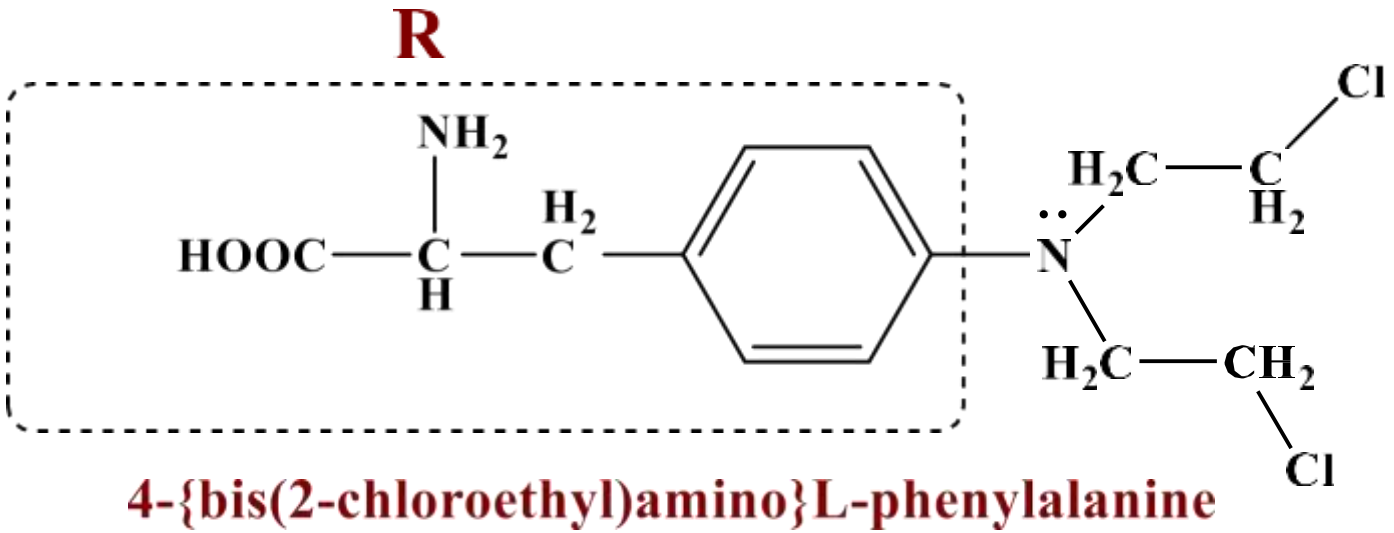
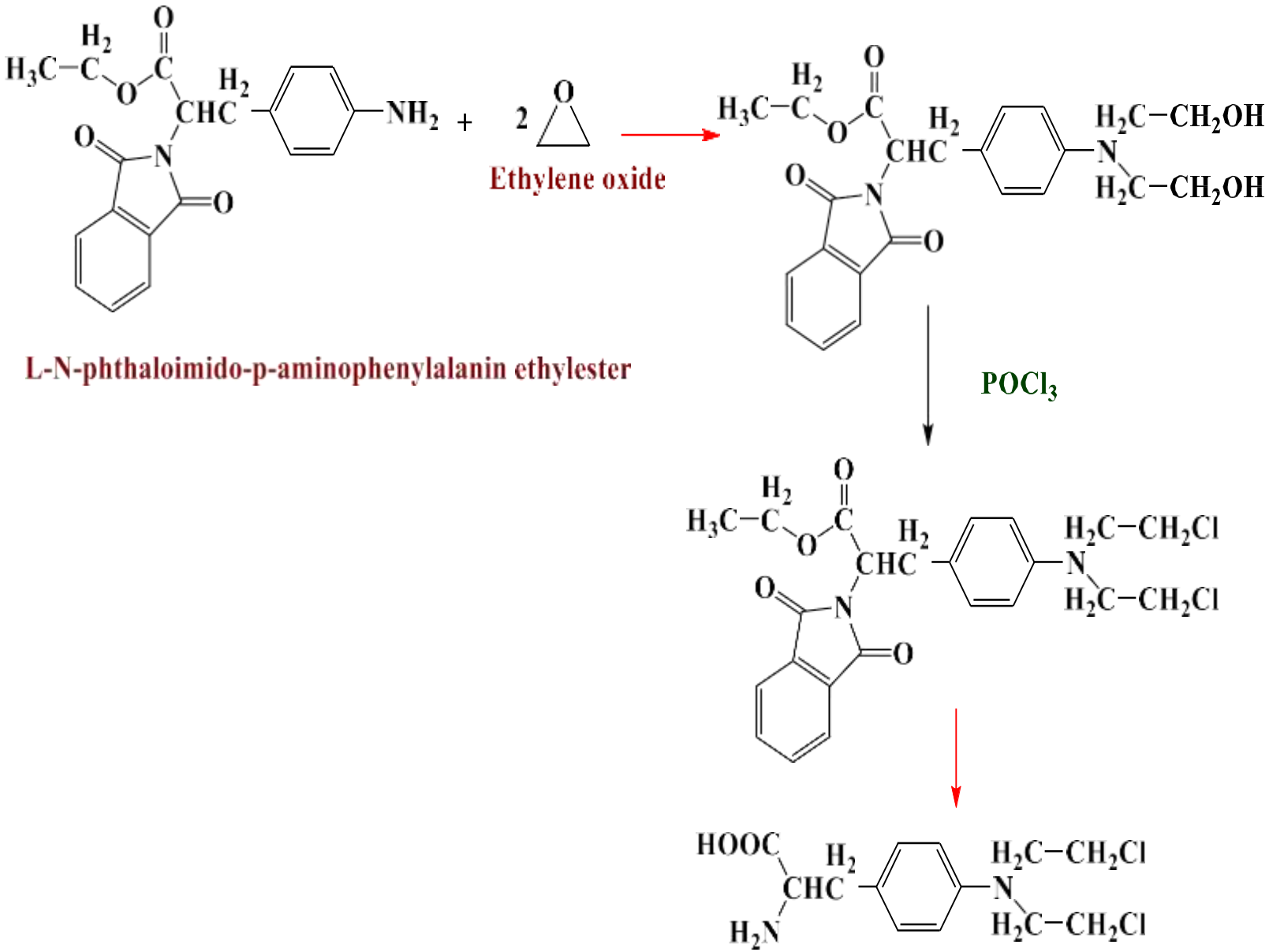
Melphalan



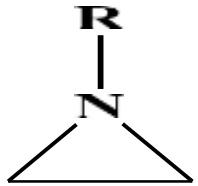
4-{bis(2-chloroethyl)amino}L-phenylalanine

Uses:- it is active against multiple myeloma and active against breast, testicular, and ovarian carcinoma.

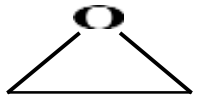
Preparation of melphalan



Ethyleneimine (aziridine) and epoxide



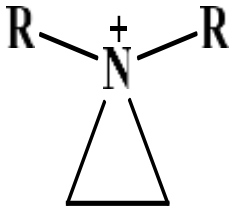
Ethylene imine
Aziridine



Epoxide

strained ring systems
do not react readily as aziridinium ion
or episulfonium ions with nucleophiles.
Their reaction are second order and are
enhanced by the presence of acid.

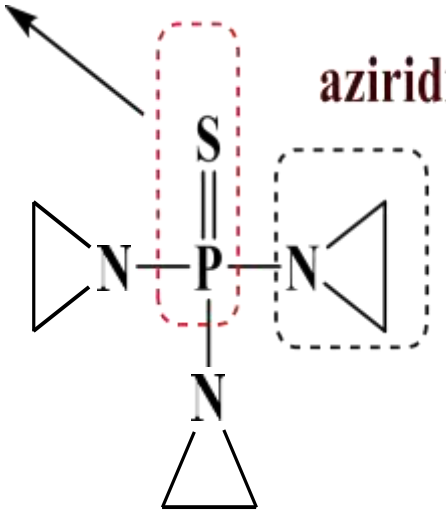
Aziridine
less reactive (slow reaction)



Aziridinium ion
more reactive (faster reaction)because of positive charge

Thiotepa•

thiophosphoramide(e' withdrawing) → ↓ reactivity of aziridine



less reactive aziridine compared with aziridinium ion formed in mechlorethamine

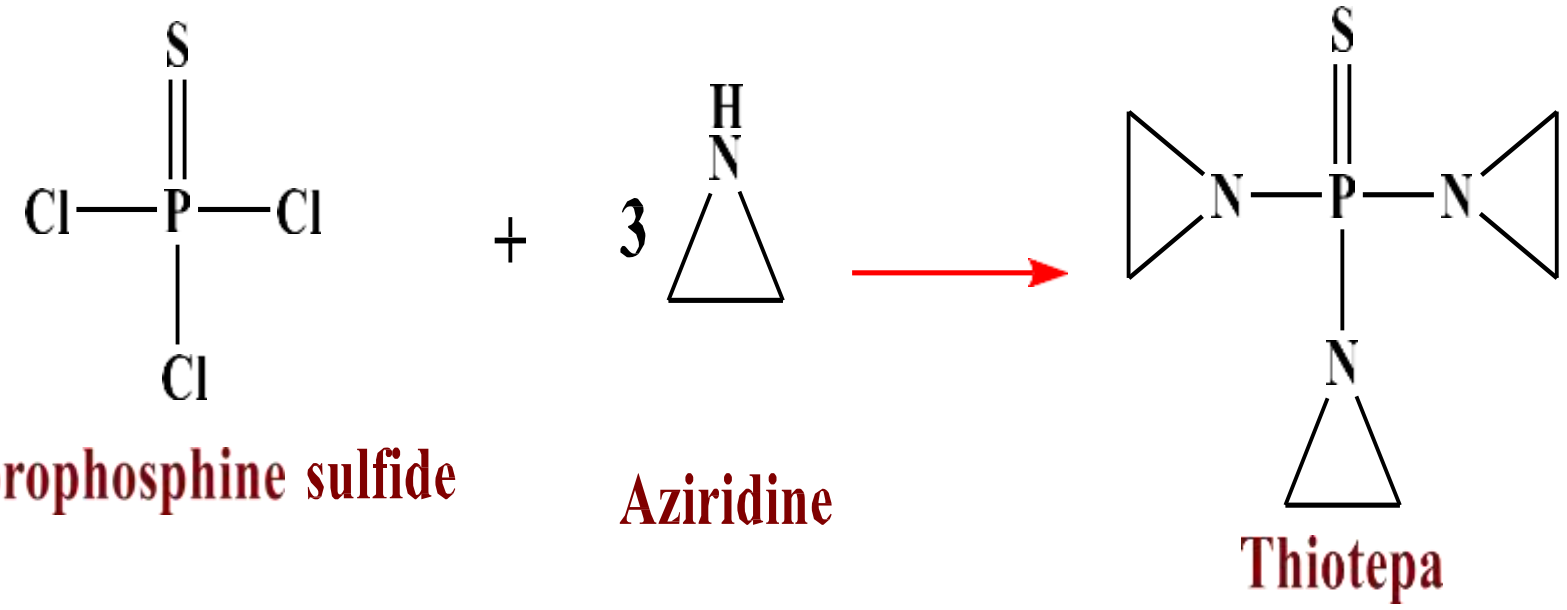
N,N',N''-triethylenethiophosphoramide
tris(1-aziridinyl) phosphine sulfide

Thiotepa is aziridine and not aziridinum ion

slow alkylator

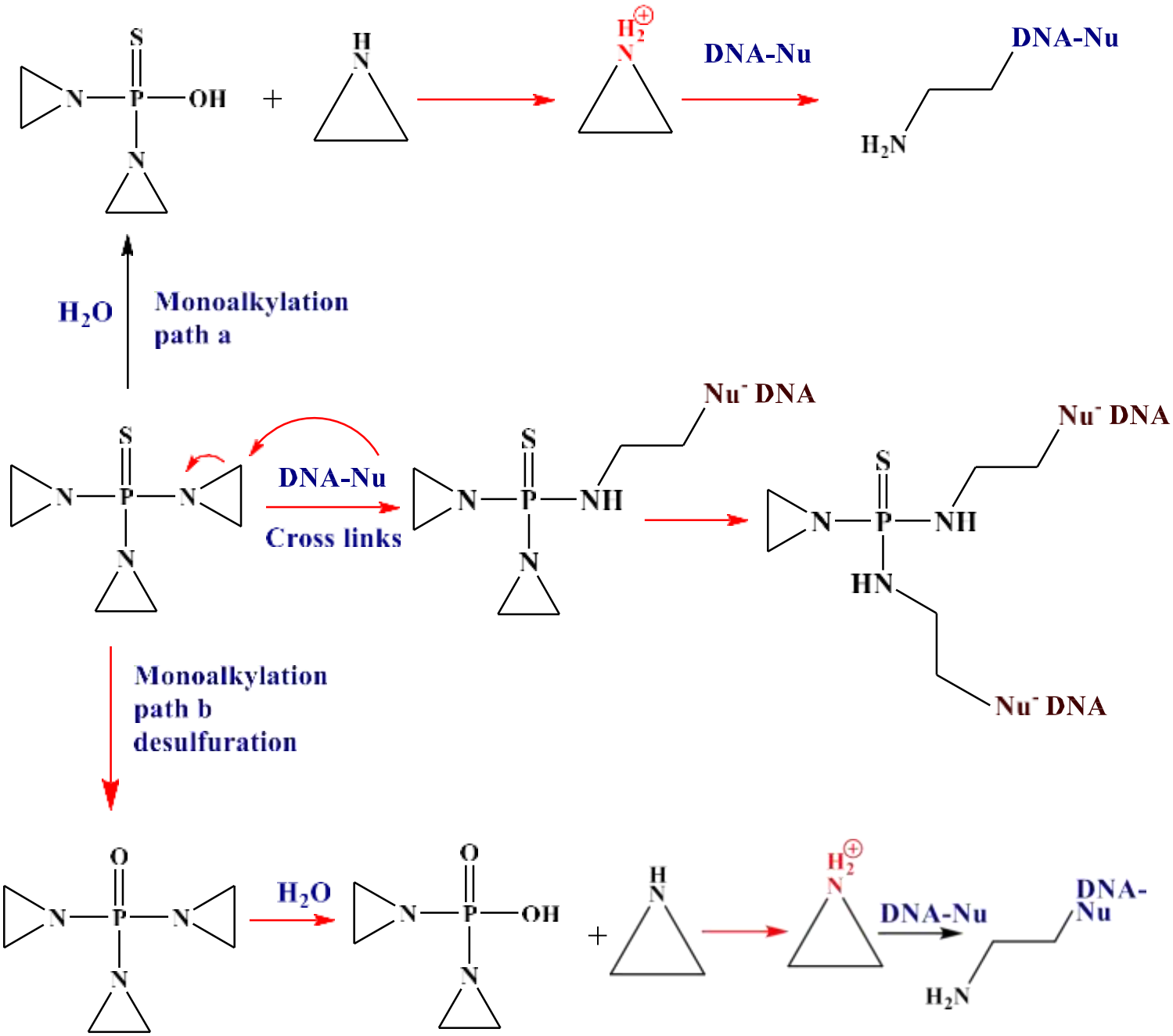
alkylation through second order reaction.

Preparation of Thiotepa



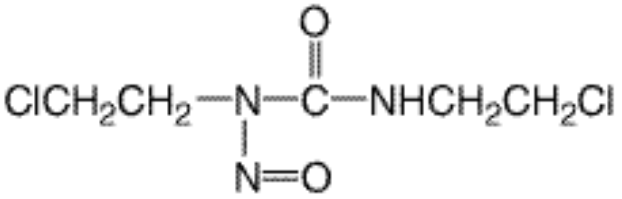
Uses: - used as palliative in breast, ovarian, bronchogenic carcinoma and malignant lymphomas.

Dosage form: - (15mg) vial


DNA-Nu
DNA-Nu
H2O
Monoalkylation
path a
Nu- DNA
DNA-Nu
Cross links
Nu- DNA
Monoalkylation
path b
desulfuration
Nu- DNA
H2O
DNA-Nu
DNA-Nu

Nitrosoureas

Inhibits DNA, RNA and protein synthesis
lipid soluble (cross blood-brain barrier)
Carmustine (BCNU) :
IV infusion over 1-2hrs
Lomustine (CCNU) : taken orally



CARMUSTINE (BCNU)

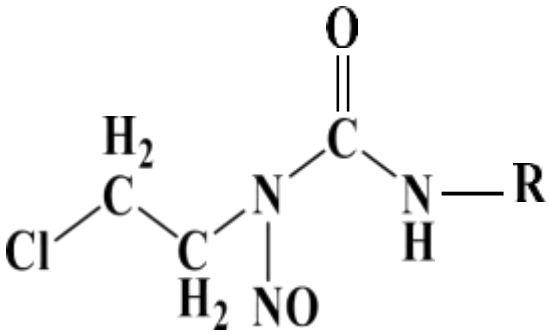
Effective against brain tumors and also in Hodgkin's lymphoma

Toxicity:

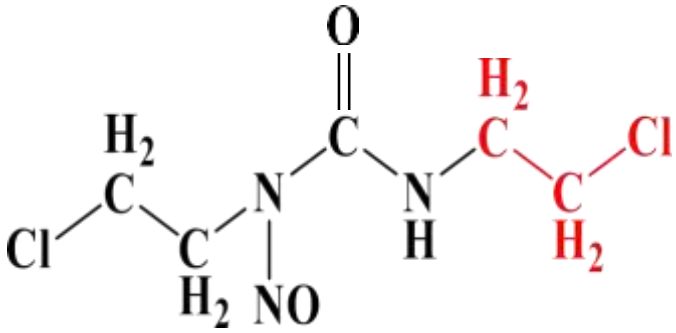
profound delayed and cumulative bone marrow depression, N&V, pulmonary fibrosis (6 months after therapy to 15 years after), renal damage, reversible liver damage and leukemia.

Basic structure of Nitrosourea

Three products:-

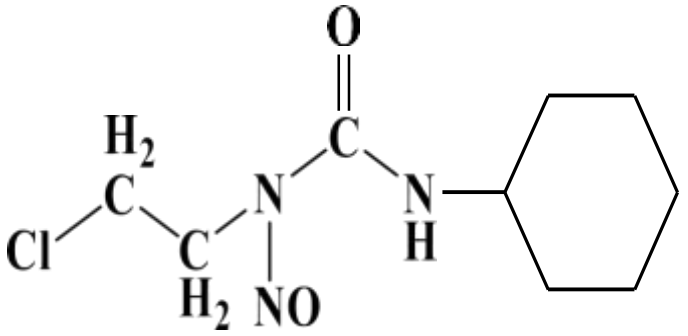


R= CH-CH_2-Cl



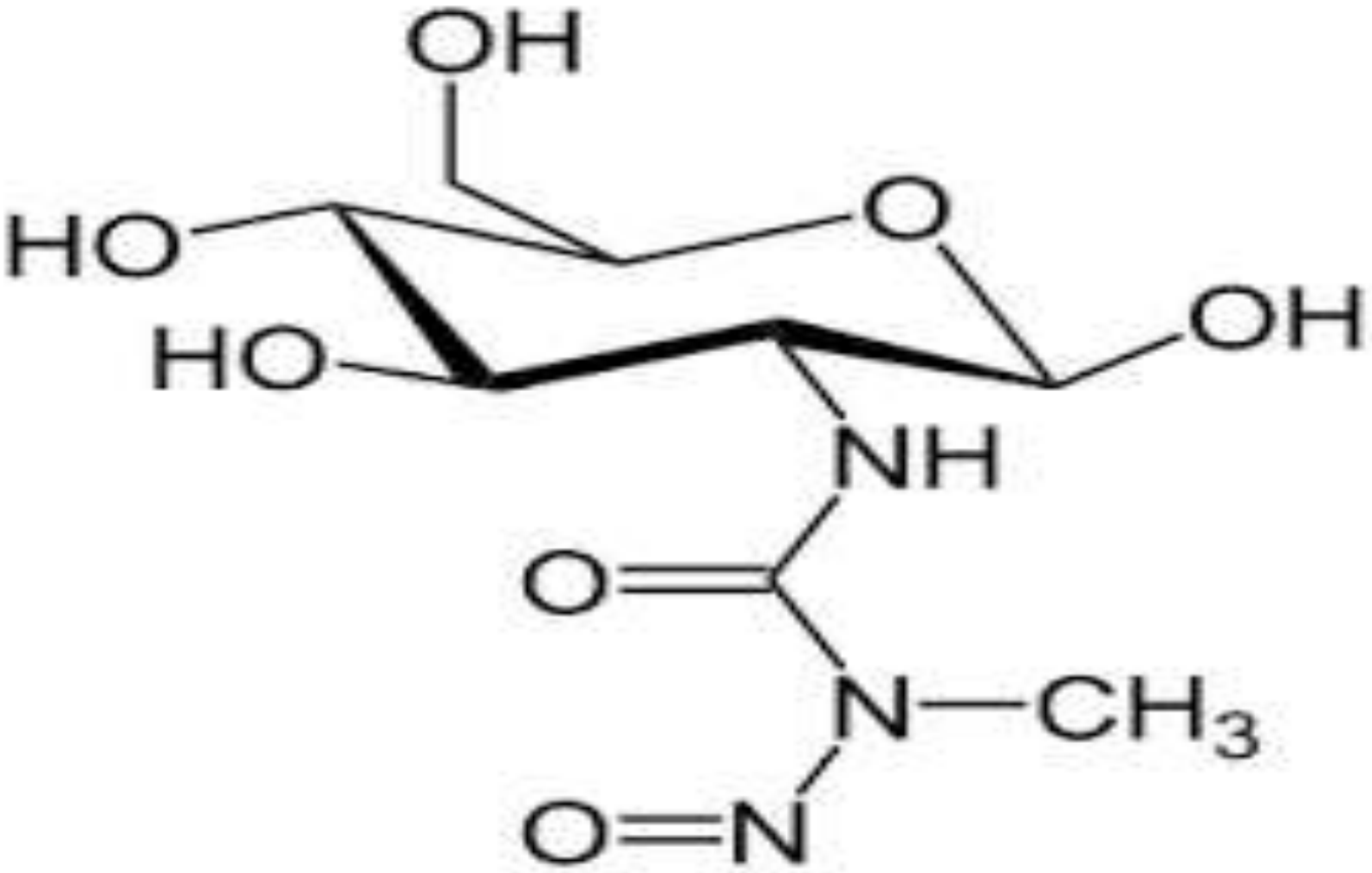
Carmustin BCNU

R=

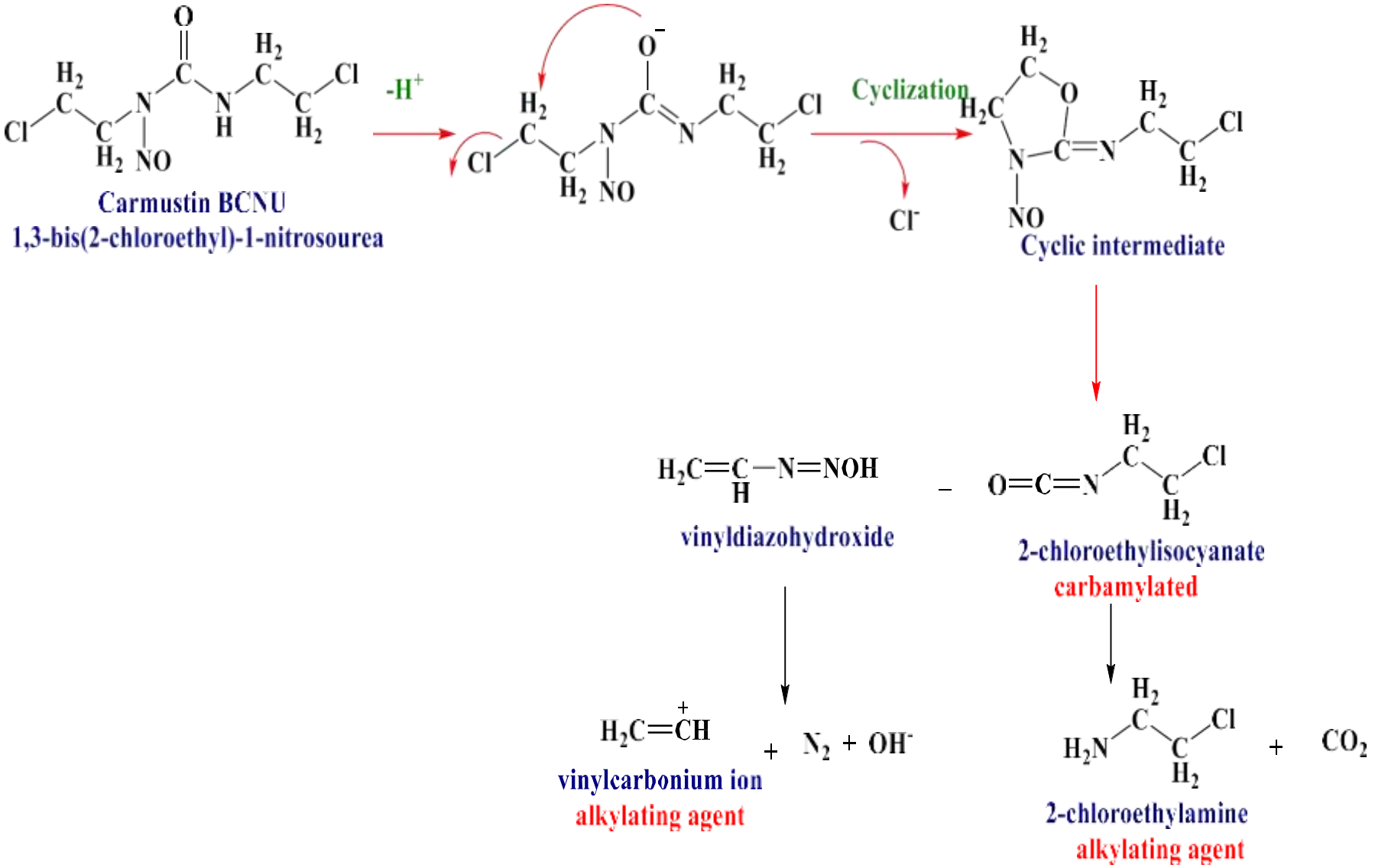


Lomustin CCNU

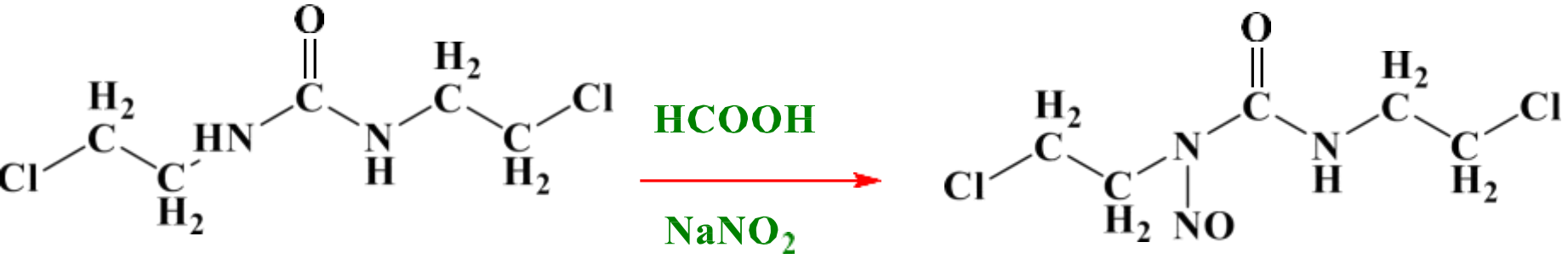
Streptozocin



Carmustine (BCNU)



Preparation of Carmustine

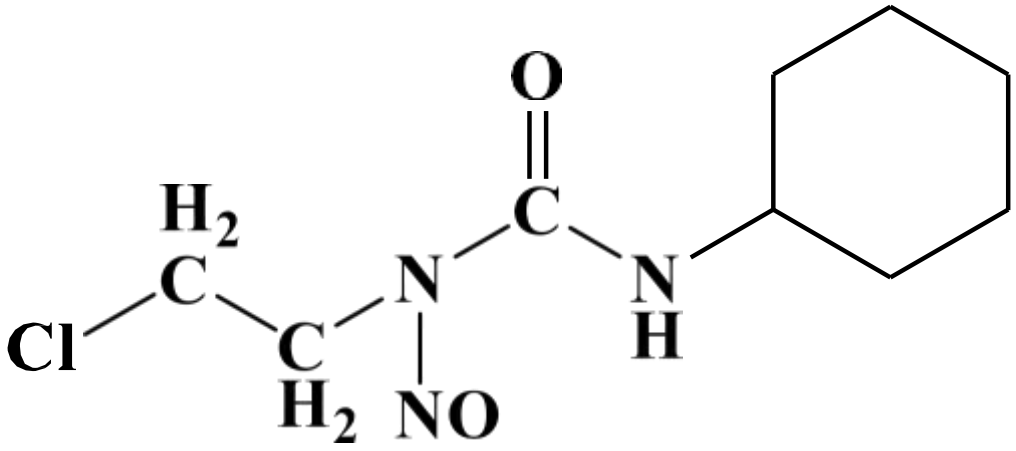


1,3-bis(2-chloroethyl)ourea

Carmustin BCNU
1,3-bis(2-chloroethyl)-1-nitrosourea

Uses:- because of it is ability to cross the BBB, it is used against brain tumor and other tumors, such as leukemia that have metastasized to the brain. It also is used as secondary therapy in combination with other agents for Hodgkin's disease and other lymphomas. Combination with prednisone useful in multiple myeloma.

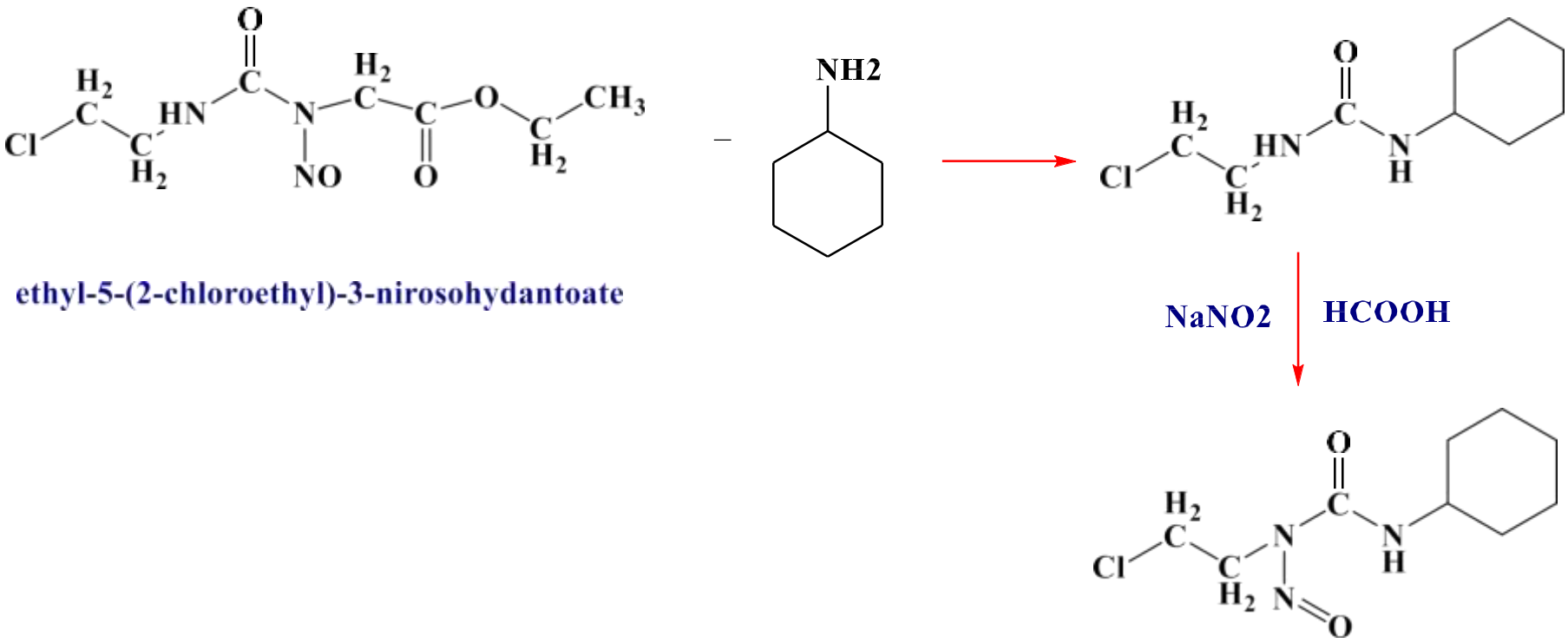
Dosage form: - IV inj (100 mg) it is administered IV because metabolism is very rapid.



Lomustine CCNU

1-(2-chloroethyl)-3-cyclohexyl-1-nirosoourea

Preparation of lomustine



ethyl-5-(2-chloroethyl)-3-nirosohydantoate

Uses:- The high lipid solubility of lumostine allows it to cross the BBB, and it is used for primary and metastatic brain tumors and as secondary therapy in Hodgkin's disease.

Dosage form:- given orally (capsules,10,40, and 100 mg), because it is sufficiently stable to metabolism.

repair enzyme, DNA nucleotidyltransferase of L 1210 leukemia cells is

Alkylsulphonate.

Busulfan is an alkylating agent that has been used extensively in the treatment of chronic granulomatous leukemia, although currently it is used mainly as a conditioning agent prior to stem cell transplantation

Alkylating agents

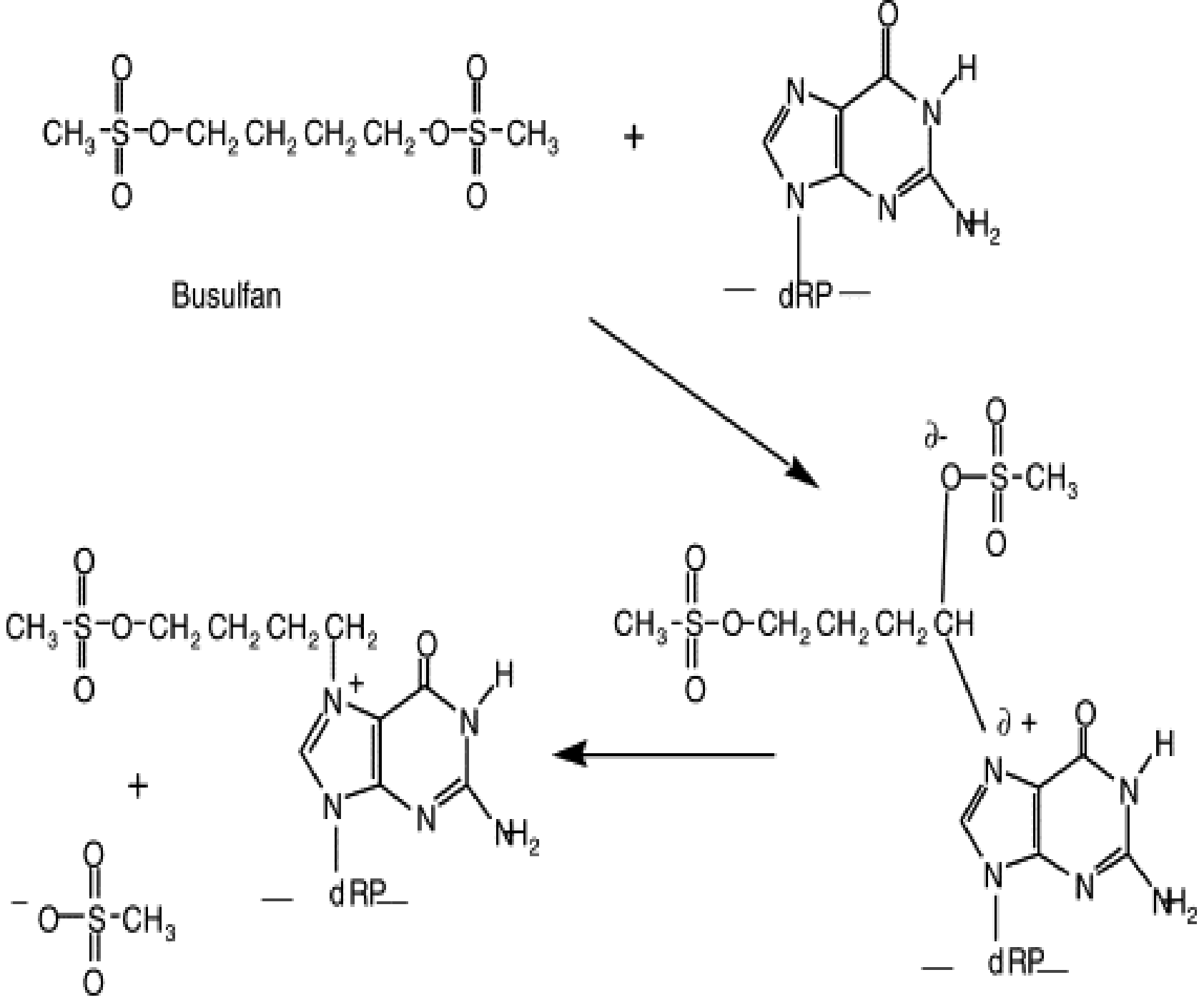
Alkyl sulfonates

Busulfan

Well absorbed orally;
plasma half-life 2-3hrs

Active against Chronic Myeloid Leukemia

Toxicity:
N&V, bone marrow depression (stem cells), pulmonary infiltrates and fibrosis.


Busulfan
dRP
dRP
dRP