بسم الله الرحمن الرحيم

Lecture four

University of karbala

: seven Collage of pharmacy

e:18 / 11/2012 3rd Stage

rse title: Inorganic medicinal and
armaceutical Chemistry.

c Title: **Electronic structure of atoms:(chap1)**

Complex and chelating agent:

Complexation play an important role in analytical chemistry and pharmacy where:

1-The concentration of metal can be determined by titration with complexing agents.

2-chelating agent is used to solubilize the metal and stabilized its oxidation state.

3- Tow solution are used in the identification of reducing substance eig sugars.

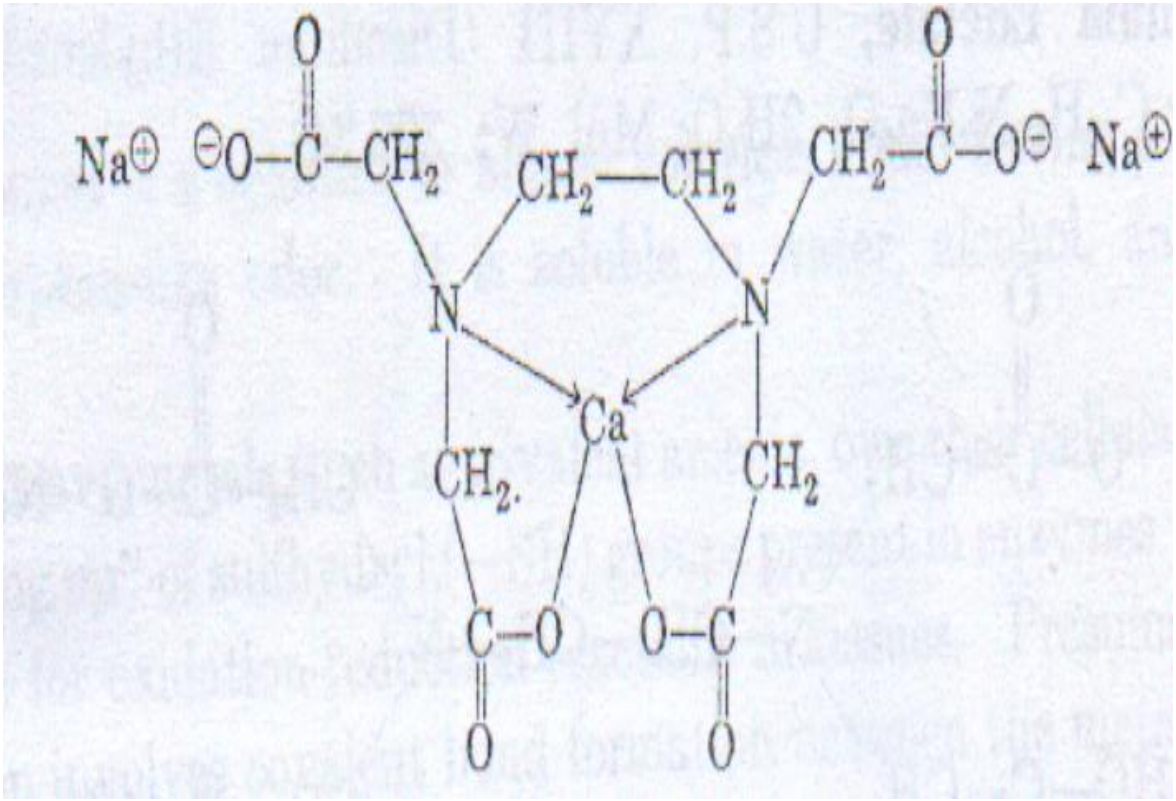
These solutions are:
Fehlings solution and Benedicts solution.
Both of these solutions contain Cu(II) ions which are chelated by citric acid in Benedicts solution and by tartaric acid in Fehlings solution.

4-Chelating agents are also used as preservative in preparation subject to decomposition due to trace quantities of metals ,such as preparation contains H_2O_2 . Chelating agents occupy a rather unique place in drug therapy, they show much efficacy in the treatment of heavy metal poisoning from such elements as lead, mercury ,iron, etc.

They are also used to treat certain metabolic disorders where metals such as copper are accumulated in abnormal amount in various tissues. We have some particular chelatig agents

1-**Calcium Disodium Edetate.**

Which is calcium disodium Ethyldiaminetetracetate,$C_{10}H_{12}CaN_2Na_2O_8.xH_2O$


Na⊕
⊖O–C–CH2
CH2—CH2
CH2–C–O⊖
Na⊕
N
N
Ca
CH2
CH2
C–O
O–C

This compound is a mixture of di hydrate and tri hydrate (predominantly) which is white crystalline granule or a white crystalline powder.

It is odorless, slightly hydroscopic and has a faint saline taste freely soluble in water .and the pH of an aqueous solution is between 6.5 and 8.0

The compound is actually the calcium complex of the di sodium salt of EDTA

Its used in the treatment of heavy metal poisoning, primarily that caused by lead(plumbism).

It may also be employed in poisonings due to copper, nickel, cadmium ,zinc ,chromium. And manganese but it is no value in the treatment of toxicities produced by mercury, arsenic or gold

EDTA preparations have high or strong affinity for Ca, therefore the di sodium calcium form is used to avoid inducing hypocalcemic state(low Ca level in serum) This chelating agent removes lead from the tissue by forming an inactive soluble complex which can be removed from the circulation by the kidneys and excreted in the urine.

The found that the urinary excretion of lead as much as 40 times through the use of calcium edentate.

The compound is poorly absorbed from GIT(gastrointestinal tract),and may even aid the absorption of lead which may be in the gut, there by producing toxic reactions or aggravating an established toxicity.

So the usually route of administration is by intravenous injection (I.V)

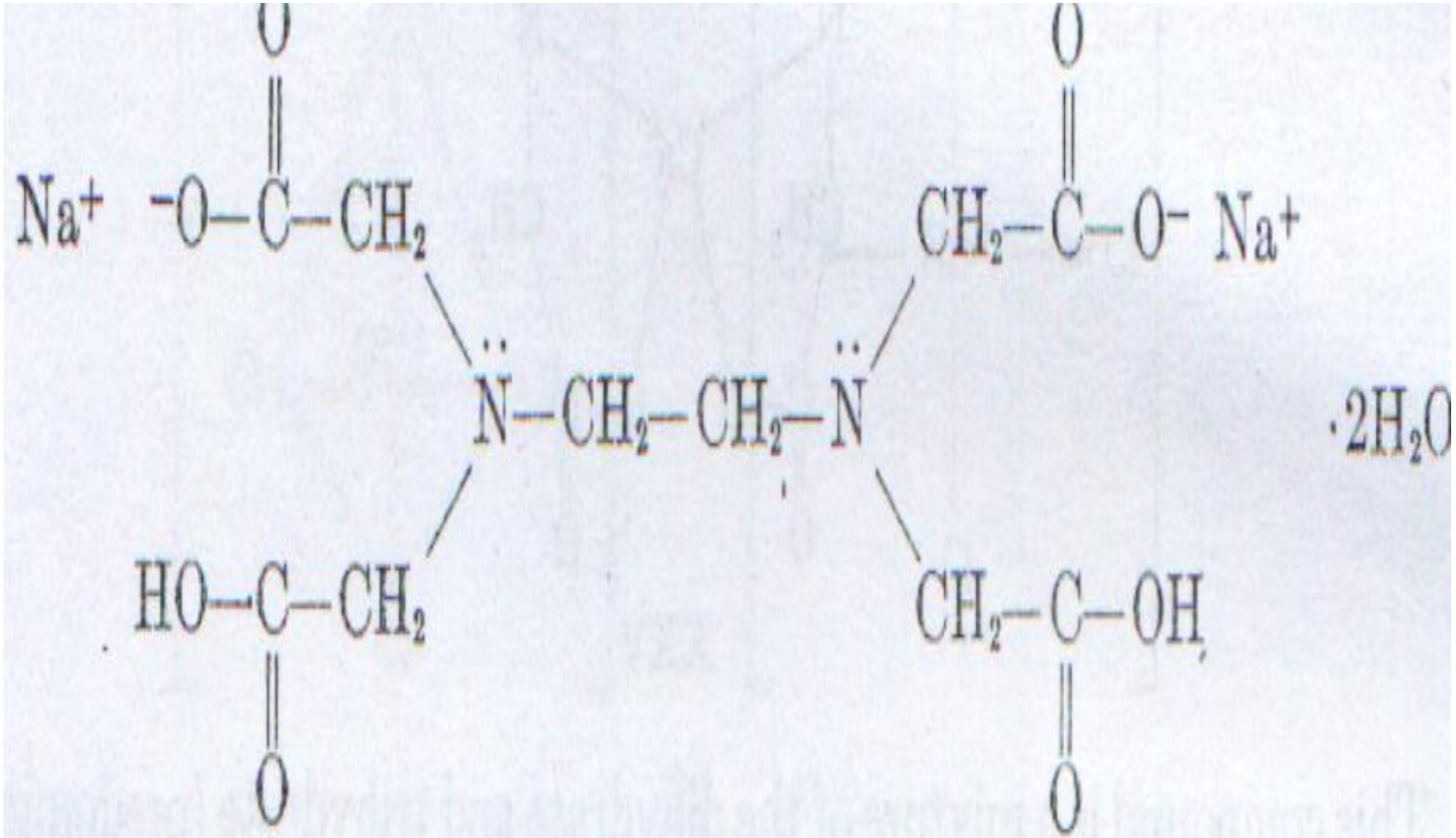
Should contain not less than 180mg and not more than 220mg of compound in each ml.

Intra muscular(I.M) administration is used in diagnosis of metal poisonings.

2-Disodium Edetate:

(Disodium Ethelyenediamineteteraacetate)

$C_{10}H_{14}N_2Na_2O_8.2H_2O$.Mol. Wt.372.24)



XXVI

This compound is a white crystalline powder soluble in water providing an aqueous solution of pH 4.0-6.0 .

Disodium Edetate chelate with the same metals as di sodium calcium form but it has an added affinity for calcium that will limit its usefulness in the treatment.

So it used in conditions related to hypercalcemic state (high serum calcium).

It may be useful in treating such problems as occlusive vascular disease and cardiac arrhythmias when associated with high blood level of calcium.

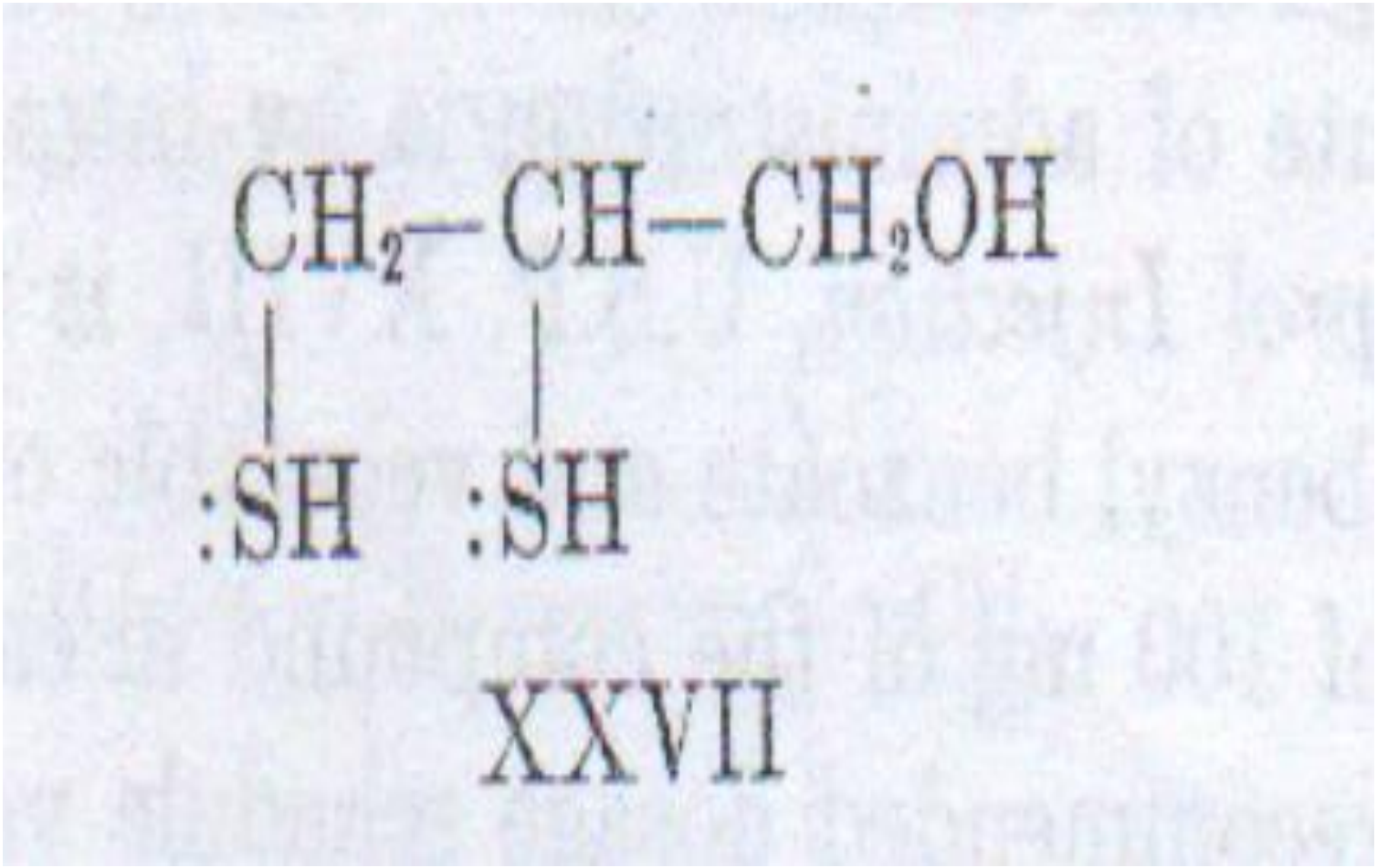
It is of no value in aiding dissolution of urinary calculi(calcium-containing stones in the urinary tract). The official Disodium Edetate U.S.P contains varying amount of the di sodium and tri sodium salts due to the effects of pH adjustment.

The Dose is 50 mg/kg of body weight dissolved in 500ml of isotonic sodium chloride or 5%dextrose.

The rate of administration is by intra venous injections.

3-Dimercaprol 2,3-Dimercapto-1-propanol or named as BAL.

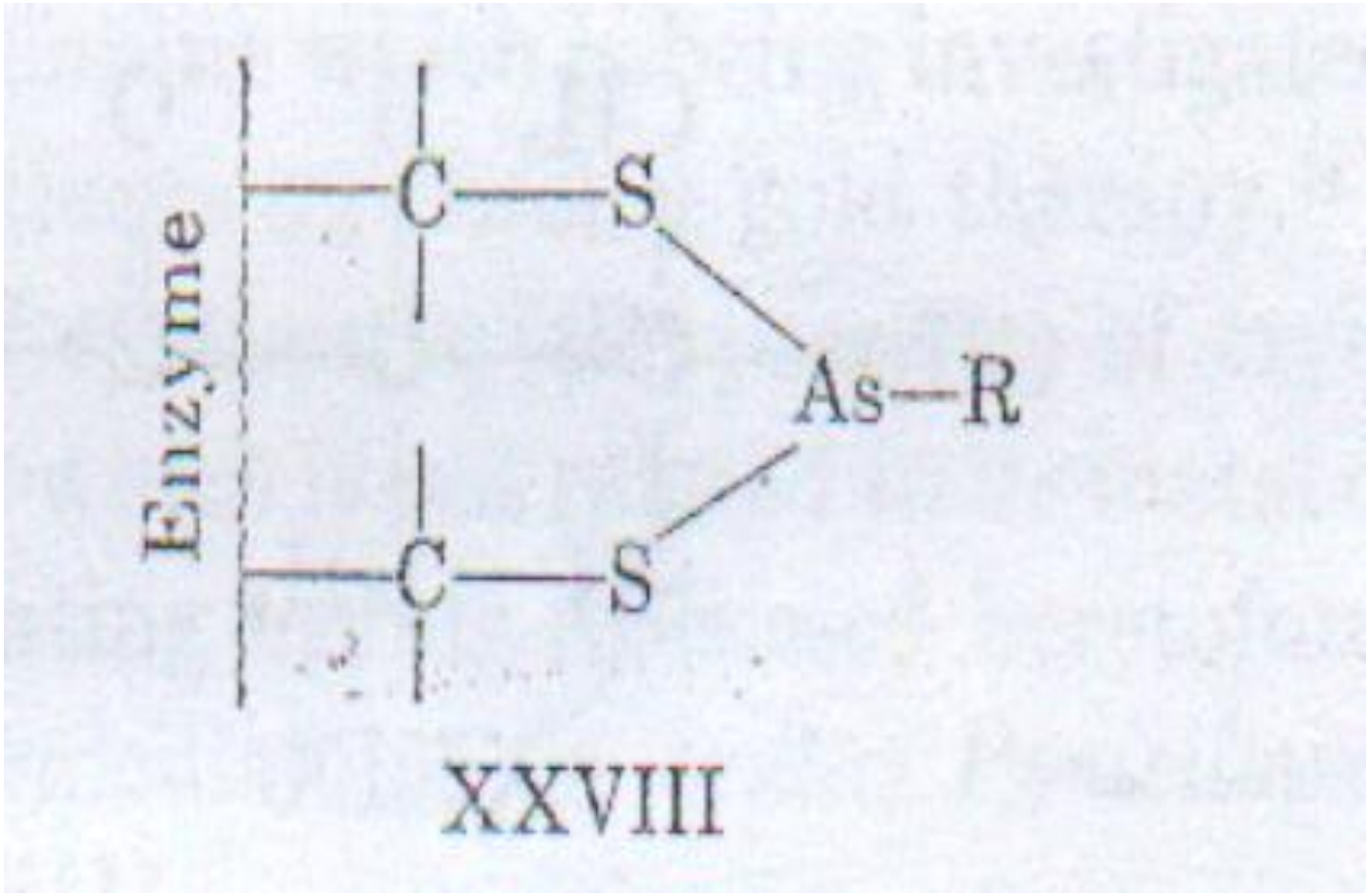
$C_3H_8OS_2$ Mol.Wt.124.22.



XXVII

This compound is a colorless liquid having a disagreeable, mercaptan-like odor. It is soluble in water, alcohol, benzyl benzoate. **Certain heavy metal such** as trivalent Arsenic,owe their cellular toxicity due to the tying up of sulfhydryl (-SH) groups present in enzymes which are responsible for oxidation-reduction reaction in tissues.

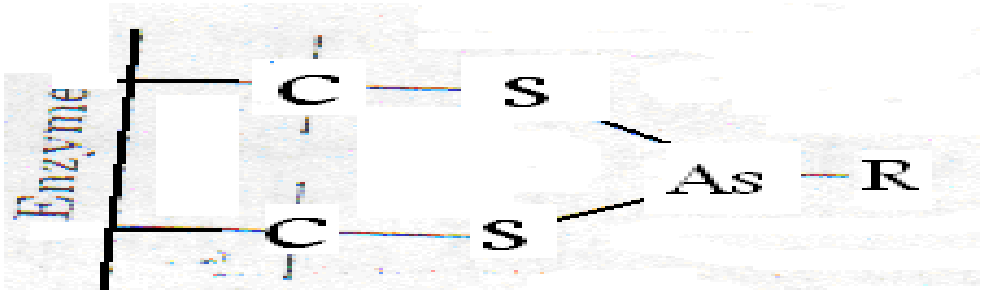
This inactivation involves covalent bond formation between the metal and the sulfhydryl groups, as in bellow.

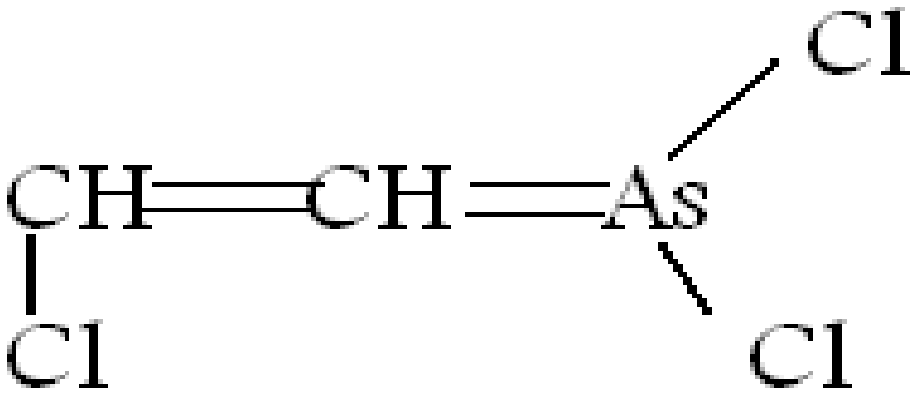


XXVIII

So the use of simple dithiol compounds(those containing sulfhyryl groups) as competitors with enzymes for these metal might serve to prevent toxic reactions.

The idea proved to be successful and subsequent work result in the introduction of dimercaprol or BAL (British anti- lewisite). As an effective neutralization agent for arsenical war gases, such as lewisite


Enzyme
C
S
As
R
C
S


Cl
CH
CH
As
Cl
Cl

Following this use, the compound was used with marked success in the treatment of arsenic poisoning from other sources, and has been extended to the treatment of mercury and gold poisoning.

The compound forms stable mercaptides of the metals which are excreted in the urine. It appears to be value in the treatment of toxic reactions due to arsenic and gold .

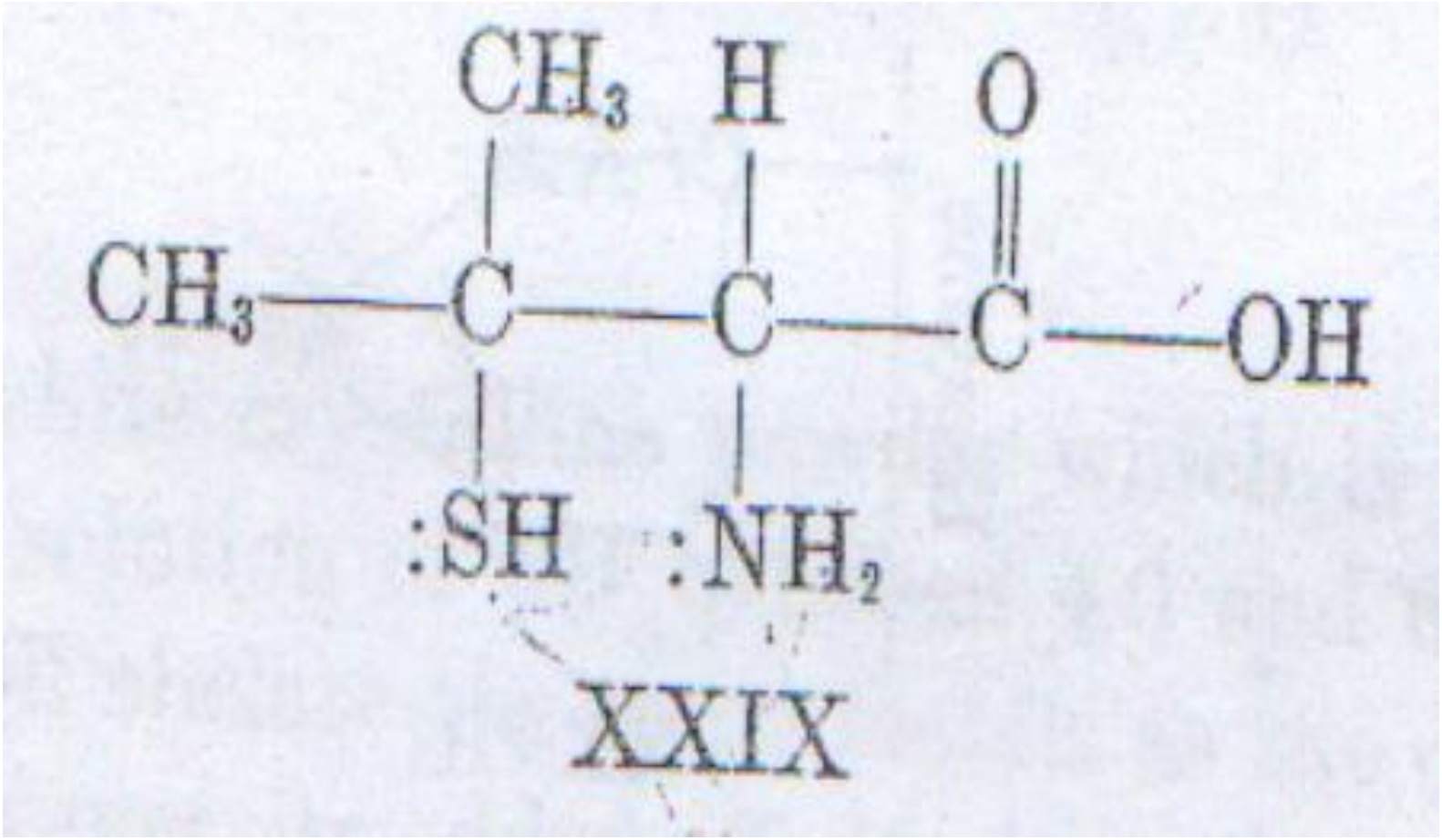
Its effectiveness in the treatment of toxic reactions o mercury is depend upon its use within a few hours following ingestion. Dimercaprol has also been shown to improve the excretion of lead and copper(Wilsons disease), but it is not the agent of choice for these metals.

It is contraindicated in poisonings due to iron, cadmium or selenium because the resulting complexes have greater renal(kidney) toxicities than do the free metals.

The Dimercaprol-metal chelates tend to dissociate in acid media therefore in therapy the urine should be alkalinized e.g with sodium bicarbonate to prevent the release of free metal, producing renal toxicity.

The usual route of administration is by intramuscular injection.

4-Penicillamine D-(-)-3-Mercaptovaline or β, β-Dimethyl-cysteine,$C_5H_{11}NO_2S$ Mol.Wt.149.21.



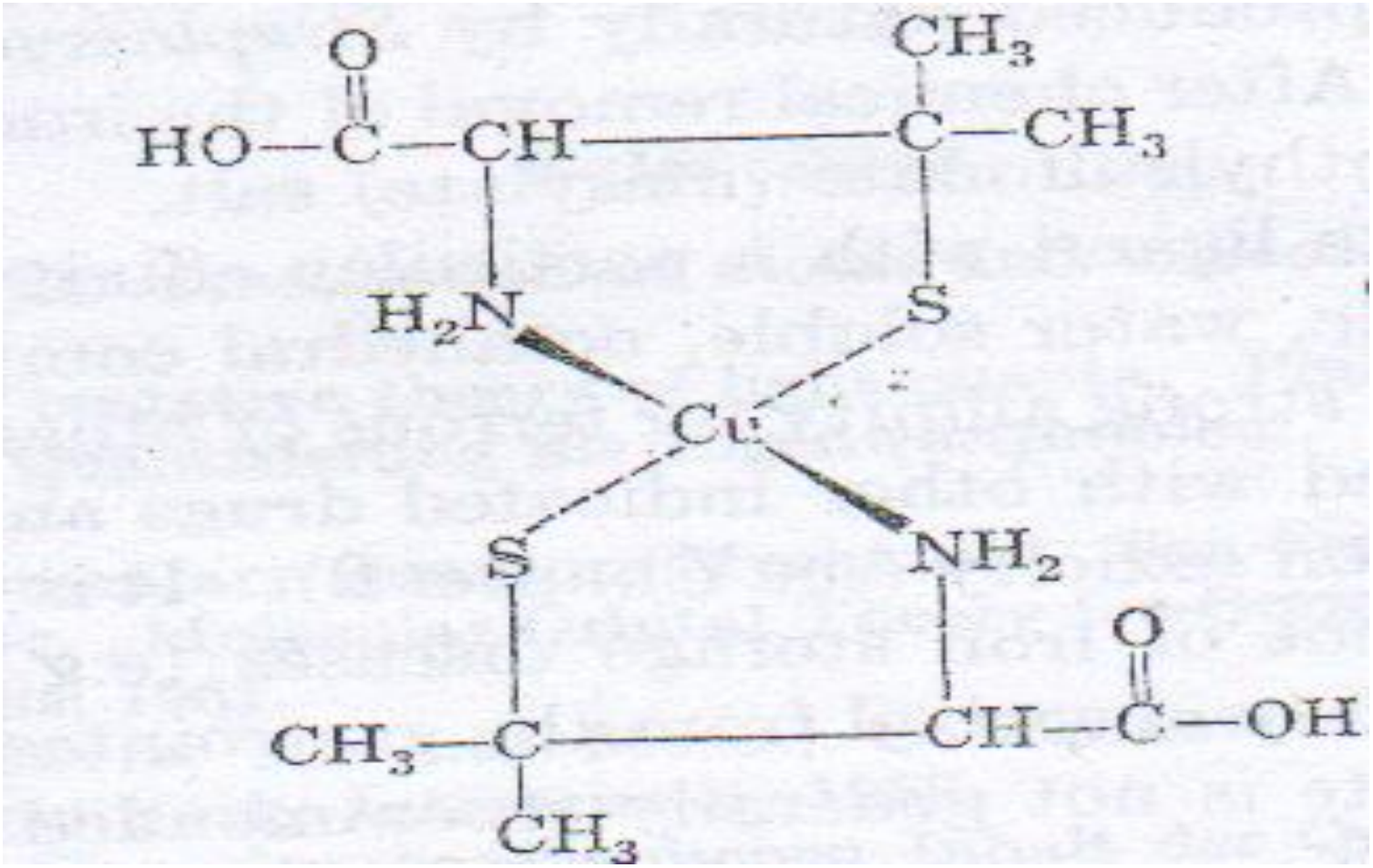
XXIX

it’s a white or off white crystalline powder ,having a slight characteristic odor.
Its freely soluble in water, and slightly soluble in alcohol. the pH of an aqueous solution is between 4.5and 5.5.
Penicillamine is a chelating agent capable of forming soluble complexes with copper ,iron, mercury ,lead ,gold, and other metals.

Its use has been reserved for the improvement of copper excretion in patients with hepatolenticular degeneration(degenerative change in the brain associated with increased levels of copper in the tissues and degeneration of the liver, also known as Wilsons disease).

Penicillamine has been shown to be more effective in promoting urinary excretion of the excess copper in the chelated form.
The effectiveness of Penicillamine is related to its resistance to metabolic inactivation by amino acid oxidase since it lacks a hydrogen in the beta-carbon atom.

The ability of its sulfhydryl group to reduce the Cu(II) in the tissues to Cu(I).
Protein-copper (II) complexes have square planar geometries. Cu(I) must be complexes tetrahedrally, which may limit competing reactions between tissue protein and tetrahedral di Penicillamine-copper (I) complex.

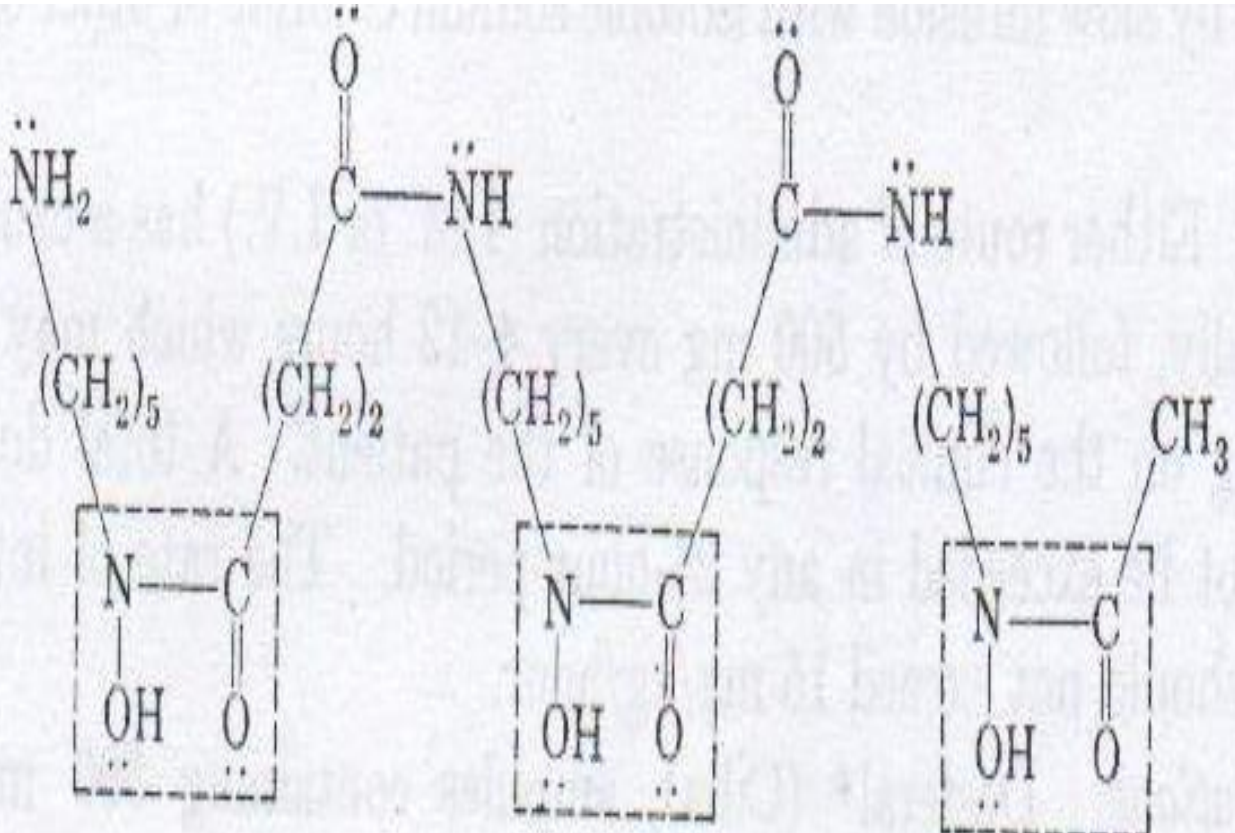

O
CH3
HO—C—CH—C—CH3
H2N
S
Cu
S
NH2
O
CH3—C—CH—C—OH
CH3

Another use of Penicillamine is the treatment of gold dermatitis patients on chronic gold therapy. Also used in the treatment of cystinuria not related to its metal chelating abilities.

Route of administration of Penicillamine is oral . Penicillamine capsules are officinal in the U.S.P.

5.Defroxamine Mesylate :

It has the following chemical structure :-



XXXI

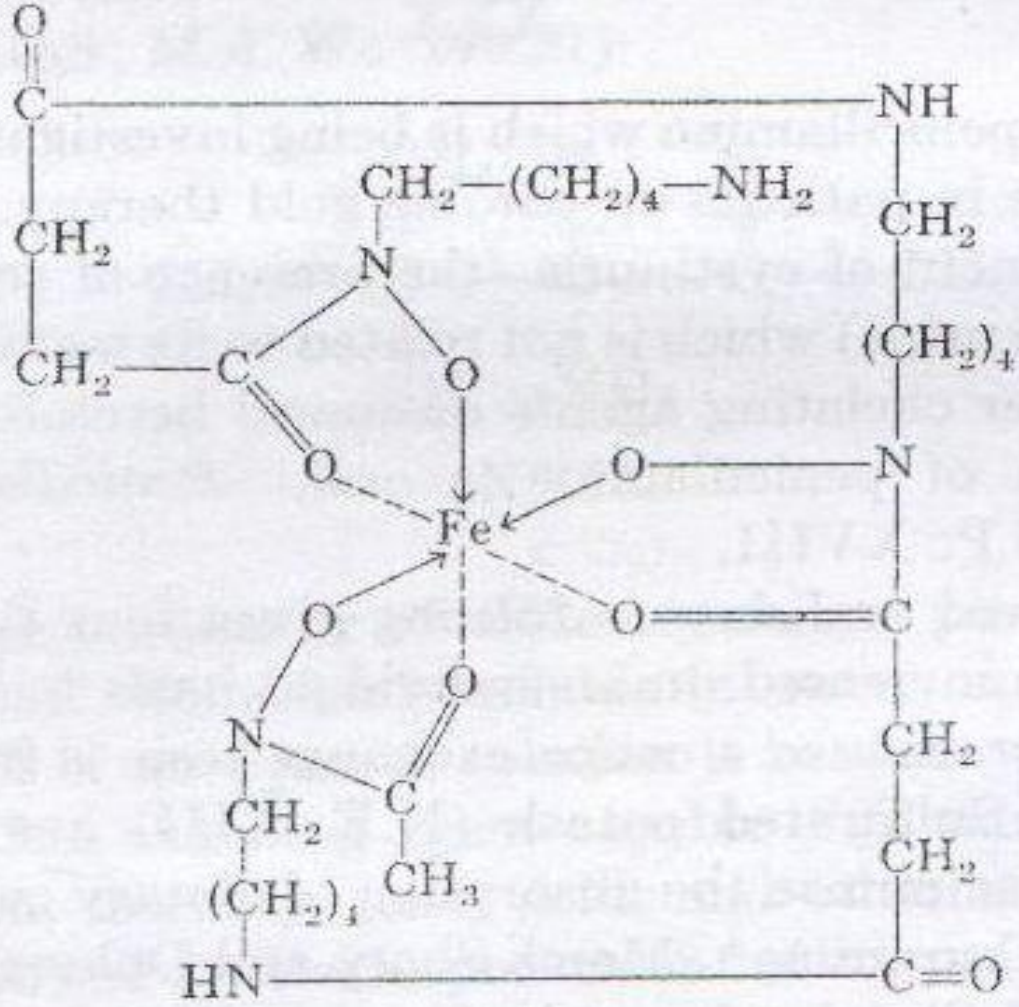
Defroxamine Mesylate is produce naturally by streptomyces pilosus as a ferric [Fe(III)]complex. After chemical removal of iron the chaleting agent is purified as the methylsulfonate (mesylate) salt.

It’s a polydenate ligand with a particular affinity for ferric ions with which it forms stable, water soluble octahydral complexes .

It does not have a very strong affinity for ferrous and other divalent metal ions .
It is used for the treatment of acute iron toxicity. It also under investigation for the treatment of iron storage diseases (eg hemochromatosis).
The compound is poorly absorbed from GIT.

Administration by this route is not generally recommended .
The usual route is by intramuscular or intravenous injection .
The former is preferred intravenous administration is generally done by slow infusion with isotonic sodium chloride or other electrolyte solution the trade name for preparation is Desferal .

Ampoules containing 500 mg of the lyophilized powder for injection .



XXXII

A number of other chelating agents are being investigated for various uses .
One of the uses is for improving the excretion of some long-lived radioactive isotopes.
One of these agent is trisodium calcium diethylene triaminepenta acetate[tri sodium calcium pentate].
The penta acid form is known DTPA..

The end