PHARM.D • YEAR 1

Pharmaceutical Organic Chemistry

CHAPTER 16

# Study of Official Compounds

PPT CHAPTER COVER

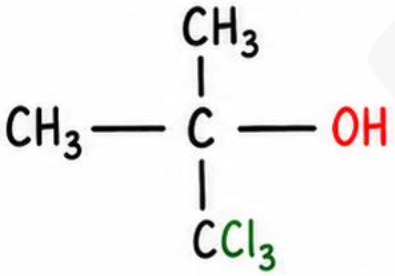


DOCTOR OF PHARMACY

# CHLOROBUTANOL — IDENTITY & PREPARATION

## 1. IDENTITY & STRUCTURE

- Common name: chlorobutanol (chlorbutol)
- IUPAC name: 1,1,1-trichloro-2-methylpropan-2-ol
- Chemical formula: $C_4H_7Cl_3O$
- It is a tertiary alcohol and a chlorinated derivative of butanol.



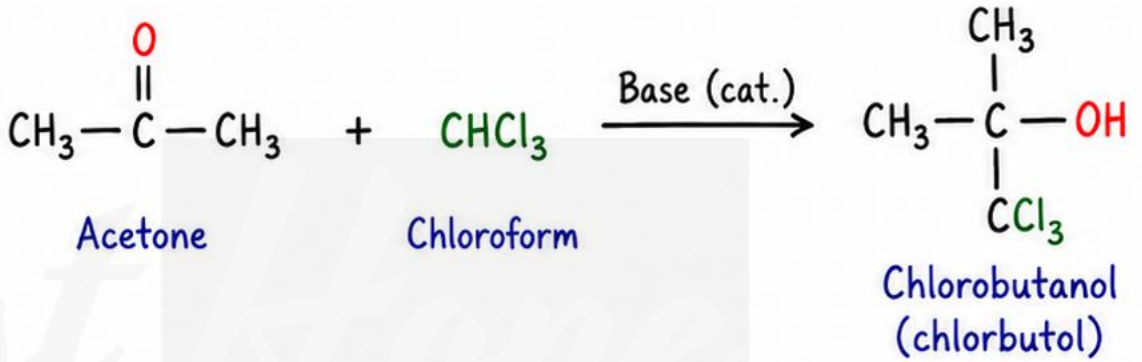
Condensed structure: $(CH_3)_2C(OH)CCl_3$

**RECOGNITION:**
- Tertiary alcohol bearing a trichloromethyl group.
- Not 4-chloro-1-butanol.

**CAUTION:**
Actual manufacturing and compendial specifications follow validated procedures.

## 2. PREPARATION

Chlorobutanol (chlorbutol) is synthesized by the reaction of acetone with chloroform in the presence of a catalytic base.




## 3. MECHANISM (Base-catalysed)

① $CHCl_3 + OH^- \rightleftharpoons CCl_3^- + H_2O$ — hydroxide removes the acidic proton.

② $CCl_3^- + (CH_3)_2C{=}O \longrightarrow (CH_3)_2C(O^-)CCl_3$ — nucleophilic addition to acetone gives the alkoxide.

③ $(CH_3)_2C(O^-)CCl_3 + H_2O \longrightarrow (CH_3)_2C(OH)CCl_3 + OH^-$ — water protonates the alkoxide and hydroxide catalyst is regenerated.

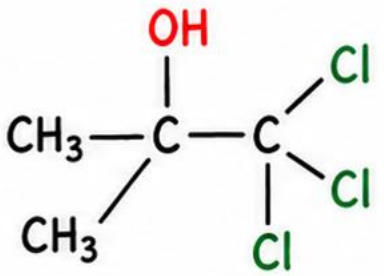
# Chlorobutanol — Properties, Quality & Uses

## Identity Reminder

Chlorobutanol (chlorbutol)

Structure: $(CH_3)_2C(OH)CCl_3$

Molecular formula: $C_4H_7Cl_3O$




## Properties

- Appearance: white crystalline material.
- Solubility: slightly soluble in water; more soluble in alcohol and chloroform.
- Commonly encountered as a hemihydrate.
- Melting behavior/specification is monograph-dependent; often around 95–97 °C for the common form.

## Quality / Identification & Assay

Identification:

- Appearance: white crystalline material.
- Melting range: per applicable monograph.
- Identity: by IR spectrum or by a suitable chromatographic procedure as specified.

Tests:

- Water (or loss on drying) / content: within monograph limits.
- Related substances / impurities: comply with monograph limits.

Assay:

- Determine content by the method specified in the applicable pharmacopoeial monograph (validated chromatographic assay or halogen-content method).

## Uses

- Antimicrobial preservative in selected ophthalmic, otic and other pharmaceutical formulations.
- Historically used as a sedative and local anesthetic (limited contemporary use).
- Concentration and compatibility must follow the requirements of the finished product monograph or formulation.

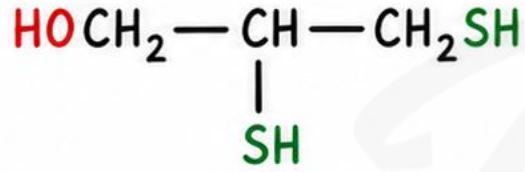
## Safety

Irritant and toxic at excessive exposure. Handle with care. Use only at validated levels in accordance with product requirements.

# DIMERCAPROL — IDENTITY & PREPARATION

## IDENTITY

- British Anti-Lewisite (BAL)
- IUPAC name: 2,3-dimercaptopropan-1-ol
- Molecular formula: $C_3H_8OS_2$
- Condensed structure:




Three-carbon molecule with two adjacent thiol (–SH) groups at C2 and C3 and a primary alcohol (–OH) at C1.

### KEY FEATURE

The two neighboring –SH groups bind certain soft metal ions (e.g., $As^{3+}$, $Hg^{2+}$, $Au^{1+}$) to form a chelate, thereby reducing toxicity. The –OH group improves polarity and aqueous dispersibility.

### FORMULATION

- Oily liquid.
- Readily oxidized in air (thiol groups can form disulfides).
- Commonly formulated in a suitable oily vehicle for intramuscular administration.

## PREPARATION (HIGH-LEVEL ROUTE)

- A three-carbon precursor bearing two leaving groups on adjacent carbons is converted to vicinal dithiol in two stages:

Three-carbon precursor (epichlorohydrin or another 1,2-dihalogenated glycerol derivative) → Treatment with a sulfur nucleophile (e.g., hydrosulfide, sulfide, or other suitable sulfide source) → Hydrolysis / work-up to furnish 2,3-dimercaptopropan-1-ol (dimercaprol)

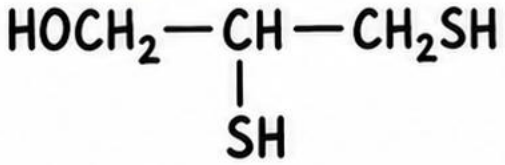
- The route yields the vicinal dithiol with the primary alcohol intact; final purification affords dimercaprol.

### SAFETY / QUALITY

- Protect from oxidation—store in well-closed containers with inert headspace or antioxidants as appropriate.
- Confirm identity and purity by compendial methods (e.g., identification, assay, related substances, elemental impurities, and residual solvents).
- Manufacture under validated controls to ensure consistent quality, potency, and safety.

# DIMERCAPROL — CHELATION, ASSAY & CLINICAL USE

## 1. STRUCTURE & IDENTITY

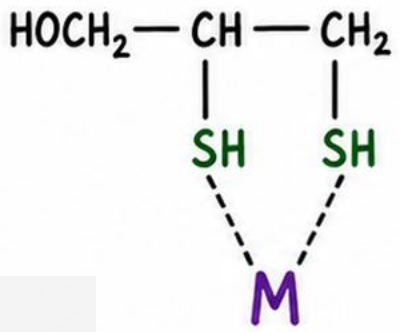



- 2,3-dimercaptopropan-1-ol
- Molecular formula: $C_3H_8OS_2$

Dimercaprol (British Anti-Lewisite, BAL) is a sulfhydryl chelating agent that binds heavy metals via its two adjacent –SH groups to form stable, excretable complexes.

## 2. CHELATION MECHANISM

- The two adjacent thiol (–SH) groups chelate the same metal ion (M) to form a stable five-membered chelate ring.
- Metal binding can reduce interaction with critical tissue thiols and facilitate redistribution and excretion, depending on the metal.




M = metal ion (e.g., $As^{3+}$, $Hg^{2+}$, $Pb^{2+}$, $Au^{+}/Au^{3+}$)

## 3. ASSAY / QUALITY

- Dimercaprol can be assayed by a validated iodometric oxidation of thiol groups (iodine reacts with –SH to form disulfides; excess iodine back-titrated with sodium thiosulfate using starch indicator).
- Alternatively, use the current compendial method specified in the selected pharmacopoeial monograph.
- Report equivalence (e.g., mg/mL or % of label claim) only from the selected monograph. Do not invent a factor.

## 4. CLINICAL USES, LIMITATIONS & SAFETY

**Uses:** Specialist antidote for poisoning with arsenic, gold (inorganic) and inorganic mercury.

- May be used with another chelator (e.g., succimer or $CaNa_2EDTA$) in severe lead encephalopathy under specialist protocols.
  - Not a routine first-line treatment for lead poisoning.

**Limitations / Safety:** Painful intramuscular injection. Hypertension, tachycardia, nausea and fever can occur.

**Contraindications & Dosing:** Refer to current toxicology guidance and specialist protocols; dosing is metal- and patient-specific.

★ **KEY TAKEAWAY:** Two adjacent thiol (–SH) groups form the metal-binding pharmacophore. This chelation underpins dimercaprol's clinical utility as a specialist antidote.

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