2 ANESTETICI U OBLIKU INJEKCIJA (INTRAVENOZNI I DR.)

**Monograph Number: 6011 Title: Methohexital Sodium CAS Registry Number: 22151-68-4**

**CAS Name: 1-Methyl-5-(1-methyl-2-pentynyl)-5-(2-propenyl)-2,4,6(1H,3H,5H)-pyrimidinetrione sodium salt**
**Additional Names:**
**5-allyl-1-methyl-5-(1-methyl-2-pentynyl)barbituric acid sodium salt; α-dl-1-methyl-5-(1-methyl-2-pentynyl)-5-allylbarbituric acid sodium salt; α-dl-1-methyl-5-allyl-5-(1-methyl-2-pentynyl)barbituric acid sodium salt; methohexitone sodium**
**Trademarks: Brevital (Lilly); Brevital Sodium (Lilly); Brevimytal Sodium (Lilly); Brietal Sodium (Lilly)**

**Molecular Formula: $C_{14}H_{17}N_2NaO_3$ Molecular Weight: 284.29.**
**Percent Composition: C 59.15%, H 6.03%, N 9.85%, Na 8.09%, O 16.88%**
**Literature References: Prepn: Doran, US 2872448 (1959 to Lilly).**

**Properties: Minute crystals. Soluble in water.**

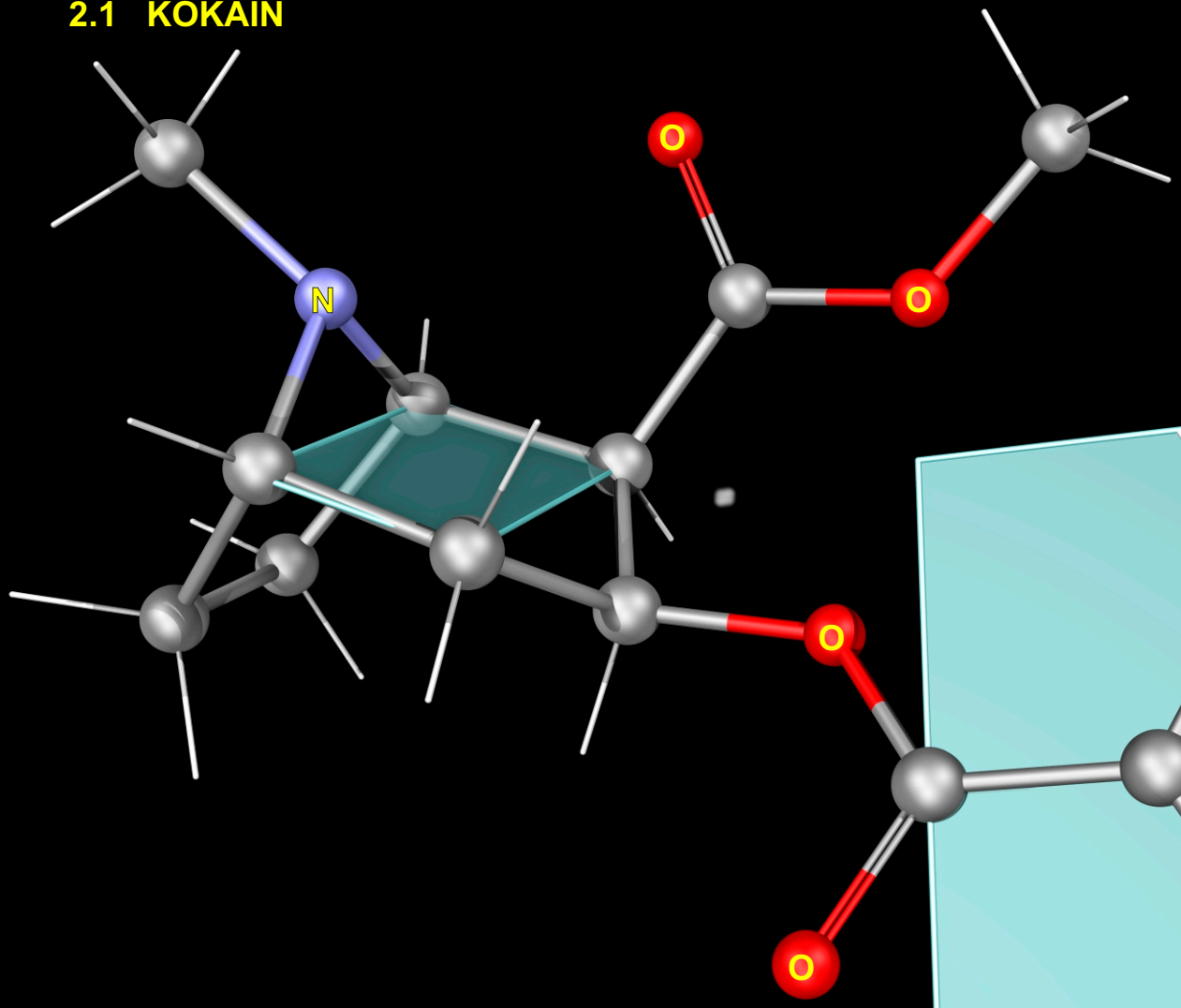
**CAUTION: May be habit forming: 21 CFR, 329.1 and is a controlled substance (depressant): 21 CFR, 1308.14.**

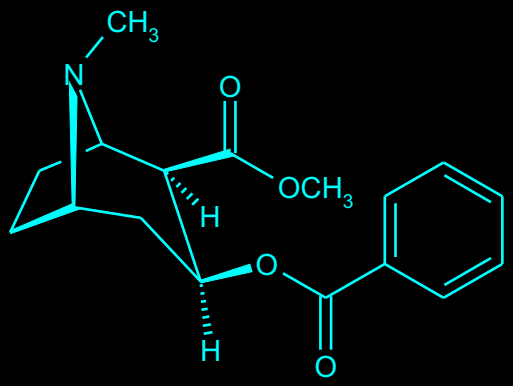
**Therap-Cat: Anesthetic (intravenous).**
**Therap-Cat-Vet: Ultra-short acting anesthetic.**

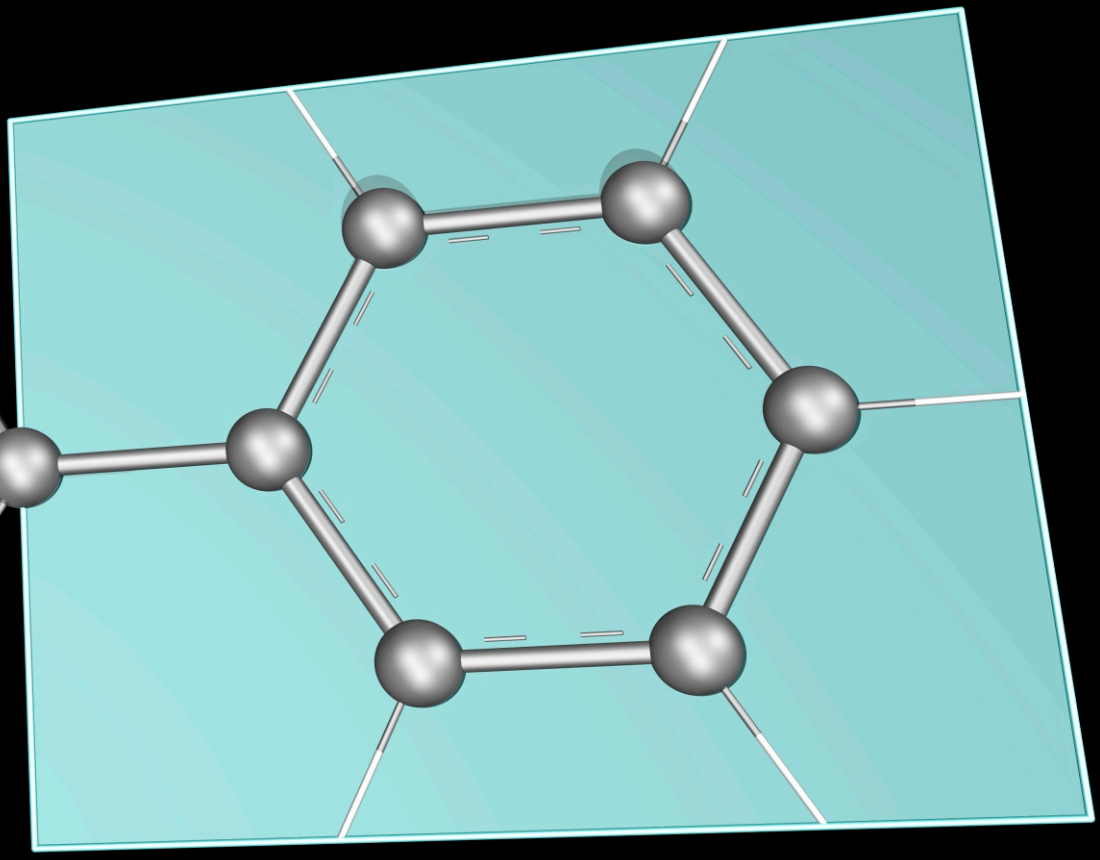
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

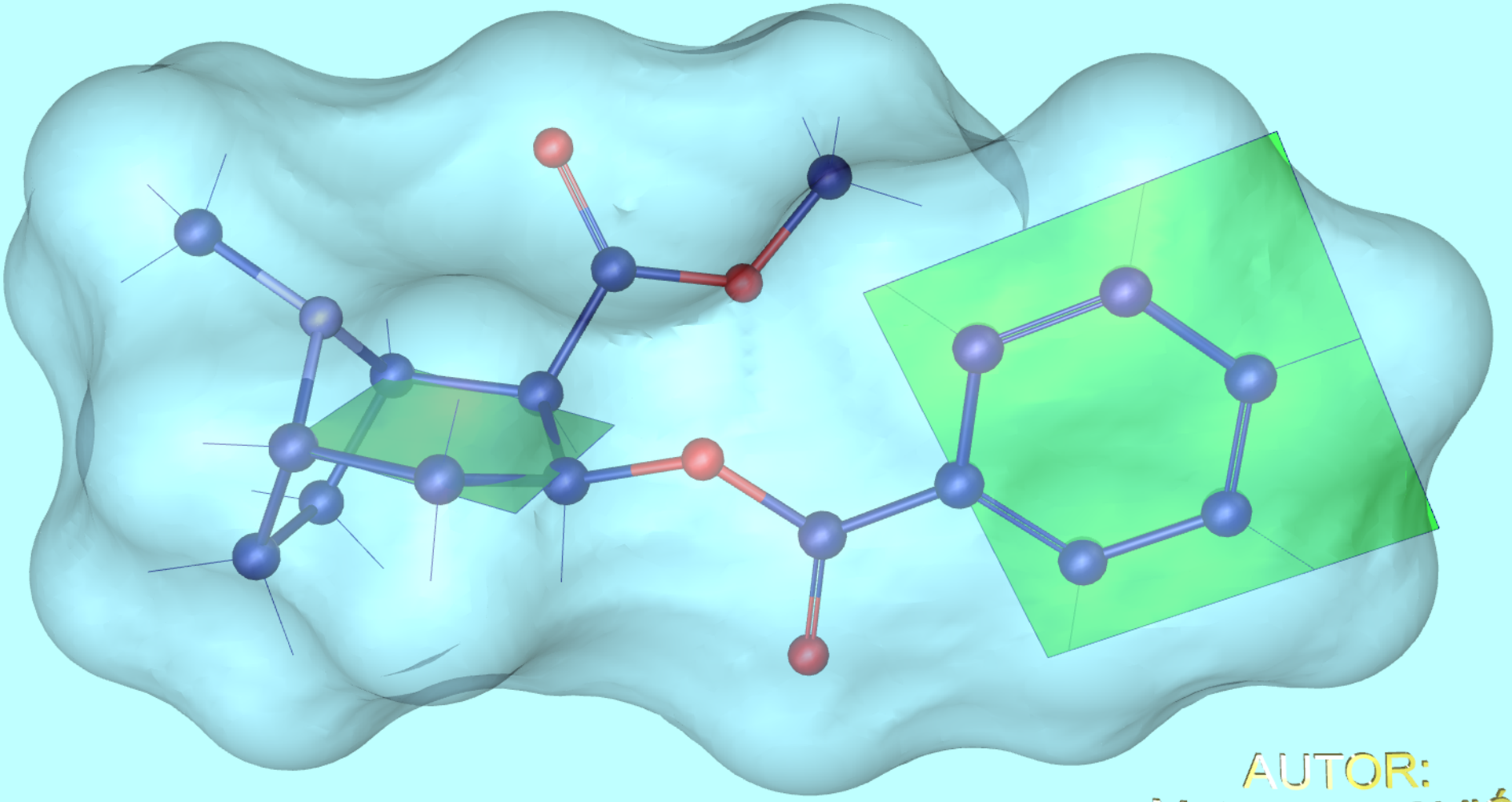
## 2. LOKALNI ANESTETICI

### 2.1 KOKAIN




AUTOR:
M. D. IVANOVIĆ
'09.

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

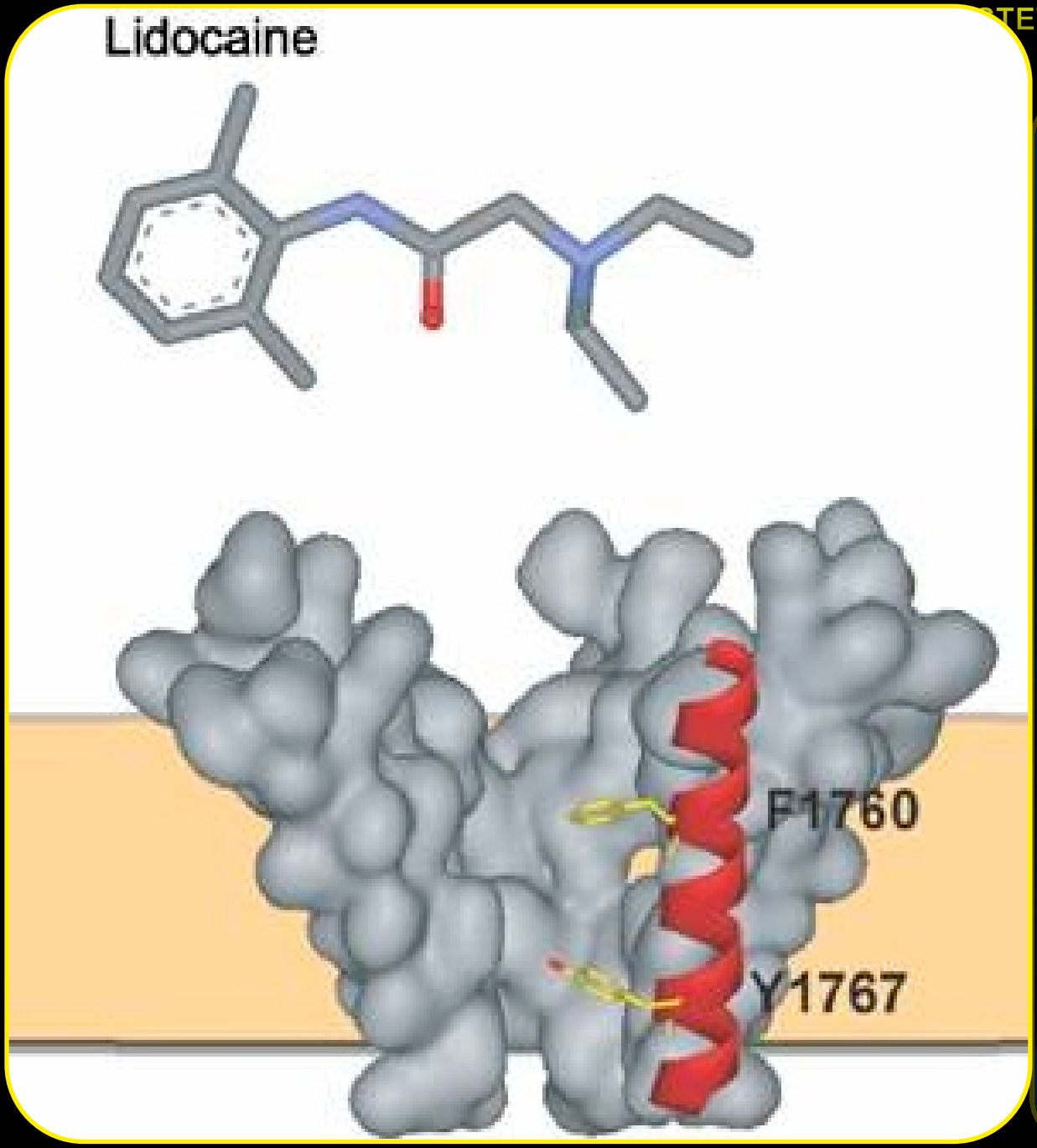
### 2.1 KOKAIN

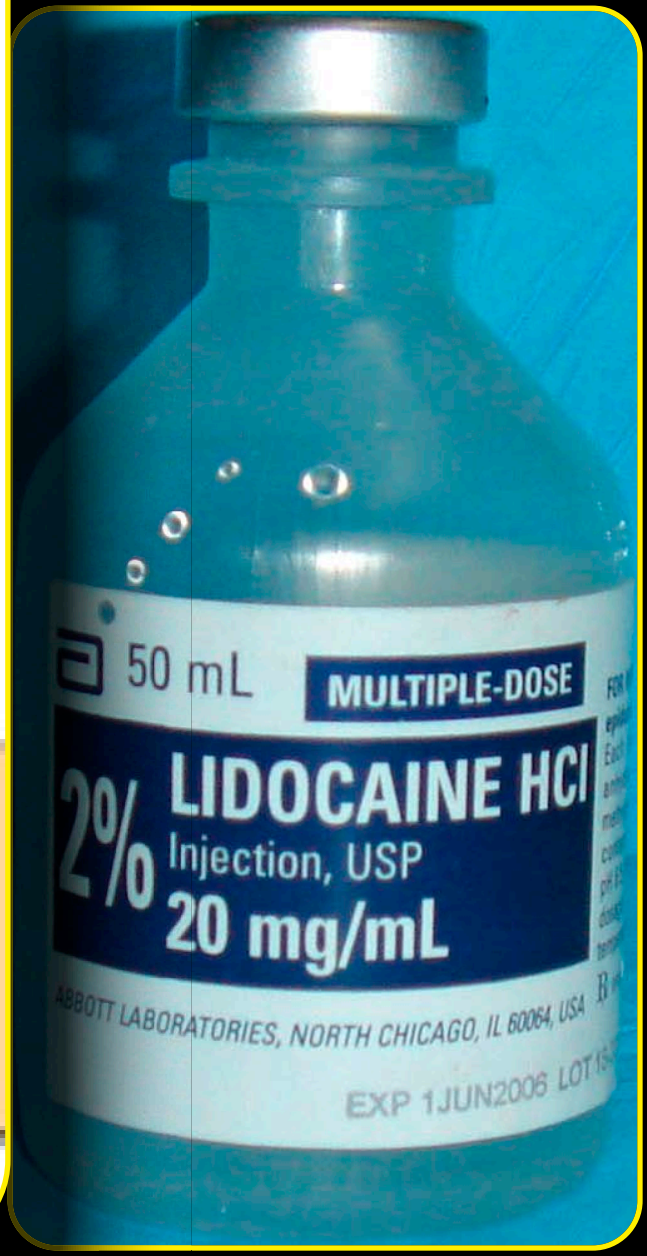
Monograph Number: 2480 Title: Cocaine CAS Registry Number: 50-36-2
CAS Name: [1R-(exo,exo)]-3-(Benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester
Additional Names: l-cocaine; Molecular Formula: $C_{17}H_{21}NO_4$ Molecular Weight: 303.35.
Percent Composition: C 67.31%, H 6.98%, N 4.62%, O 21.10%
Literature References: From the leaves of Erythroxylon coca Lam. and other species of Erythroxylon, Erythroxylaceae or by synthesis. Extraction procedure: Squibb, Pharm. J. [3] 15, 775, 796; 16, 67 (1885); Emde in Ullmann's Enzyklopädie der Technischen Chemie; Schwyzer, Die Fabrikation pharmazeutischer und chemisch-technischer Produkte (Berlin, 1931). Configuration: Findlay, J. Am. Chem. Soc. 76, 2855 (1954); O. Kovacs et al., Helv. Chim. Acta 37, 892 (1954). Synthesis: R. Willstätter et al., Ann. 434, 111 (1923). Stereospecific synthesis of dl-form: J. J. Tufariello et al., Tetrahedron Letters 1978, 1733; eidem, J. Am. Chem. Soc. 101, 2435 (1979). Biosynthesis: E. Leete, S. H. Kim, J. Am. Chem. Soc. 110, 2976 (1988). Absorption spectrum: J. J. Dobbie, J. J. Fox, J. Chem. Soc. 103, 1193 (1913); Fischer, Arch. Exp. Pathol. Pharmakol. 170, 610 (1933). Toxicity: C. L. Rose et al., J. Lab. Clin. Med. 15, 731 (1930). Vapor pressure studies: A. H. Lawrence et al., Can. J. Chem. 62, 1886 (1984). Comprehensive description: F. J. Muhtadi, A. A. Al-Badr, Anal. Profiles Drug Subs. 15, 151-231 (1986).
Properties: Monoclinic tablets from alcohol, mp 98°. Volatile, esp above 90°, but the sublimate is not crystalline. bp0.1 187-188°. $[\alpha]_D^{18}$ -35° (50% alcohol); $[\alpha]_D^{20}$ -16° (c = 4 in chloroform). Aq solns are alkaline to litmus. pKa (15°) 8.61. pKb (15°) 5.59. One gram dissolves in 600 ml water, 270 ml water at 80°, 6.5 ml alcohol, 0.7 ml chloroform, 3.5 ml ether, 12 ml oil turpentine, 12 ml olive oil, 30-50 ml liquid petrolatum. Also sol in acetone, ethyl acetate, carbon disulfide. LD50 i.v. in rats: 17.5 mg/kg (Rose).
Melting point: mp 98° Boiling point: bp0.1 187-188° pKa: pKa (15°) 8.61; pKb (15°) 5.59
Optical Rotation: $[\alpha]_D^{18}$ -35° (50% alcohol); $[\alpha]_D^{20}$ -16° (c = 4 in chloroform)
Toxicity data: LD50 i.v. in rats: 17.5 mg/kg (Rose)

Derivative Type: Hydrochloride Additional Names: Cocaine muriate Molecular Formula: $C_{17}H_{21}NO_4.HCl$
Molecular Weight: 339.82. Percent Composition: C 60.09%, H 6.53%, N 4.12%, O 18.83%, Cl 10.43%
Properties: Crystals, granules, or powder; saline, slightly bitter taste; numbs tongue and lips. mp ~195°. $[\alpha]_D$ -72° (c = 2 in aq soln pH 4.5). One gram dissolves in 0.4 ml water; 3.2 ml cold, 2 ml hot alcohol; 12.5 ml chloroform. Also sol in glycerol, acetone. Insol in ether or oils. Avoid heat in preparing soln as it decomposes. Preserve in well-closed, light-resistant containers.
Melting point: mp ~195° Optical Rotation: $[\alpha]_D$ -72° (c = 2 in aq soln pH 4.5)
CAUTION: May be habit forming: 21 CFR, 329.1 and is a controlled substance: 21 CFR, 1308.12.
Therap-Cat: Anesthetic (local). Therap-Cat-Vet: Topical anesthetic (ophthalmic).

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

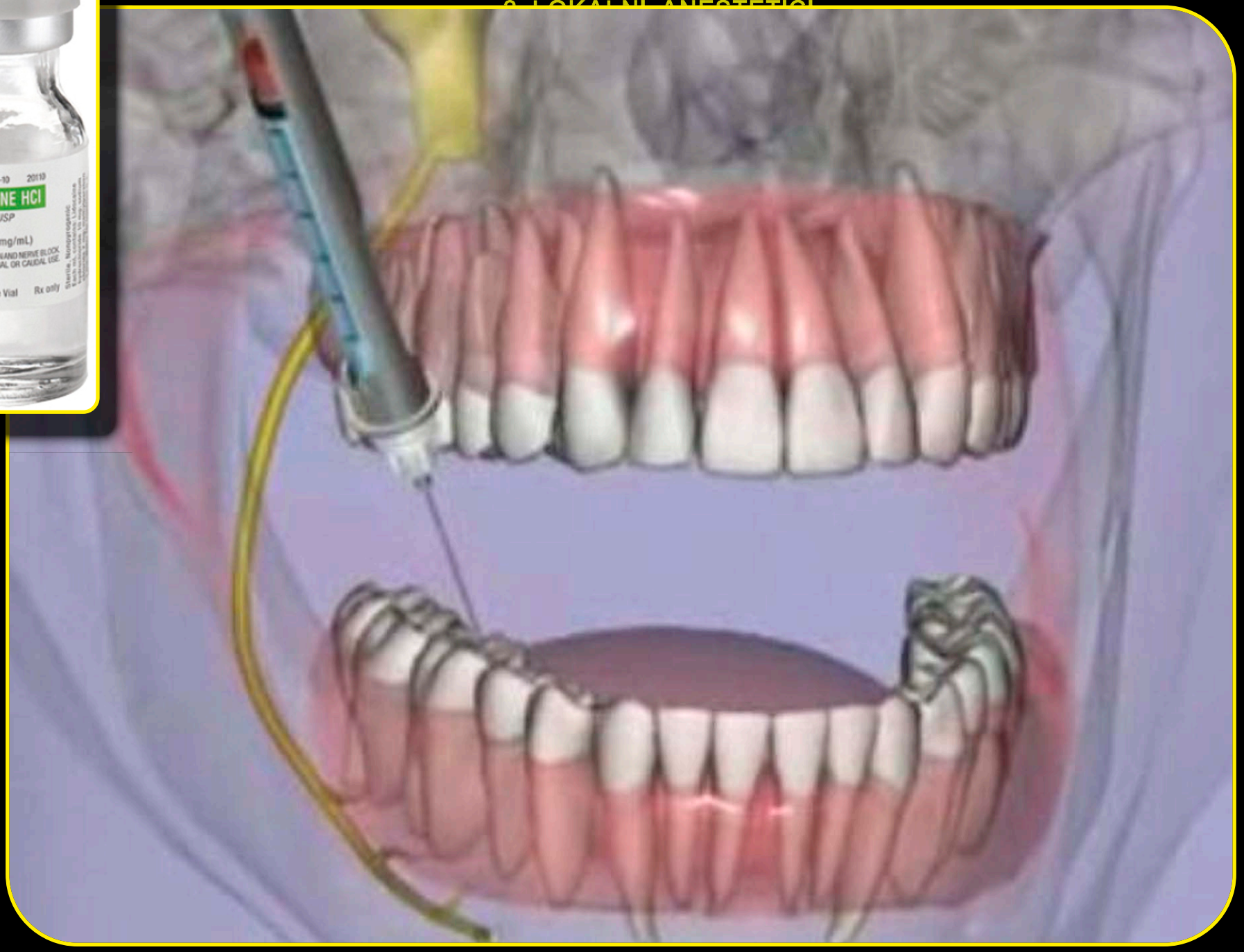
## ...STETICI



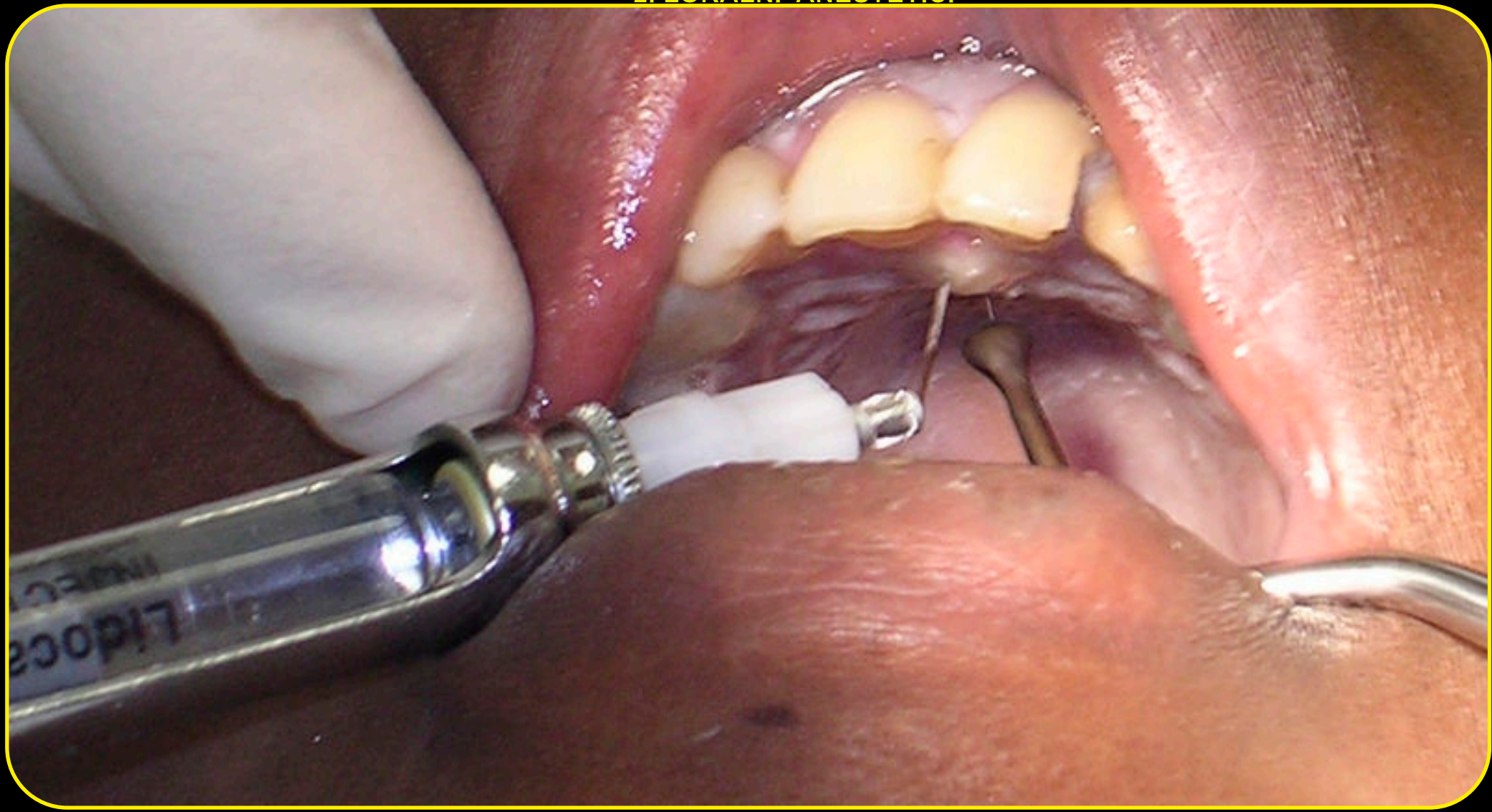
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 8. LOKALNI ANESTETICI

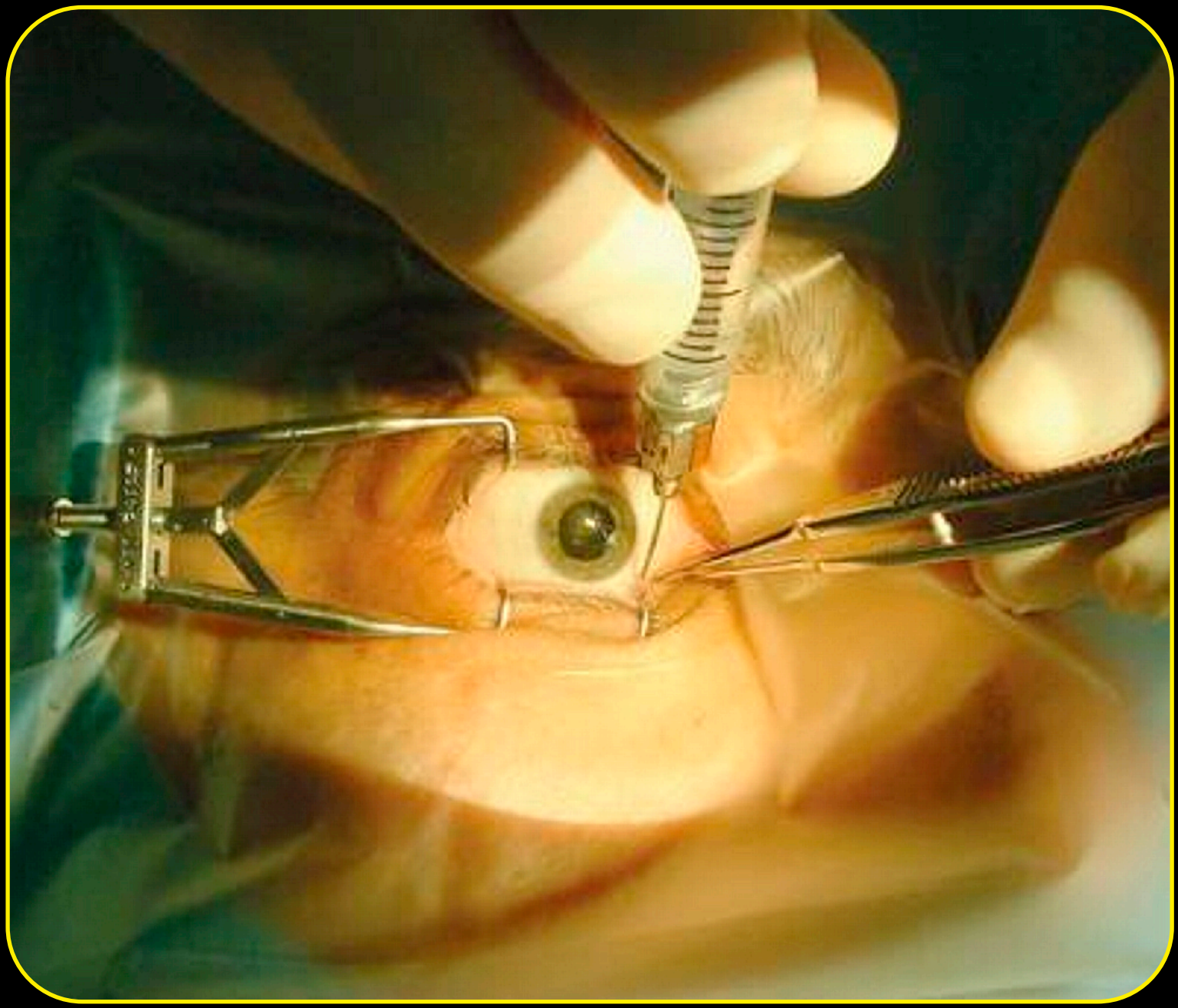
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI



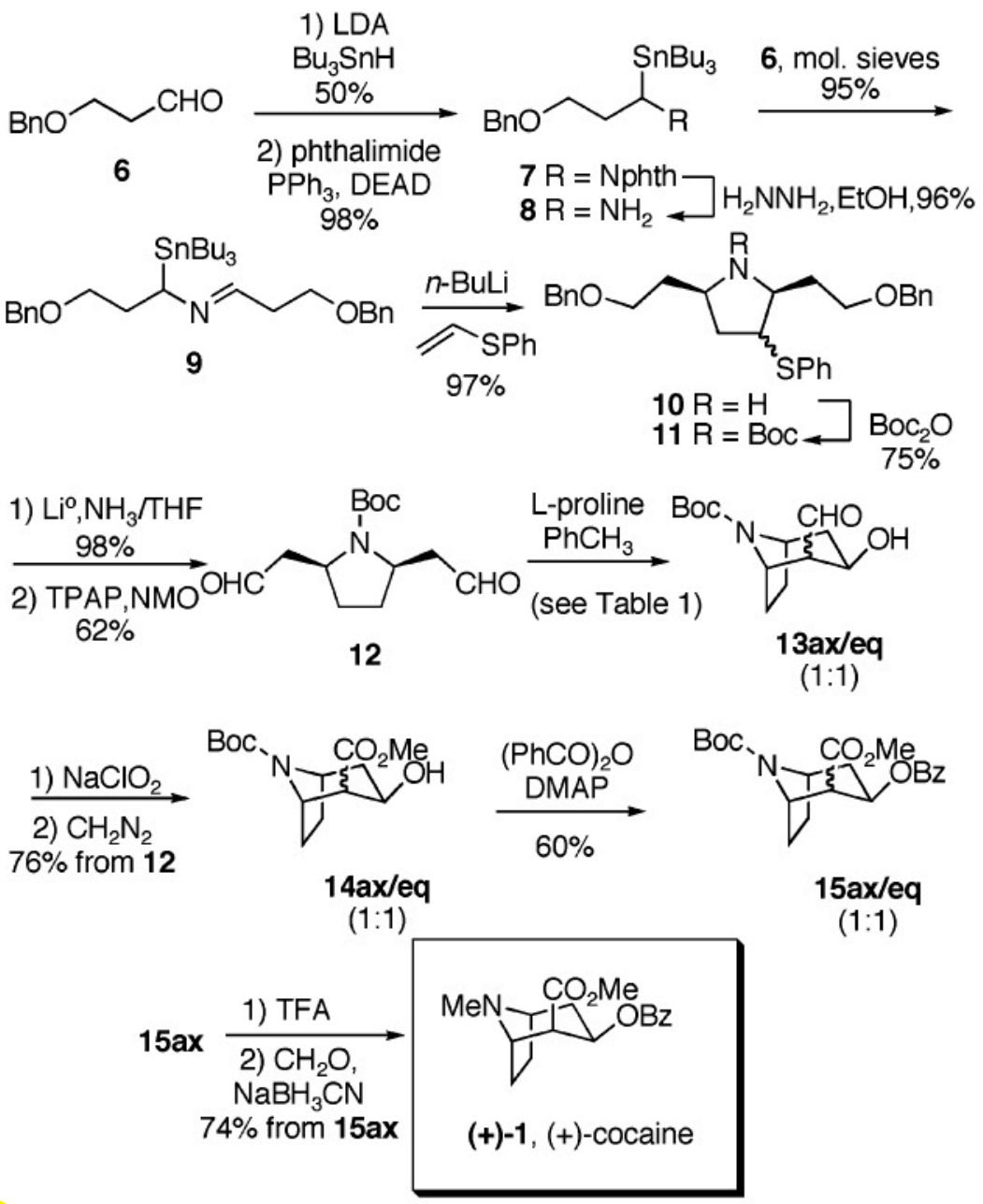
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI



# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NOVIJI PRIMER

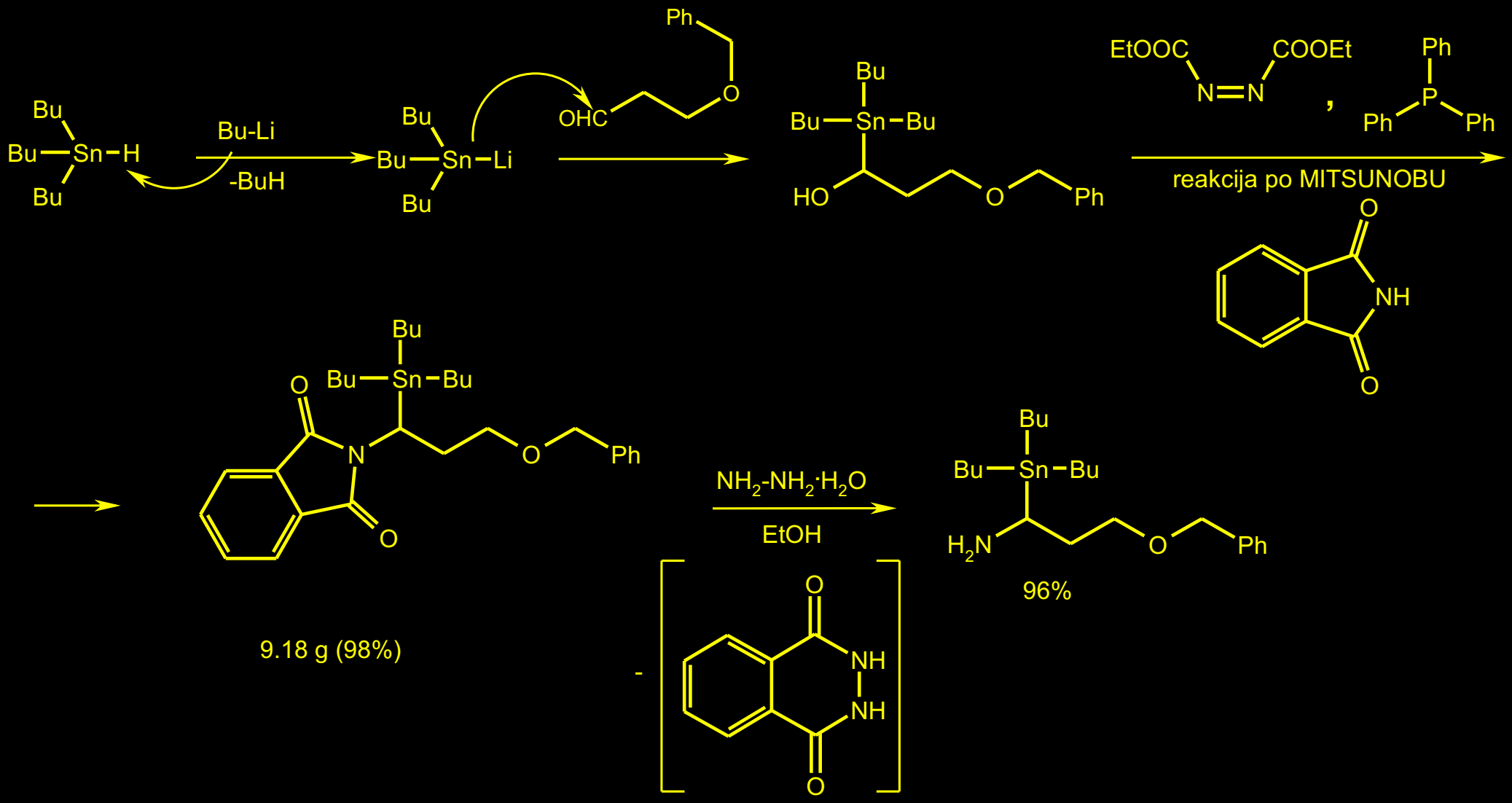
**Scheme 2.** Total Synthesis of (+)-Cocaine



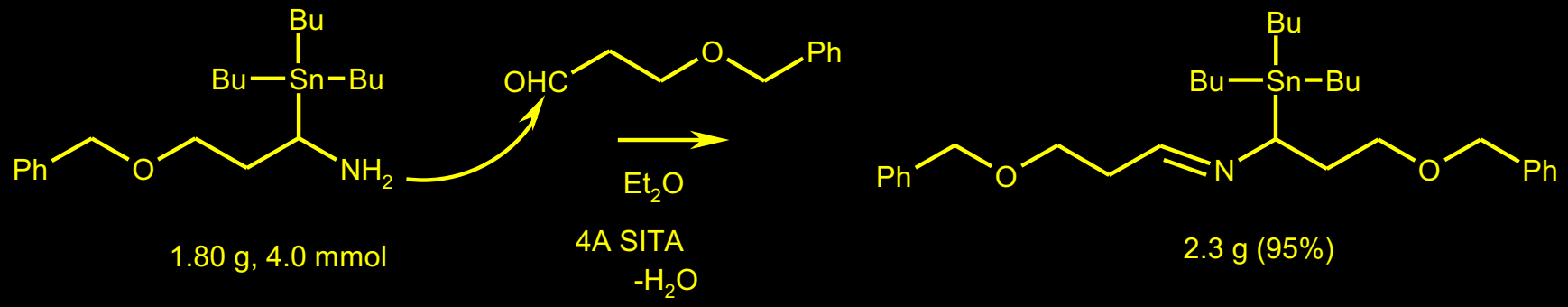

ORGANIC LETTERS 2004 Vol. 6, No. 19
3305-3308
Total Synthesis of (+)-Cocaine via Desymmetrization of a meso-Dialdehyde
Douglas M. Mans and William H. Pearson

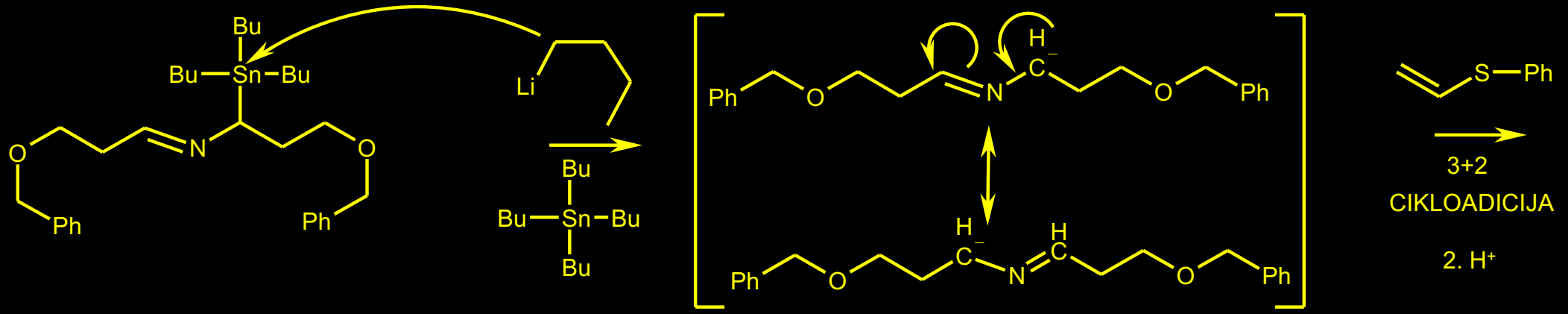
# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NOVIJI PRIMER

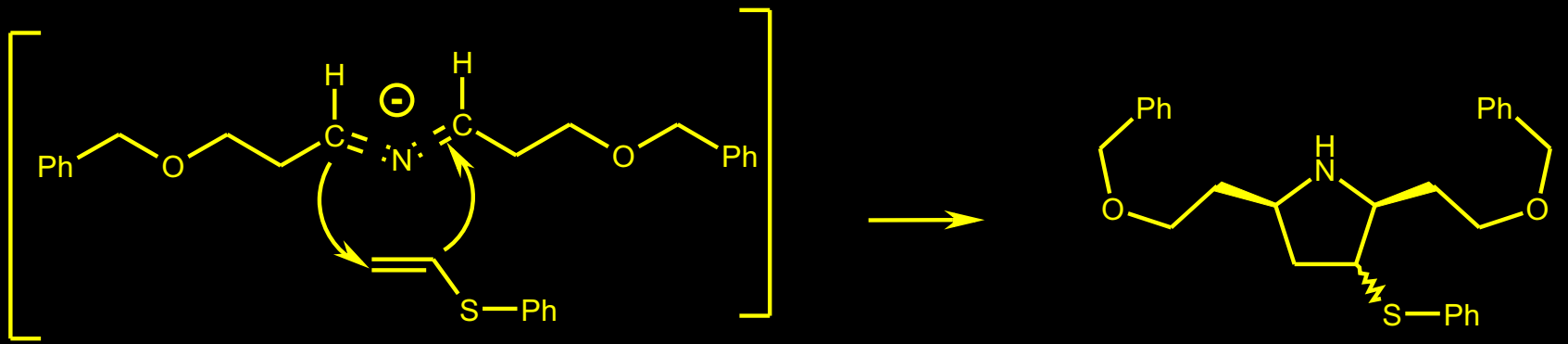
ORGANIC LETTERS 2004 Vol. 6, No. 19 3305-3308
Total Synthesis of (+)-Cocaine via Desymmetrization of a meso-Dialdehyde
Douglas M. Mans and William H. Pearson



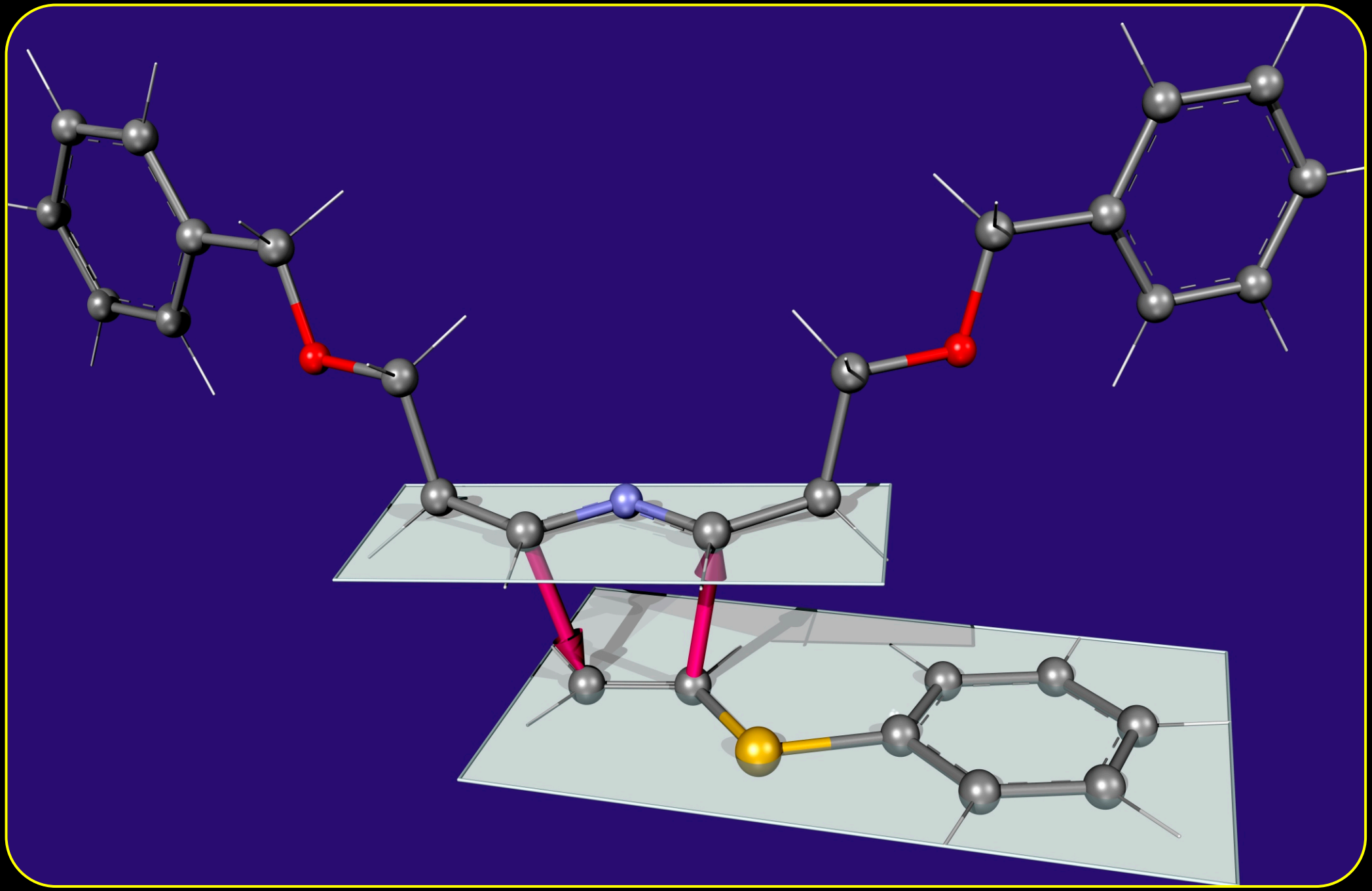
# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NASTAVAK



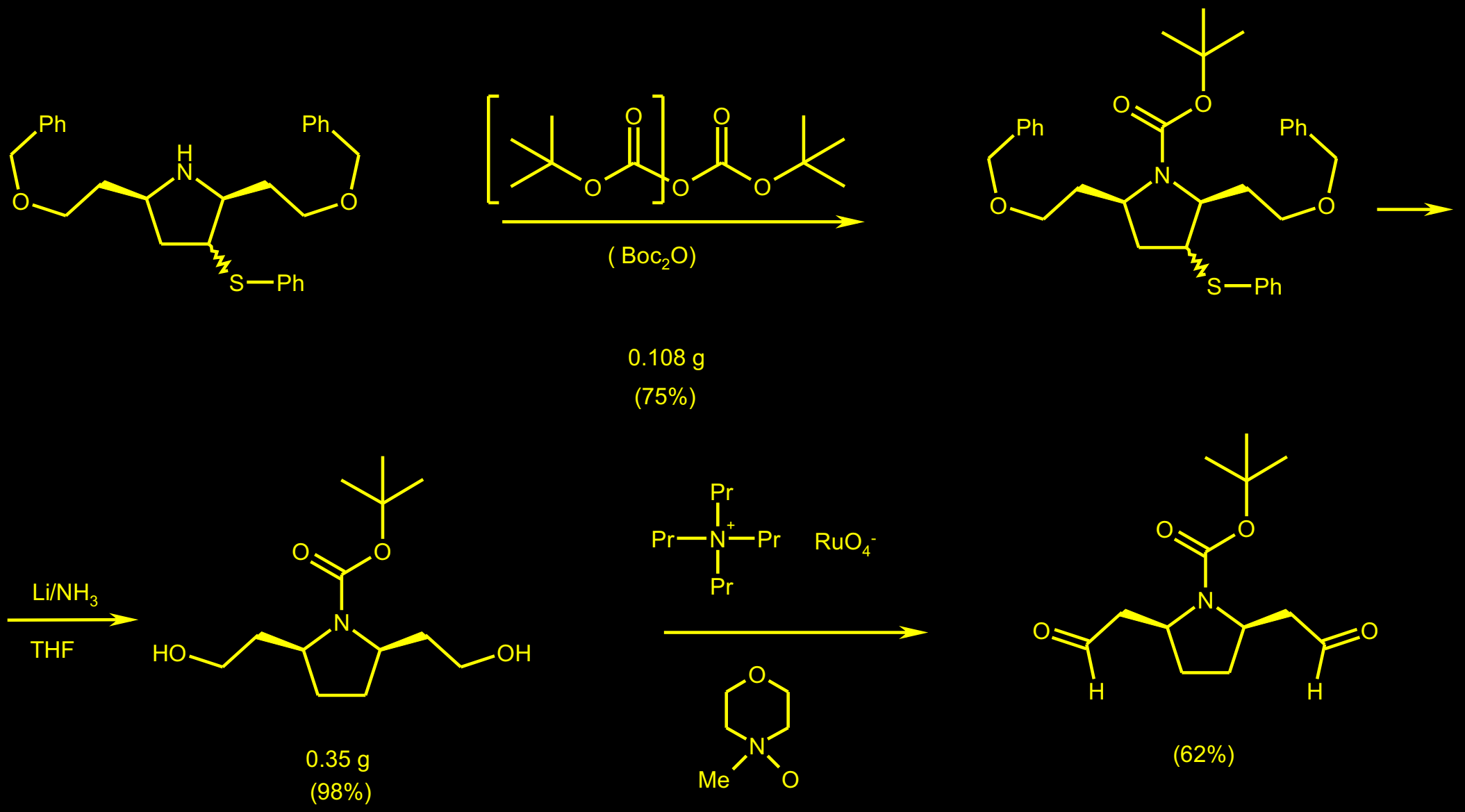



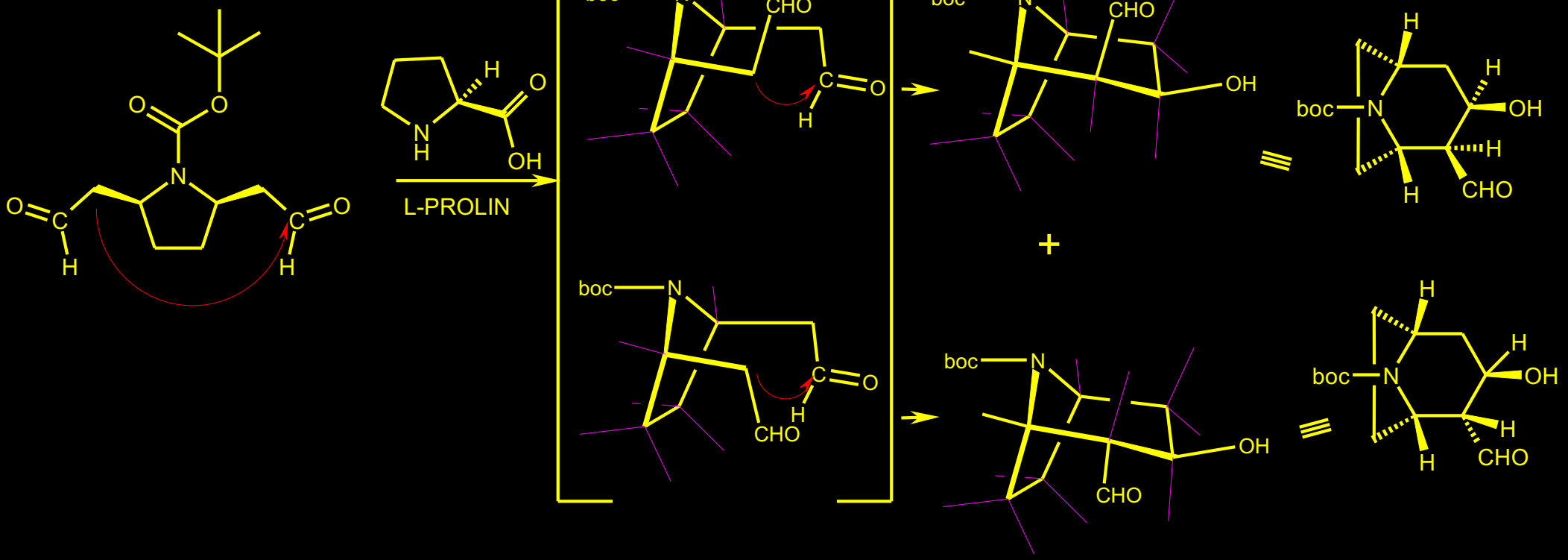
# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NASTAVAK

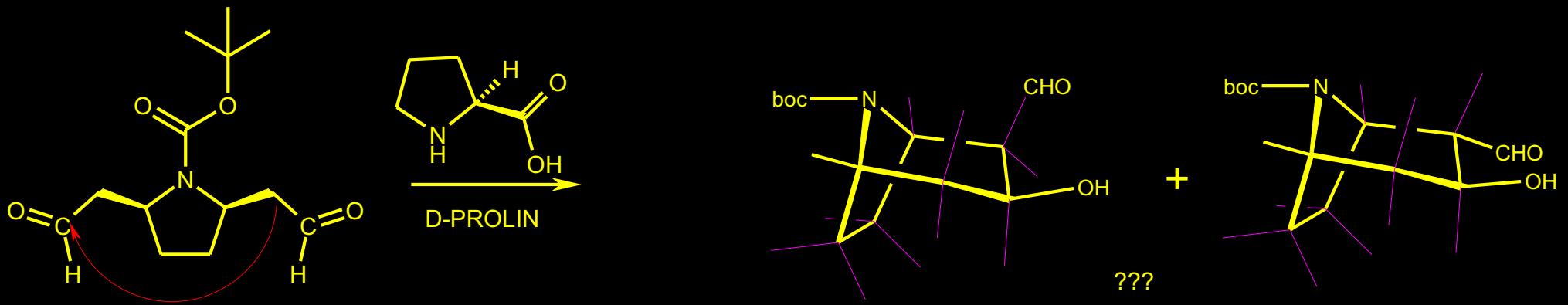


# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NASTAVAK



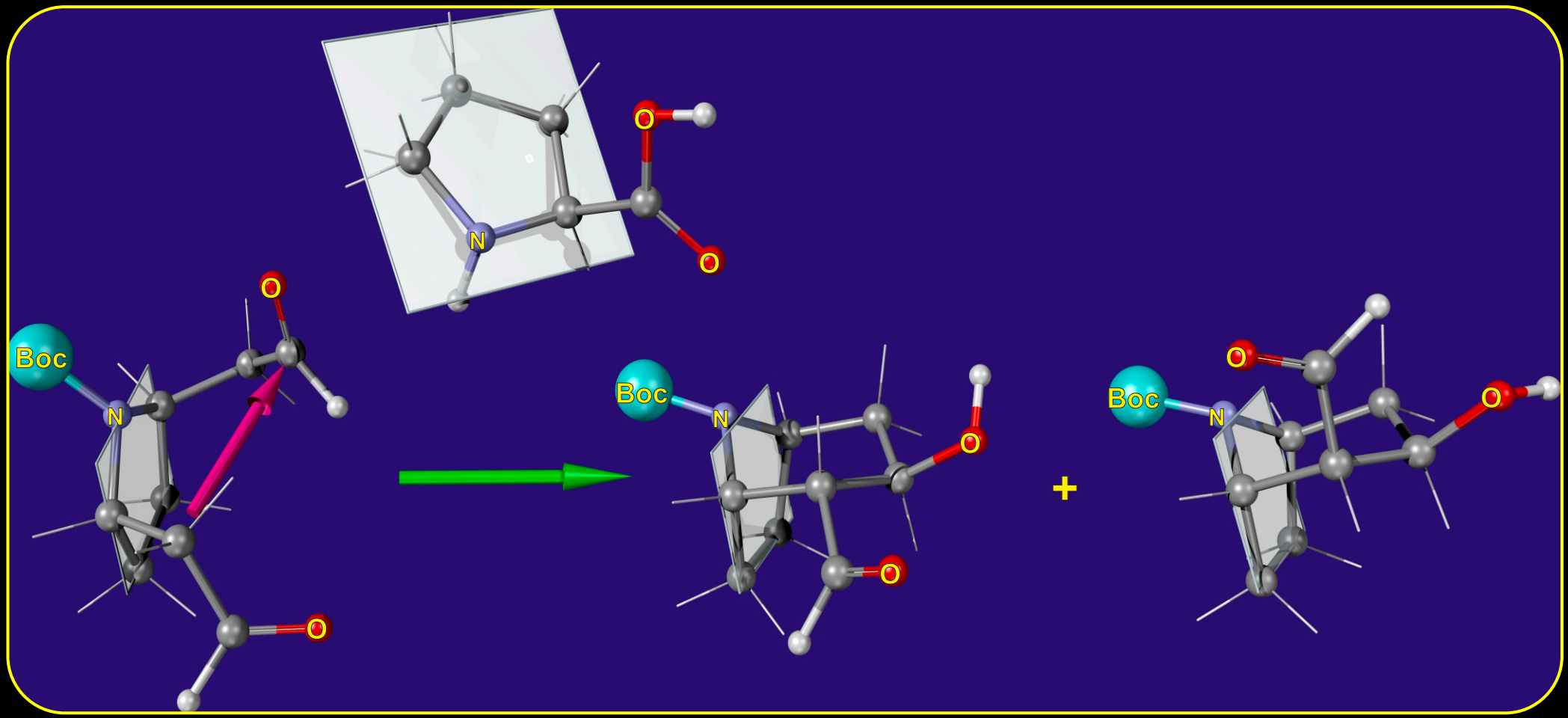
# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NASTAVAK



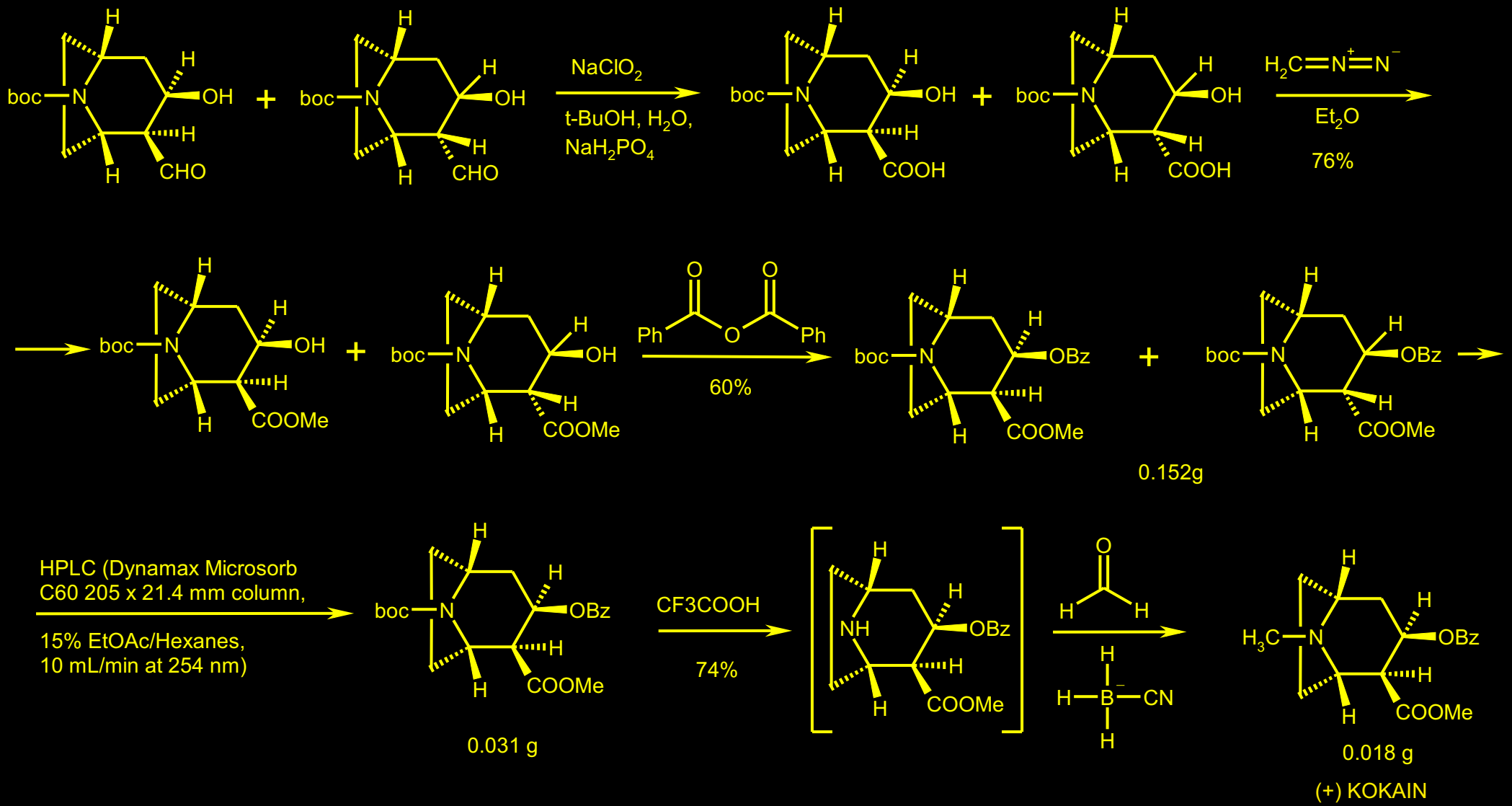



# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NASTAVAK

## SHEMA SA PRETHODNE STRANE, 3D



# TOTALNA SINTEZA (+)KOKAINA (SUPROTAN ENANTIOMER OD PRIRODNOG) - NASTAVAK

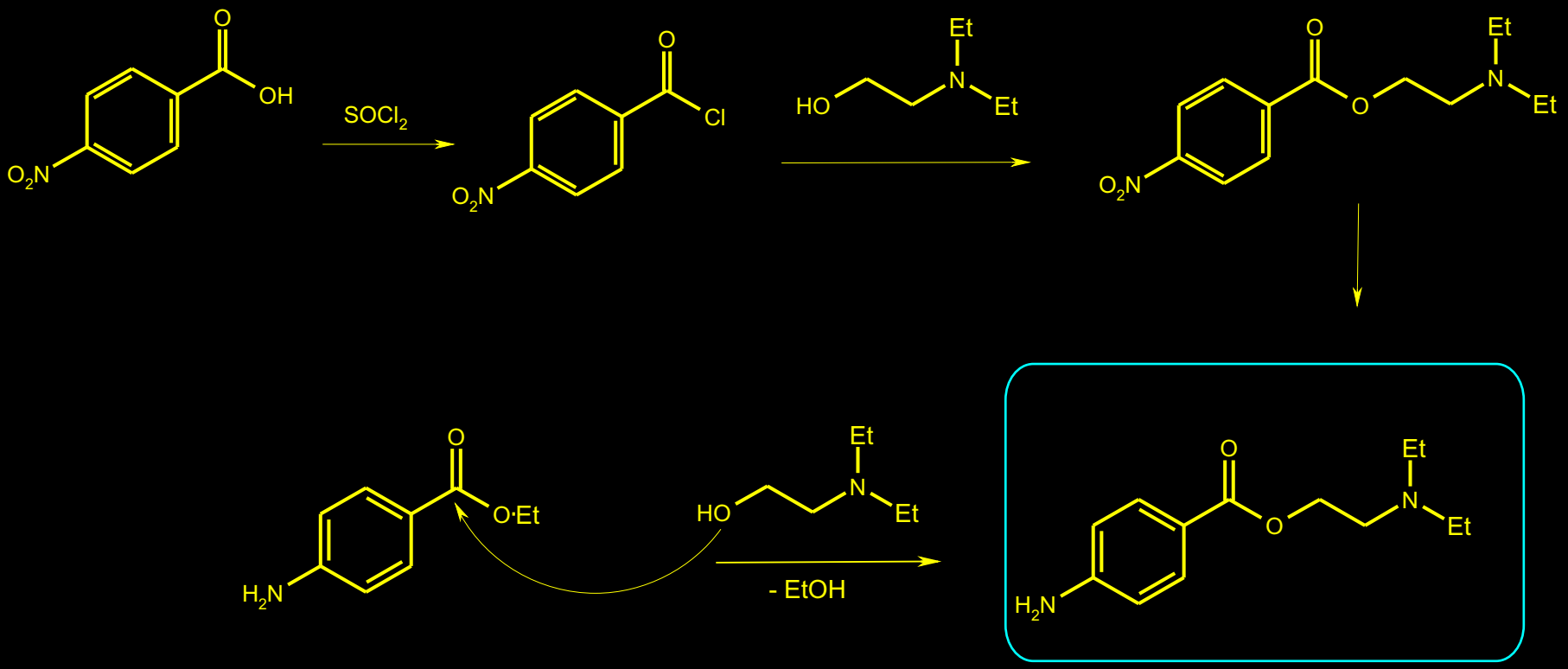


# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

### 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-ESTRI, DERIVATI p-AMINO-BENZOEVE KISELINE

### PROCAINE (PROKAIN)



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

Monograph Number: 7846
Title: **Procaine**
CAS Registry Number: 59-46-1
CAS Name: 4-Aminobenzoic acid 2-(diethylamino)ethyl ester
Additional Names: p-aminobenzoyldiethylaminoethanol; 2-diethylaminoethyl p-aminobenzoate
Molecular Formula: C13H20N2O2
Molecular Weight: 236.31.
Percent Composition: C 66.07%, H 8.53%, N 11.85%, O 13.54%
Literature References: Benzoic acid derivative with anesthetic activity. Prepn: A. Einhorn, US 812554 (1906); idem, Ann. 371, 125 (1909); A. Einhorn, E. Uhlfelder, ibid. 131. CNS effects: C. G. Peterson, Anesthesiology 16, 976 (1955). Intravenous pharmacokinetics in humans: A. B. Seifen et al., Anesth. Analg. (Cleveland) 58, 382 (1979). Clinical evaluation as anti-arrhythmic and cough suppressant during anesthesia: D. S. Thompson et al., Am. J. Surg. 138, 798 (1979). Stabilization of vascular smooth muscle in vitro: K. Kitamura et al., Drugs Exp. Clin. Res. 12, 773 (1986). Toxicity data: W. C. North, K. F. Urbach, J. Am. Pharm. Assoc. Sci. Ed. 45, 382 (1956); E. I. Goldenthal, Toxicol. Appl. Pharmacol. 18, 185 (1971).
Properties: Hygroscopic, anhydr plates, tablets from ligroin or ether, mp 61°. When freshly precipitated, one gram dissolves in 200 ml water. Sol in alc, ether, benzene, chloroform. LD50 in mice (mg/kg): 195 i.p.; 45 i.v. (North, Urbach).
Melting point: mp 61°
Toxicity data: LD50 in mice (mg/kg): 195 i.p.; 45 i.v. (North, Urbach)

Derivative Type: Hydrochloride CAS Registry Number: 51-05-8 Trademarks: Anestil; Enpro (Kobayashi); Gero (URPAC); Jenacaine; Medaject (Neda); Naucaine; Neocaine; Novocain (Sanofi Winthrop); Omnicain (Daiichi); Planocaine (M & B); Rocain (Fuso); Syntocain (Sintetica) Molecular Formula: C13H20N2O2.HCl Molecular Weight: 272.78. Percent Composition: C 57.24%, H 7.76%, N 10.27%, O 11.73%, Cl 13.00% Properties: Crystals. Six-sided plates, monoclinic or triclinic. mp 153-156°. Numbing taste. Stable in air. One gram dissolves in 1 ml water and in 30 ml alcohol. Slightly sol in chloroform. Almost insol in ether. The pH of a 0.1M aq soln is 6.0. Aq solns may be sterilized by boiling. LD50 in mice (mg/kg): 660 ± 60 s.c. (Goldenthal). Melting point: mp 153-156° Toxicity data: LD50 in mice (mg/kg): 660 ± 60 s.c. (Goldenthal)

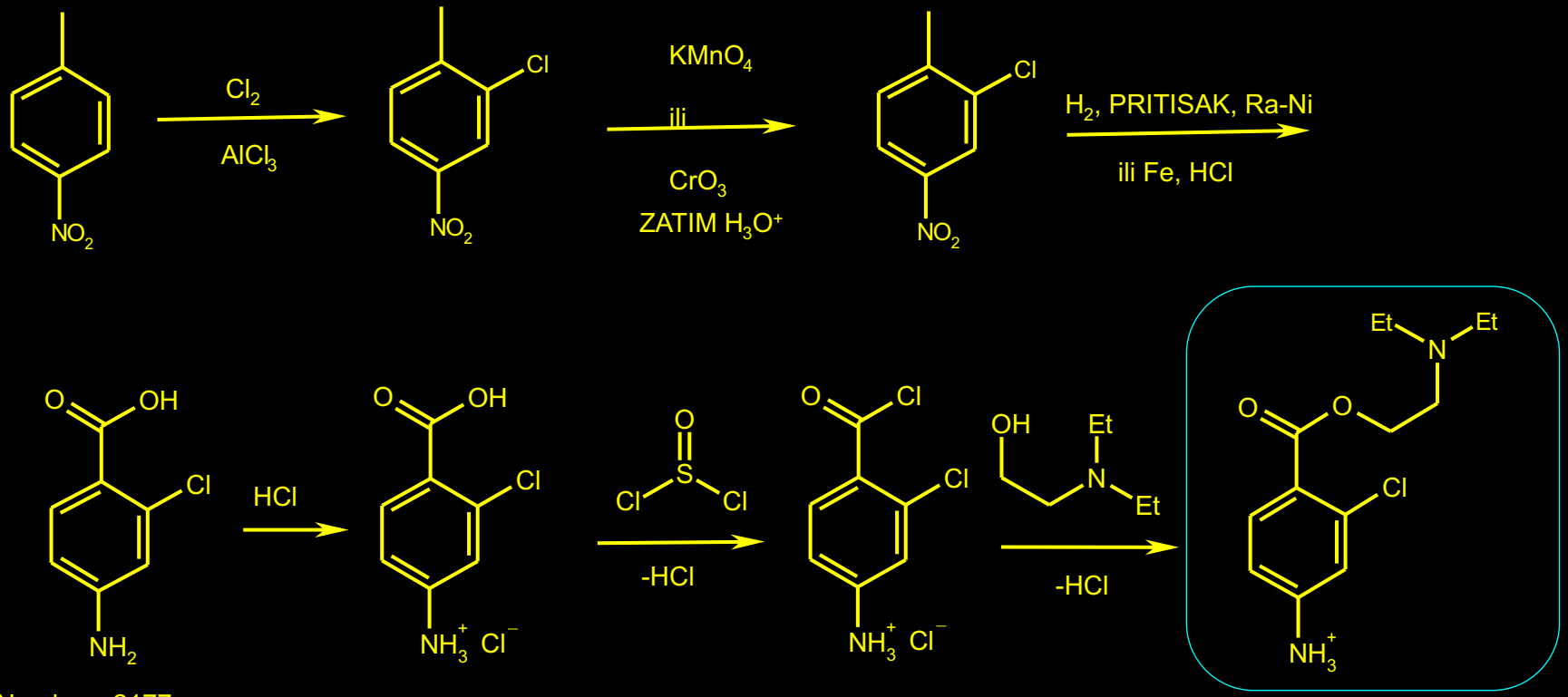
Therap-Cat: Anesthetic (local).

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

## 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-ESTRI, DERIVATI p-AMINO-BENZOEVE KISELINE

## CHLOROPROCAINE (HLOR-PROKAIN)




Monograph Number: 2177
Title: Chloroprocaine Hydrochloride
CAS Registry Number: 3858-89-7
CAS Name: 4-Amino-2-chlorobenzoic acid 2-(diethylamino)ethyl ester monohydrochloride
Additional Names: 2-chloro-4-aminobenzoic acid diethylaminoethyl ester hydrochloride
Trademarks: Nesacaine (Astra); Molecular Formula: C13H20Cl2N2O2; Molecular Weight: 307.22.
Percent Composition: C 50.82%, H 6.56%, Cl 23.08%, N 9.12%, O 10.42%; Literature References: Description: Hädicke, Pharm. Zentralh. 94, 384 (1955). ; Properties: Crystals, mp 176-178° (microstage). Bitter taste. Slowly sol in water. Soly in water at 20° about one gram in 22 ml. Aq solns are just acid to litmus and turn yellow on standing. Soly in 95% ethanol about one gram in 100 ml. ; Melting point: mp 176-178° (microstage)

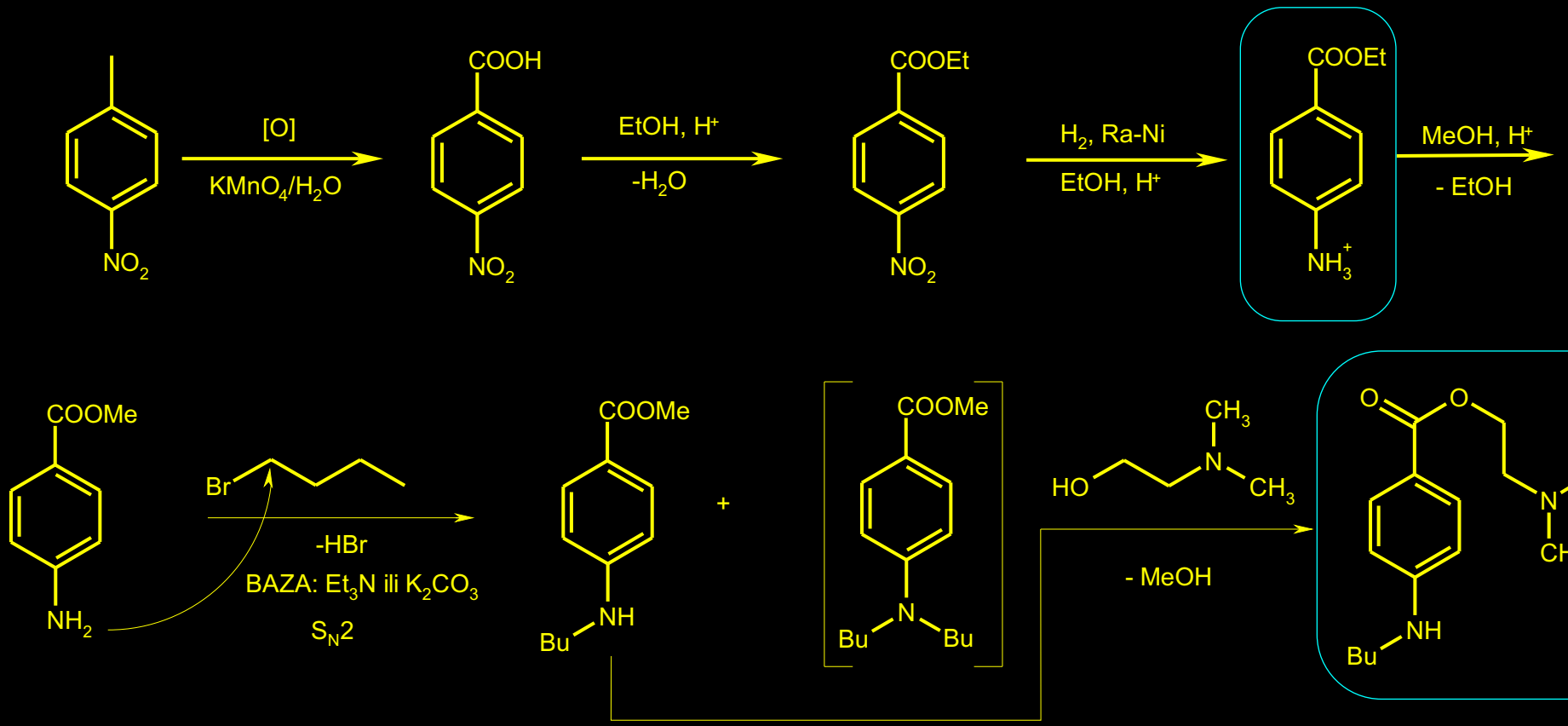
**Therap-Cat: Anesthetic (local).**

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

## 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-ESTRI, DERIVATI p-AMINO-BENZOEVE KISELINE

## BENZOCAINE (BENZOKAIN) I TETRACAINE (TETRAKAIN)




CENA: BENZOCAINE ~ 15 eura/Kg (na veliko); GODIŠNA POTROŠNJA U V. BRITANIJI ~ 10 t. (http://www.bbc.co.uk/news/uk-10909884)

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

Monograph Number: 1087
Title: **Benzocaine**
CAS Registry Number: 94-09-7
CAS Name: 4-Aminobenzoic acid ethyl ester; Additional Names: ethyl aminobenzoate
Trademarks: Americaine (Medeva); Anaesthesin (Ritsert); Flavamed (Berlin-Chemie); Subcutin (Ritsert) ; Molecular Formula: C9H11NO2
Molecular Weight: 165.19. ; Percent Composition: C 65.44%, H 6.71%, N 8.48%, O 19.37%
Literature References: Prepd by the esterification of p-aminobenzoic acid: Salkowski, Ber. 28, 1921 (1895); Vorländer, Meyer, Ann. 320, 135 (1902); by the reduction of ethyl p-nitrobenzoate: Limpricht, ibid. 303, 278 (1898); R. Adams, F. L. Cohen, Org. Syn. coll. vol. I, 240 (2nd ed., 1941). In industrial practice the reducing agent is usually iron and water in the presence of a little acid. Comprehensive description: S. L. Ali, Anal. Profiles Drug Subs. 12, 73-104 (1983). ; Properties: Rhombohedra from ether, mp 88-90°. Stable in air. One gram dissolves in about 2500 ml water, 5 ml alcohol, 2 ml chloroform, in about 4 ml ether, and in 30 to 50 ml of expressed almond oil or olive oil. Also sol in dil acids. pKa 2.5. ; Melting point: mp 88-90°; pKa: pKa 2.5
**Therap-Cat: Anesthetic (local).**
Therap-Cat-Vet: Local (usually surface) anesthetic.

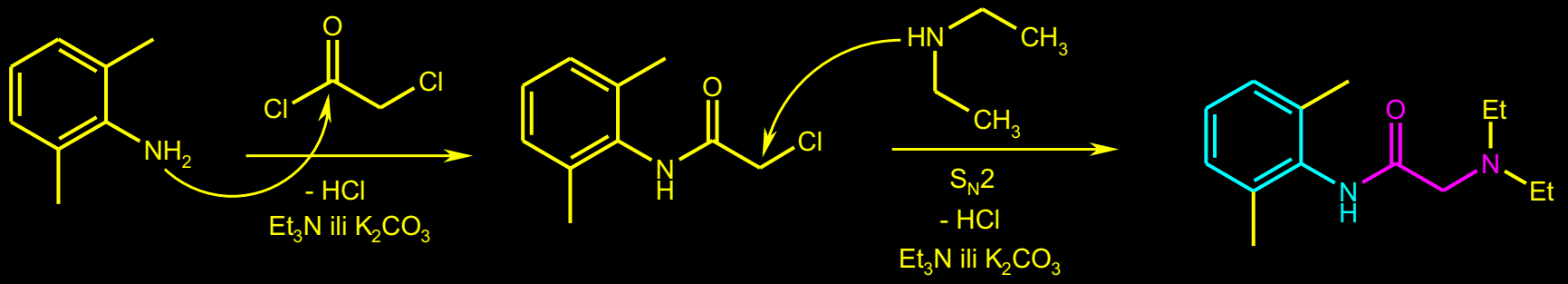
Monograph Number: 9263
Title: **Tetracaine Hydrochloride**
CAS Registry Number: 136-47-0
CAS Name: 4-(Butylamino)benzoic acid 2-(dimethylamino)ethyl ester monohydrochloride
Additional Names: p-butylaminobenzoyl-2-dimethylaminoethanol hydrochloride; 2-dimethylaminoethyl 4-n-butylaminobenzoate hydrochloride; dicain; amethocaine hydrochloride
Trademarks: Anethaine (Glaxo); Decicain (Winthrop); Pantocaine (Hoechst); Pontocaine Hydrochloride (Sanofi Winthrop); Tonexol (Pharmaton)
Molecular Formula: C15H25ClN2O2
Molecular Weight: 300.83.
Percent Composition: C 59.89%, H 8.38%, Cl 11.79%, N 9.31%, O 10.64%
Literature References: Prepn: US 1889645 (1932); GB 815144 (1959 to Abbott). Prepn of pharmaceutical dosage forms: Shupe, US 3272700 (1966 to Sterling Drug). Mechanism of action studies: Y.-W. Leung et al., J. Infect. Dis. 136, 679 (1977). Toxicity study: Dawes, Brit. J. Pharmacol. Chemother. 1, 90 (1946). Acute toxicity: B. A. Bopp et al., J. Pharm. Sci. 67, 882 (1978). Comprehensive description: M. Riaz, Anal. Profiles Drug Subs. 18, 379-411 (1989).
Properties: Faintly bitter crystals producing transient numbness of the tongue. mp 147-150°. pKa 8.39. uv max (water): 225, 310 nm (e 14108, 26352); (0.1N H2SO4): 229, 281, 312 nm (E1%1cm 509, 55, 76); (methanol): 226, 310 nm (e 7586, 29512); (chloroform): 308 nm (e 27542). Sol at 20° in 7.5 parts water, 40 parts alcohol; 30 parts chloroform. Practically insol in ether, benzene, acetone. The aq soln is neutral to litmus. Aq solns are stable and may be sterilized by brief boiling. LD50 i.p. in mice: 70 mg/kg (Dawes); also reported as LD50 in female mice (mg/kg): 13 i.v.; 35 s.c. (Bopp).
Melting point: mp 147-150°
pKa: pKa 8.39
Absorption maximum: uv max (water): 225, 310 nm (e 14108, 26352); (0.1N H2SO4): 229, 281, 312 nm (E1%1cm 509, 55, 76); (methanol): 226, 310 nm (e 7586, 29512); (chloroform): 308 nm (e 27542)
Toxicity data: LD50 i.p. in mice: 70 mg/kg (Dawes); also reported as LD50 in female mice (mg/kg): 13 i.v.; 35 s.c. (Bopp)
**Therap-Cat: Anesthetic (local).**
Therap-Cat-Vet: Anesthetic (topical).

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

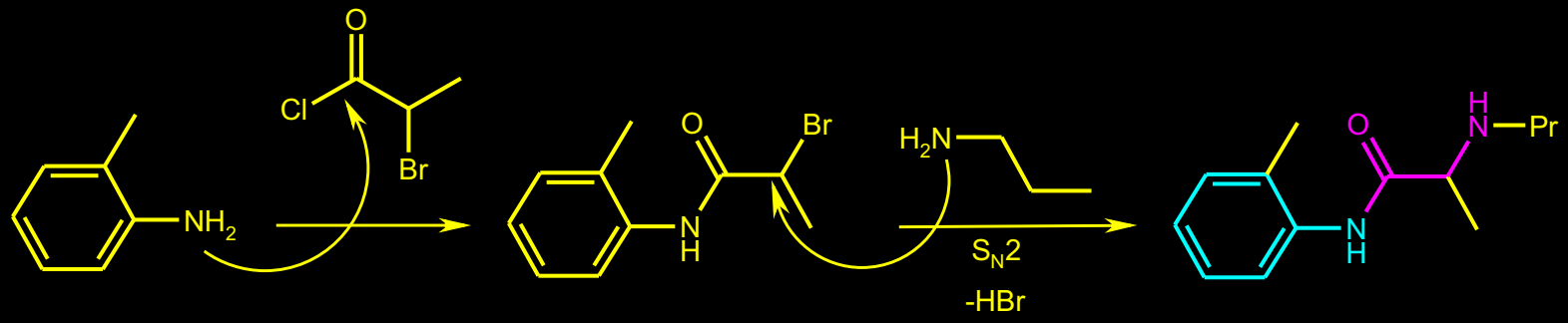
## 2. LOKALNI ANESTETICI

### 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-AMIDI, DERIVATI SUPSTITUISANIH ANILINA I α-AMINO KISELINA

#### LIDOCAINE (LIDOKAIN)




#### PRILOCAINE (PRILOKAIN)

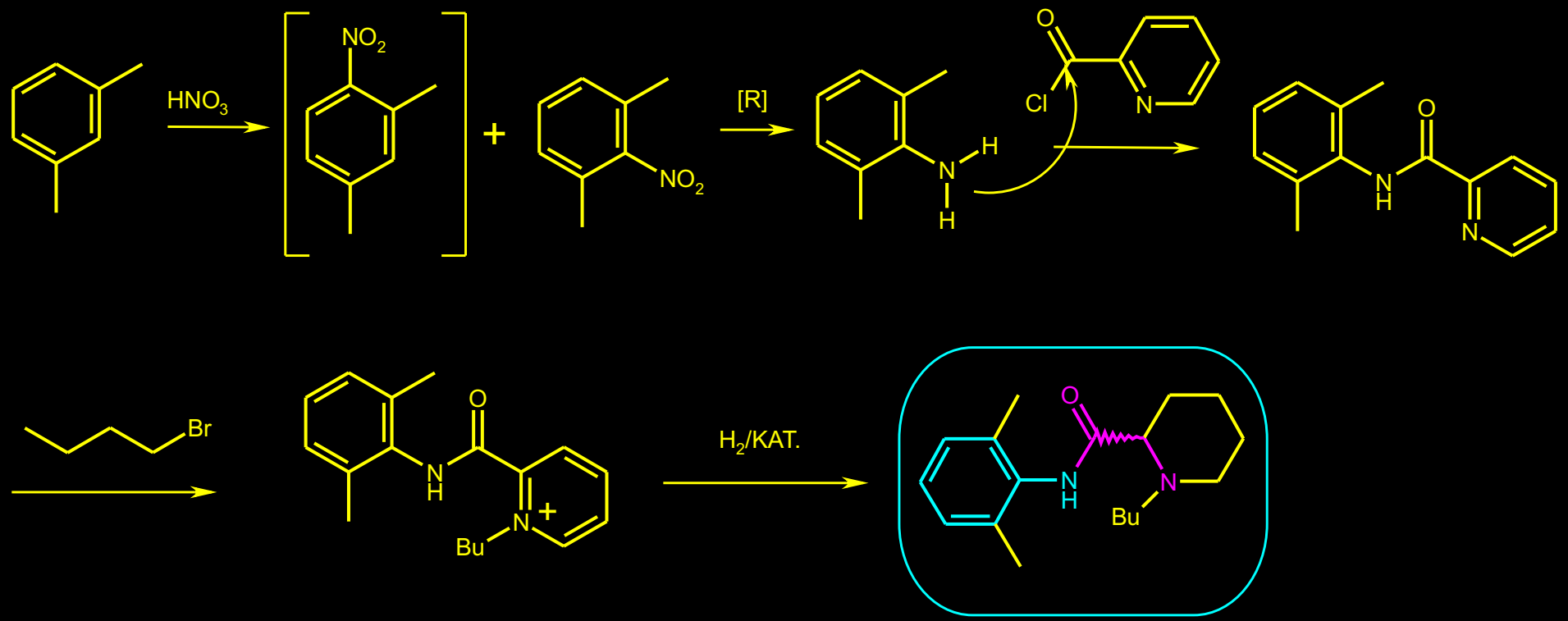


# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

### 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-AMIDI, DERIVATI SUPSTITUISANIH ANILINA I α-AMINO KISELINA

### BUPIVACAINE (BUPIVAKAIN)

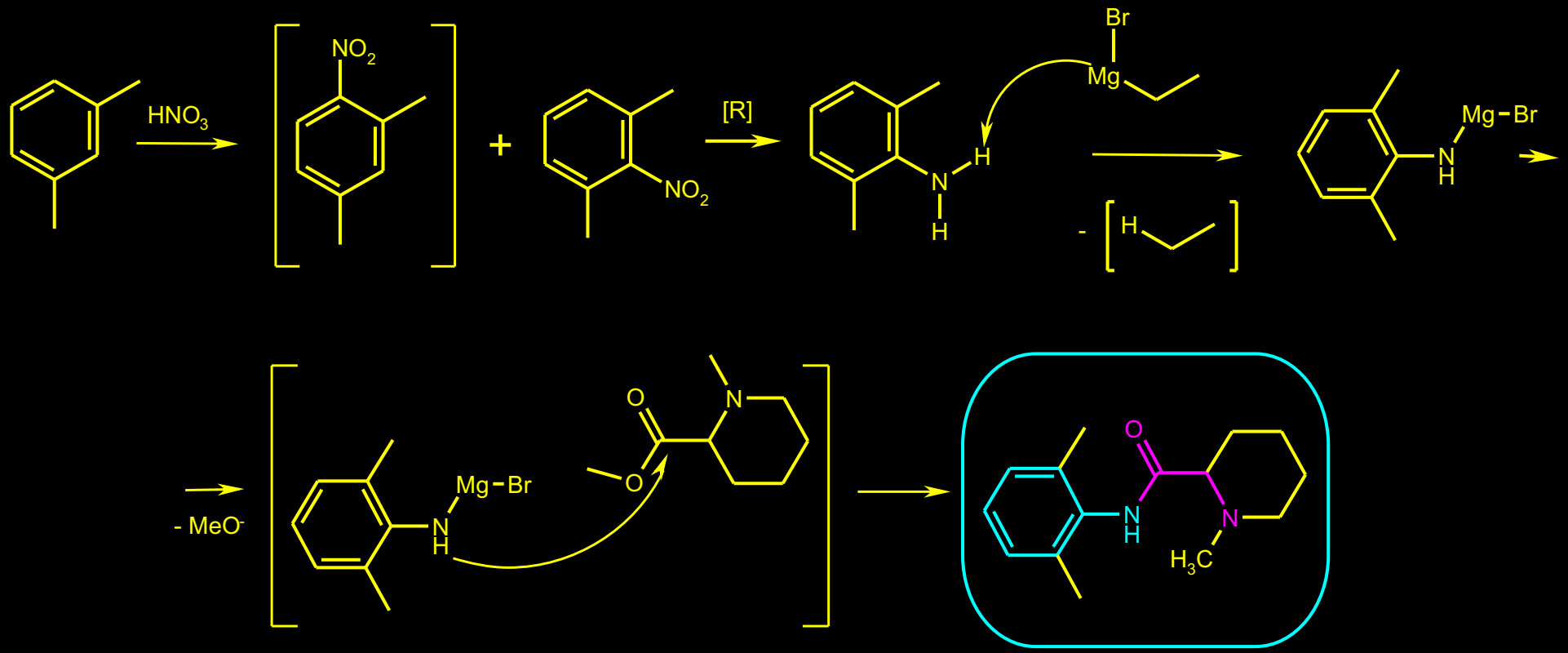


# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

### 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-AMIDI, DERIVATI SUPSTITUISANIH ANILINA I α-AMINO KISELINA

### MEPIVACAINE (MEPIVAKAIN)

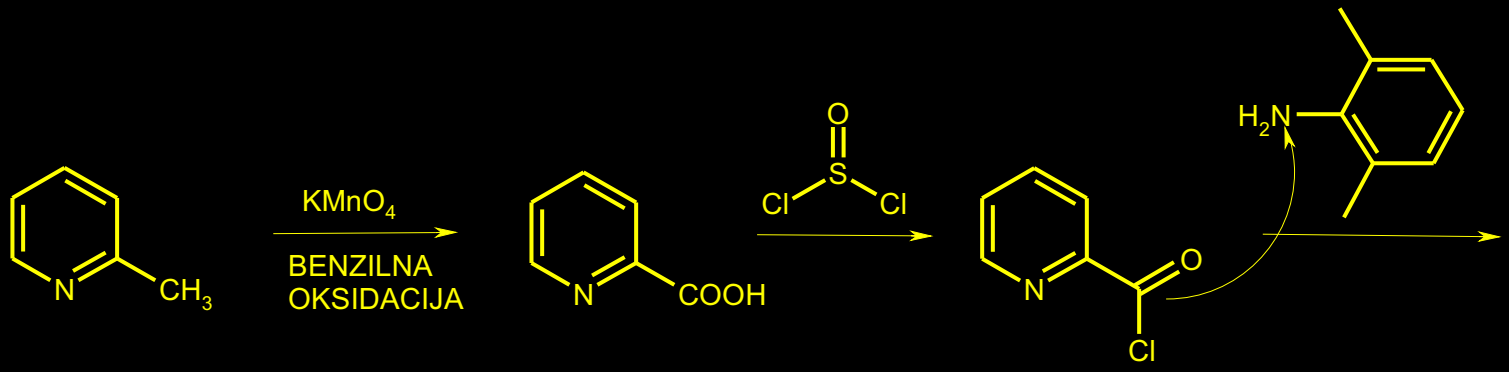


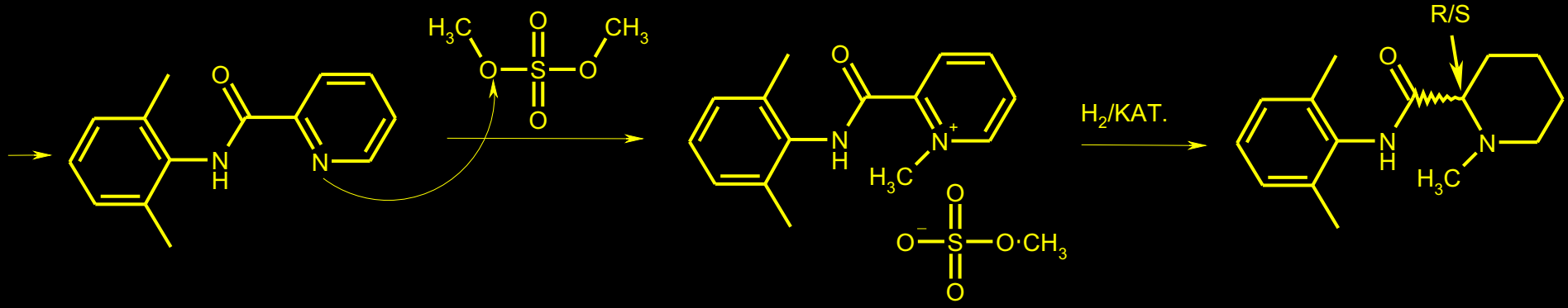
# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

### 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-AMIDI, DERIVATI SUPSTITUISANIH ANILINA I α-AMINO KISELINA

### MEPIVACAINE (MEPIVAKAIN) -ALTERNATIVNA SINTEZA



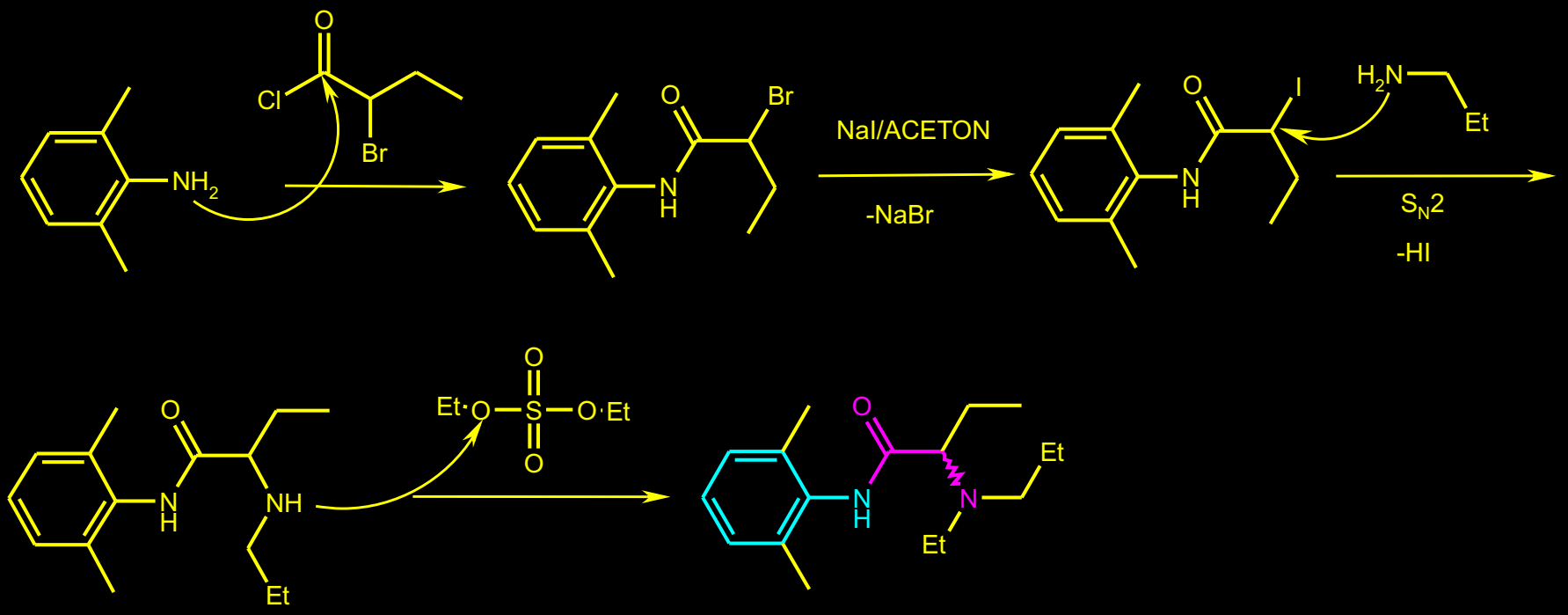



# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

### 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-AMIDI, DERIVATI SUPSTITUISANIH ANILINA I α-AMINO KISELINA

ETIDOCAINE (ETIDOKAIN)

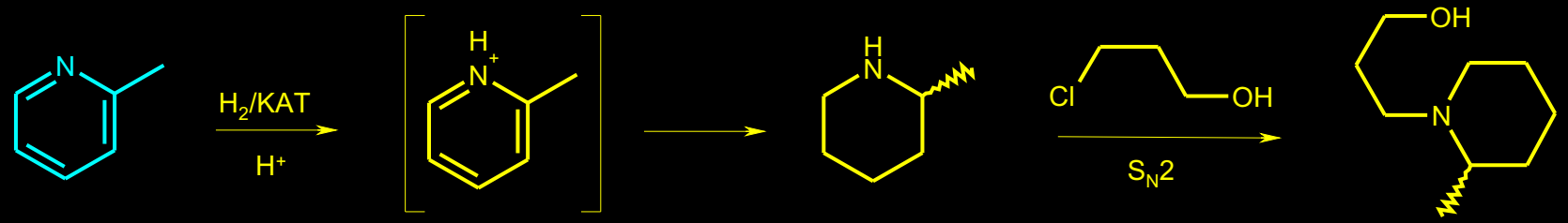


# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

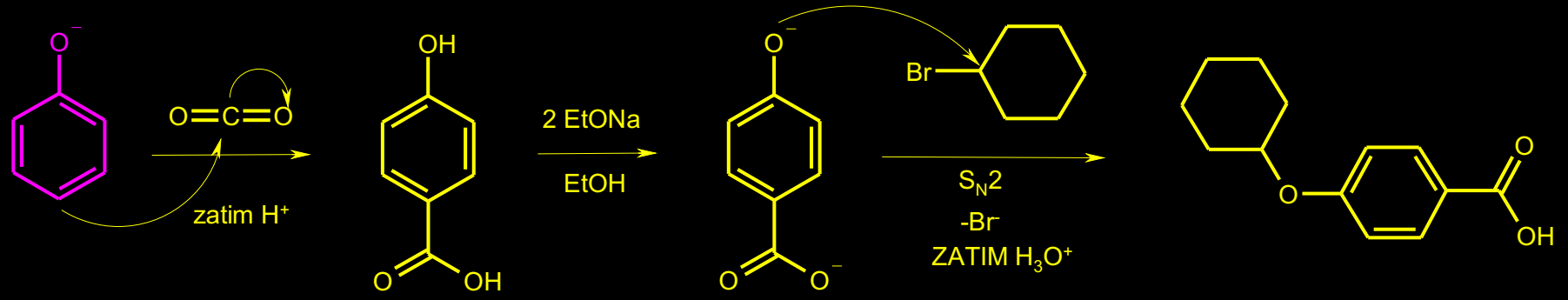
## 2. LOKALNI ANESTETICI

### 2.2 LOKALNI ANESTETICI - PO STRUKTURI AMINO-ESTRI, DERIVATI p-HIDROKSI BENZOEVE KISELINE

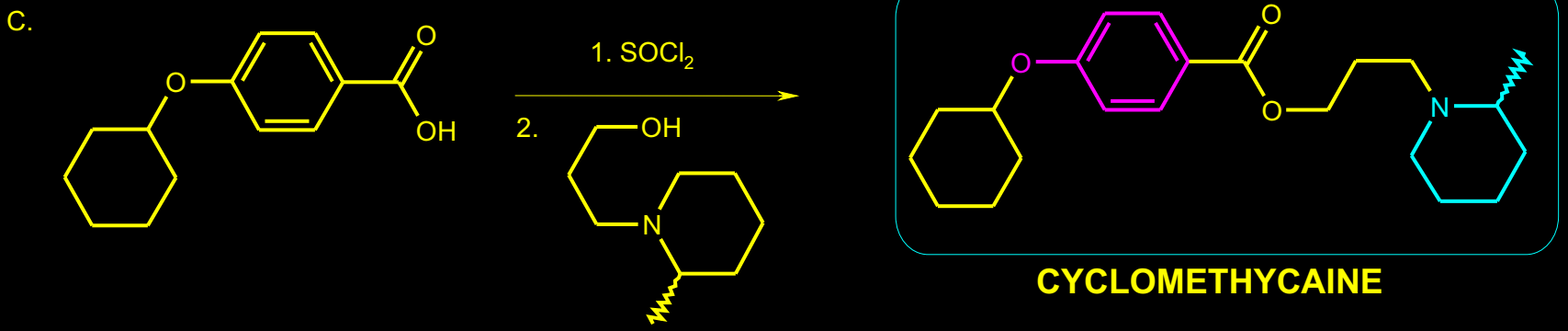
A.




B.




C.




**CYCLOMETHYCAINE**

# SINTEZE LEKOVA - PODELA PREMA FARMAKOLOŠKOM KRITERIJUMU

## 2. LOKALNI ANESTETICI

ZLOUPOTREBA:

SINTETIČKI LOKALNI ANAESTETICI SE NE MOGI DIREKTNO ZLOUPOTRBLJAVATI KAO DROGE, JER NE DELUJU NA CNS.

MEĐUTIM, POŠTO IZAZIVAJU LOKALNU ANESTEZIJU KAO I KOKAIN, ILEGALNO SE KORISTE KAO ČVRSTI RAZBLAŽIVAČI ("PUNIOCI"), U KRIMINALNOJ DISTRIBUCIJI KOKAINA. NA TAJ NAČIN, KORISNICI, PRI UŠMRKAVANJU, OSEĆAJU LOKALNU UTRNULOST, IAKO STVARNI SADRŽAJ KOKAINA MOŽE BITI VRLO MALI ILI ČAK ODSUTAN. (DEJSTVO NA CNS PROPORCIONALNO JE ISKLJUČIVO KOLIČINI KOKAINA).


ZAPLENJENI BENZOKAIN (V. BRITANIJA), NAMENJEN ULEGALNOJ PRIMENI (MEŠANJU SA KOKAINOM).

7 September 2010 "How cutting drugs became big business" http://www.bbc.co.uk/news/magazine-11177126

Monograph Number: 2764
Title: Cyclomethycaine
CAS Registry Number: 139-62-8
CAS Name: 4-(Cyclohexyloxy)benzoic acid 3-(2-methyl-1-piperidinyl)propyl ester
Additional Names: p-cyclohexyloxybenzoic acid ester of N-(3-hydroxypropyl)pipecoline; 3-(2-methylpiperidino)propyl p-cyclohexyloxybenzoate
Trademarks: Surfacaine (Lilly); Surfathesin; Topocaine (Lilly)
Molecular Formula: C22H33NO3
Molecular Weight: 359.50.
Percent Composition: C 73.50%, H 9.25%, N 3.90%, O 13.35%
Literature References: Prepn: McElvain, Carney, J. Am. Chem. Soc. 68, 2592 (1946), eidem, US 2439818 (1948). Toxicity data: Schmidt et al., Toxicol. Appl. Pharmacol. 1, 454 (1959).

Derivative Type: Hydrochloride
CAS Registry Number: 537-61-1
Molecular Formula: C22H33NO3.HCl
Molecular Weight: 395.97.
Percent Composition: C 66.73%, H 8.66%, N 3.54%, O 12.12%, Cl 8.95%
Properties: Crystals, dec 178-180°. Soly in water: slightly >1 g/100 ml.

Derivative Type: Sulfate
Molecular Formula: (C22H33NO3)2.H2SO4
Molecular Weight: 817.10.
Percent Composition: C 64.68%, H 8.39%, N 3.43%, O 19.58%, S 3.92%
Properties: Crystals, mod sol in water.

Therap-Cat: Topical anesthetic.
Therap-Cat-Vet: Surface anesthetic.

Monograph Number:  3893
Title:  Etidocaine
CAS Registry Number:  36637-18-0
CAS Name:  N-(2,6-Dimethylphenyl)-2-(ethylpropylamino)butanamide
Additional Names:  2-(ethylpropylamino)-2¢,6¢-butyroxylidide
Molecular Formula:  C17H28N2O
Molecular Weight:  276.42.
Percent Composition:  C 73.87%, H 10.21%, N 10.13%, O 5.79%
Literature References:  Prepn:  H. J. F.  Adams et al., DE 2162744; eidem, US 3812147 (1972, 1974 both to Astra).  Activity and toxicity studies:  eidem, J. Pharm. Sci. 61, 1829 (1972).

Derivative Type:  Hydrochloride
CAS Registry Number:  36637-19-1
Manufacturers' Codes:  W-19053
Trademarks:  Duranest (Astra)
Molecular Formula:  C17H28N2O.HCl
Molecular Weight:  312.89.
Percent Composition:  C 65.26%, H 9.34%, N 8.95%, O 5.11%, Cl 11.33%
Properties:  Crystals from abs ethanol-ether and isopropanol-isopropylether, mp 203-203.5°.  LD50 in female mice (mg/kg):  6.7 i.v.; 99 s.c. (Adams, 1972).
Melting point:  mp 203-203.5°
Toxicity data:  LD50 in female mice (mg/kg):  6.7 i.v.; 99 s.c. (Adams, 1972)

Therap-Cat:  Anesthetic (local).

Monograph Number:  5884
Tite:  Mepivacaine
CAS Registry Number:  96-88-8
CAS Name:  N-(2,6-Dimethylphenyl)-1-methyl-2-piperidinecarboxamide
Additional Names:  1-methyl-2¢,6¢-pipecoloxylidide;  dl-N-methylpipecolic acid 2,6-dimethylanilide;  dl-N-methylhexahydropicolinic acid 2,6-dimethylanilide
Molecular Formula:  C15H22N2O
Molecular Weight:  246.35.
Percent Composition:  C 73.13%, H 9.00%, N 11.37%, O 6.49%
Literature References:  Prepn:  Ekenstam et al., Acta Chem. Scand. 11, 1183 (1957); US 2799679 (1957 to A. B. Bofors).  Prepn of other salts:  Rinderknecht, Helv. Chim. Acta 42, 1324 (1959); GB 826668 (1960 to Crookes Labs.).  Resolution of isomers:  Tullar, J. Med. Chem. 14, 891 (1971); Friberger, Aberg, Acta Pharm. Suecica 8, 361 (1971).  Pharmacology:  Helmy et al., J. Egypt. Med. Assoc. 50, 688 (1967).  Metabolism:  Reynolds, Brit. J. Anaesth. 43, 33 (1971).
Toxicity data:  G. Aberg, Acta Pharmacol. Toxicol. 31, 273 (1972).
Properties:  Crystals from ether, mp 150-151°.
Melting point:  mp 150-151°

Derivative Type:  Hydrochloride
CAS Registry Number:  1722-62-9
Trademarks:  Carbocaina (Astra);  Carbocaine hydrochloride (Winthrop);  Chlorocain (Pharm. Mfg.);  Meaverin (Woelm);  Mepicaton (Pharmaton);  Mepident (Parke-Davis);  Mepivastesin (Espe);  Optocain (Bayer);  Scandicain (Bofors)
Molecular Formula:  C15H22N2O.HCl
Molecular Weight:  282.82.
Percent Composition:  C 63.70%, H 8.20%, N 9.91%, O 5.66%, Cl 12.54%
Properties:  mp 262-264°.  Sol in water.  LD50 in mice, rats (mg/kg):  280, 500 s.c. (Aberg).
Melting point:  mp 262-264°
Toxicity data:  LD50 in mice, rats (mg/kg):  280, 500 s.c. (Aberg)

Derivative Type:  (+)-Form
Additional Names:  Dexivacaine

Therap-Cat:  Anesthetic (local).
Therap-Cat-Vet:  Anesthetic (local).

Monograph Number: 1483
Title: Bupivacaine
CAS Registry Number: 2180-92-9
CAS Name: 1-Butyl-N-(2,6-dimethylphenyl)-2-piperidinecarboxamide
Additional Names: dl-1-butyl-2¢,6¢-pipecoloxylidide; 1-n-butyl-2¢,6¢-dimethyl-2-piperidinecarboxanilide; dl-N-n-butylpipecolic acid 2,6-xylidide; 1-butyl-2-(2,6-xylylcarbamoyl)piperidine; dl-1-n-butylpiperidine-2-carboxylic acid 2,6-dimethylanilide
Molecular Formula: C18H28N2O
Molecular Weight: 288.43.
Percent Composition: C 74.95%, H 9.78%, N 9.71%, O 5.55%
Literature References: Prepn: B. Ekenstam et al., Acta Chem. Scand. 11, 1183 (1957); B. T. Ekenstam, B. G. Pettersson, US 2955111 (1960 to AB Bofors). Resolution of isomers: B. F. Tullar, J. Med. Chem. 14, 891 (1971). Stereospecific synthesis: B. Adger et al., Tetrahedron Letters 37, 6399 (1996). Pharmacology of racemate: F. Henn, R. Brattsand, Acta Anaesthesiol. Scand. Suppl. 21, 9 (1966), C.A. 66, 17863u (1967); of isomers: F. P. Luduena et al., Arch. Int. Pharmacodyn. 200, 359 (1972). Clinical pharmacokinetics: D. W. Blake et al., Anaesth. Intens. Care 22, 522 (1994). Comprehensive description: T. D. Wilson, Anal. Profiles Drug Subs. 19, 59-94 (1990). Review of use in spinal anesthesia: Acta Anaesthesiol. Scand. 35, 1-10 (1991). Review of pharmacology and clinical efficacy of levobupivacaine: K. J. McClellan, C. M. Spencer, Drugs 56, 355-362 (1998).
Properties: mp 107.5-108°. pKa 8.09; also reported as 8.17. Partition coefficient: (oleyl alcohol/water) 1565; (n-heptane/pH 7.4 buffer) 27.5.
Melting point: mp 107.5-108°
pKa: pKa 8.09; also reported as 8.17
Log P: Partition coefficient: (oleyl alcohol/water) 1565; (n-heptane/pH 7.4 buffer) 27.5

Derivative Type: Hydrochloride monohydrate
CAS Registry Number: 14252-80-3
Manufacturers' Codes: AH-2250; LAC-43
Trademarks: Carbostesin (Astra); Marcaine (Sanofi Winthrop); Sensorcaine (Astra)
Molecular Formula: C18H28N2O.HCl.H2O
Molecular Weight: 342.91.
Percent Composition: C 63.05%, H 9.11%, N 8.17%, O 9.33%, Cl 10.34%
Properties: White, odorless crystalline powder. mp 258.5°. Slightly sol in acetone, chloroform, ether. Soly (mg/ml): water 40; alcohol 125. LD50 in mice (mg/kg): 7.8 i.v., 82 s.c. (Henn, Brattsand).
Melting point: mp 258.5°
Toxicity data: LD50 in mice (mg/kg): 7.8 i.v., 82 s.c. (Henn, Brattsand)

Derivative Type: (-)-Form
CAS Registry Number: 27262-47-1
Additional Names: Levobupivacaine; (S)-bupivacaine
Properties: Crystals from isopropanol, mp 135-137°. [a]D25 -80.9° (c = 5 in methanol).
Melting point: mp 135-137°
Optical Rotation: [a]D25 -80.9° (c = 5 in methanol)

Derivative Type: (-)-Form hydrochloride ; CAS Registry Number: 27262-48-2; Trademarks: Chirocaine (Chiroscience) Molecular Formula: C18H28N2O.HCl Molecular Weight: 324.90. ;Percent Composition: C 66.54%, H 9.00%, N 8.62%, O 4.92%, Cl 10.91%; Properties: mp 255-257°. [a]D25 -12.3° (c = 2 in water). ; Melting point: mp 255-257° ;Optical Rotation: [a]D25 -12.3° (c = 2 in water)

Monograph Number: 5503
Title: Lidocaine
CAS Registry Number: 137-58-6
CAS Name: 2-(Diethylamino)-N-(2,6-dimethylphenyl)acetamide
Additional Names: 2-diethylamino-2¢,6¢-acetoxylidide; w-diethylamino-2,6-dimethylacetanilide; lignocaine
Trademarks: Cuivasil (IDC); Duncaine; Leostesin (Leo Pharm.); Lidothesin; Rucaina; Xylocaine (Astra Pharm.); Xylocitin; Xylotox
Molecular Formula: C14H22N2O
Molecular Weight: 234.34.
Percent Composition: C 71.75%, H 9.46%, N 11.95%, O 6.83%
Literature References: Long-acting, membrane stabilizing agent against ventricular arrhythmia. Originally developed as a local anesthetic. Prepn: N. M. Löfgren, B. J. Lundqvist, US 2441498 (1948 to Astra); A. D. H. Self, A. P. T. Easson, GB 706409 (1954 to May & Baker); I. P. S. Hardie, E. S. Stern, GB 758224 (1956 to J. F. Macfarlane & Co.); Zhuravlev, Nikolaev, Zh. Obshch. Khim. 30, 1155 (1960). Toxicity studies: E. R. Smith, B. R. Duce, J. Pharmacol. Exp. Ther. 179, 580 (1971); G. H. Kronberg et al., J. Med. Chem. 16, 739 (1973). Review of pharmacokinetics: N. L. Benowitz, W. Meister, Clin. Pharmacokinet. 3, 177 (1978). Review of action as local anesthetic: Löfgren, Studies on Local Anesthetics: Xylocaine, A New Synthetic Drug (Hoeggstroms, Stockholm, 1948); Cooper, Pharm. J. 171, 68 (1953). Reviews of anti-arrhythmic agents: J. L. Anderson et al., Drugs 15, 271 (1978); L. H. Opie, Lancet 1, 861 (1980); E. Carmeliet, Ann. N.Y. Acad. Sci. 427, 1 (1984). Comprehensive description: K. Groningsson et al., Anal. Profiles Drug Subs. 14, 207-243 (1985); M. F. Powell, ibid. 15, 761-779 (1986).
Properties: Needles from benzene or alcohol, mp 68-69°. bp4 180-182°; bp2 159-160°. Insol in water. Sol in alcohol, ether, benzene, chloroform, oils.
Melting point: mp 68-69°
Boiling point: bp4 180-182°; bp2 159-160°

Derivative Type: Hydrochloride monohydrate
CAS Registry Number: 6108-05-0
Trademarks: Lidesthesin (Ritsert); Odontalg (Giovanardi); Sedagul (Wild); Xylocard (Astra); Xyloneural (Nicholas)
Molecular Formula: C14H22N2O.HCl.H2O
Molecular Weight: 288.82.
Percent Composition: C 58.22%, H 8.73%, N 9.70%, O 11.08%, Cl 12.28%
Properties: Crystals, mp 77-78°; anhydrous, mp 127-129°. Very sol in water, alcohol; sol in chloroform. Insol in ether. pH of 0.5% aq soln: 4.0-5.5. LD50 in mice (mg/kg): 292 orally (Smith, Duce); 105 i.p.; 19.5 i.v. (Kronberg).
Melting point: mp 77-78°; mp 127-129°
Toxicity data: LD50 in mice (mg/kg): 292 orally (Smith, Duce); 105 i.p.; 19.5 i.v. (Kronberg)

Therap-Cat: Anesthetic (local); antiarrhythmic (class IB).
Therap-Cat-Vet: Anesthetic (local).

Monograph Number: 7832
Title: Prilocaine
CAS Registry Number: 721-50-6
CAS Name: N-(2-Methylphenyl)-2-(propylamino)propanamide
Additional Names: 2-(propylamino)-o-propionotoluidide; N-(a-propylaminopropionyl)-o-toluidine; a-propylamino-2-methylpropionanilide; propitocaine
Molecular Formula: C13H20N2O
Molecular Weight: 220.31.
Percent Composition: C 70.87%, H 9.15%, N 12.72%, O 7.26%
Literature References: Prepn: N. Löfgren, C. Tegner, Acta Chem. Scand. 14, 486 (1960); GB 839943; N. Löfgren, C. Tegner, US 3160662 (1960, 1964 both to Astra).
Properties: Needles, mp 37-38°. bp0.1 159-162°. nD20 1.5298.
Melting point: mp 37-38°
Boiling point: bp0.1 159-162°
Index of refraction: nD20 1.5298

Derivative Type: Hydrochloride
CAS Registry Number: 1786-81-8
Manufacturers' Codes: L-67
Trademarks: Citanest (Astra Pharm.); Xylonest (Astra Pharm.)
Molecular Formula: C13H20N2O.HCl
Molecular Weight: 256.78.
Percent Composition: C 60.81%, H 8.24%, N 10.91%, O 6.23%, Cl 13.81%
Properties: Crystals from ethanol + isopropyl ether, mp 167-168°. Readily sol in water.
Melting point: mp 167-168°

Therap-Cat: Anesthetic (local).