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Elucidation the Synthesis of an Antibiotic Medicine Chloramphenicol Palmitate with its Stepwise Mechanism

Rahul Thakur

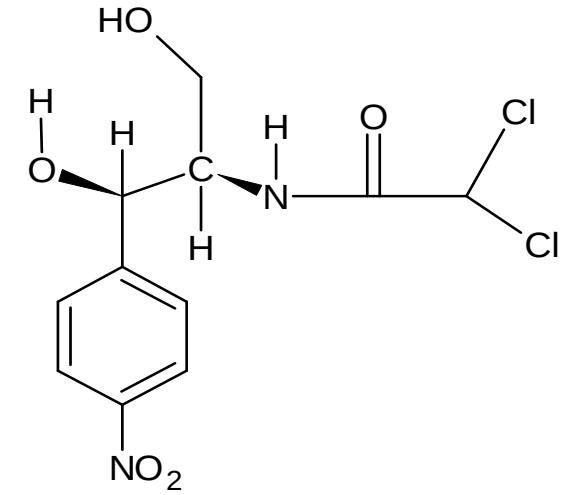
M. Sc (Pharmaceutical Chemistry), Departmentof Pharmaceutical Sciences, Lovely Professional University, Punjab, India
E- Mail: *thakurrahul214[at]gmail.com*

Abstract: ***Chloramphenicol is an antibiotic or antibacterial medicine that was the first manmade drug. Chloramphenicol is a crystalline white or yellowish - white powder and is also available in fine crystal form. It is used for various bacterial infections. An eye ointment of Chloramphenicol is used to treat conjunctivitis or pink eyes, Plague, Typhoid, Meningitis, Cholera, septicaemia etc are also treated by Chloramphenicol medicine or by its injection. Chloramphenicol is bitter in taste if we take via orally. To remove its bitterness Chloramphenicol is treated with Palmitic acid via esterification and it becomes Chloramphenicol Palmitate. Hence it becomes tasteless and water - insoluble. In this review, I present the synthesis of Chloramphenicol Palmitate with its simple and clearly understandable mechanism which is very useful to everyone to understand that how Chloramphenicol Palmitate is synthesized. I also present the explanation of its all steps with its explained mechanism.***

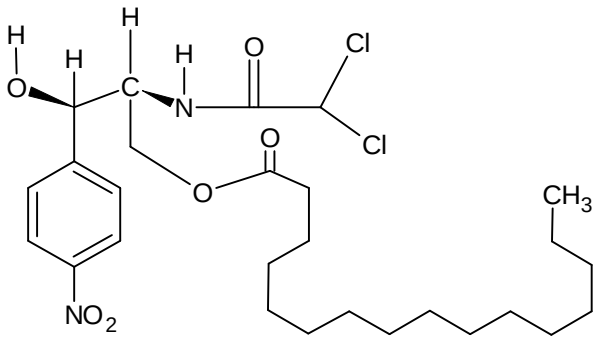
Keywords: Palmitic Acid, Chloramphenicol palmitate, Antibiotic Chloramphenicol

1. Introduction

Chloramphenicol was extracted from Streptomyces Venezuelae, in 1947. After two years in 1949, its chemical structure was identified and also synthesized by the team of scientists at Parke - Davis. Its bacteriostatic property inhibits protein synthesis.1 Bacterial Ribosome activity inhibits the peptidyl transferase caused by preventing protein chain elongation by Chloramphenicol. The two chiral centers of Chloramphenicol consist of four stereoisomers.2 The stereoisomers of Chloramphenicol are D - erythro, L - erythro, D - threo, and L - threo. D - threo isomer is the active form of Chloramphenicol. D - erythro form of Chloramphenicol has approximately 97.5% bacteriostatic potencies because D - erythro isomer geometry fits in the L - amino acids of protein. Hence it inhibits the protein synthesis. L - erythro form of Chloramphenicol consists of 2.5% bacteriostatic potencies.3, [4] There are many brand names of Chloramphenicol or Chloramphenicol Palmitate such as chloromycetin, levomycetin, etc. although its availability worldwide as in form of generic drug. Chloramphenicol is a crystalline white or yellowish - white powder and is also available in fine crystal form. Chloramphenicol Palmitate or Chloramphenicol Palmitate Ester CPE is a pro - drug form of Chloramphenicol which is inactive. When Chloramphenicol Palmitate Ester CPE is gotten hydrolyzed then it gets converted into an active form in the small intestine and also iron absorption is increased by Chloramphenicol. There is no bioavailability difference is noticed after being hydrolysis of Chloramphenicol Palmitate Ester CPE.5, [6, 7]



(Chloroampheniol)
Figure 1.8



Chloramphenicol Palmitate
Figure 2.9

Side Effects

Chloramphenicol can be caused nausea, diarrhea, bone marrow suppression. The suppression of bone marrow may cause death because of abnormal enhances of an immature white blood cell. There should be short treatment to minimize these effects. A lower dose should be prescribed

for those who are suffering from liver, kidney problems. The excessive dose of Chloramphenicol Palmitate may cause grey baby syndrome which is generally found in young children, neonates. The symptoms of grey baby syndrome are low blood pressure (hypotension), swollen stomach, cynosis. Chloramphenicol may also cause Neurotoxic reaction; headache, mild depression, mental confusion, etc.1[0, 11, 12]

Solubility

Chloramphenicol: are soluble in ethyl acetate, propylene glycol, acetone, slightly soluble in water, in alcohol.

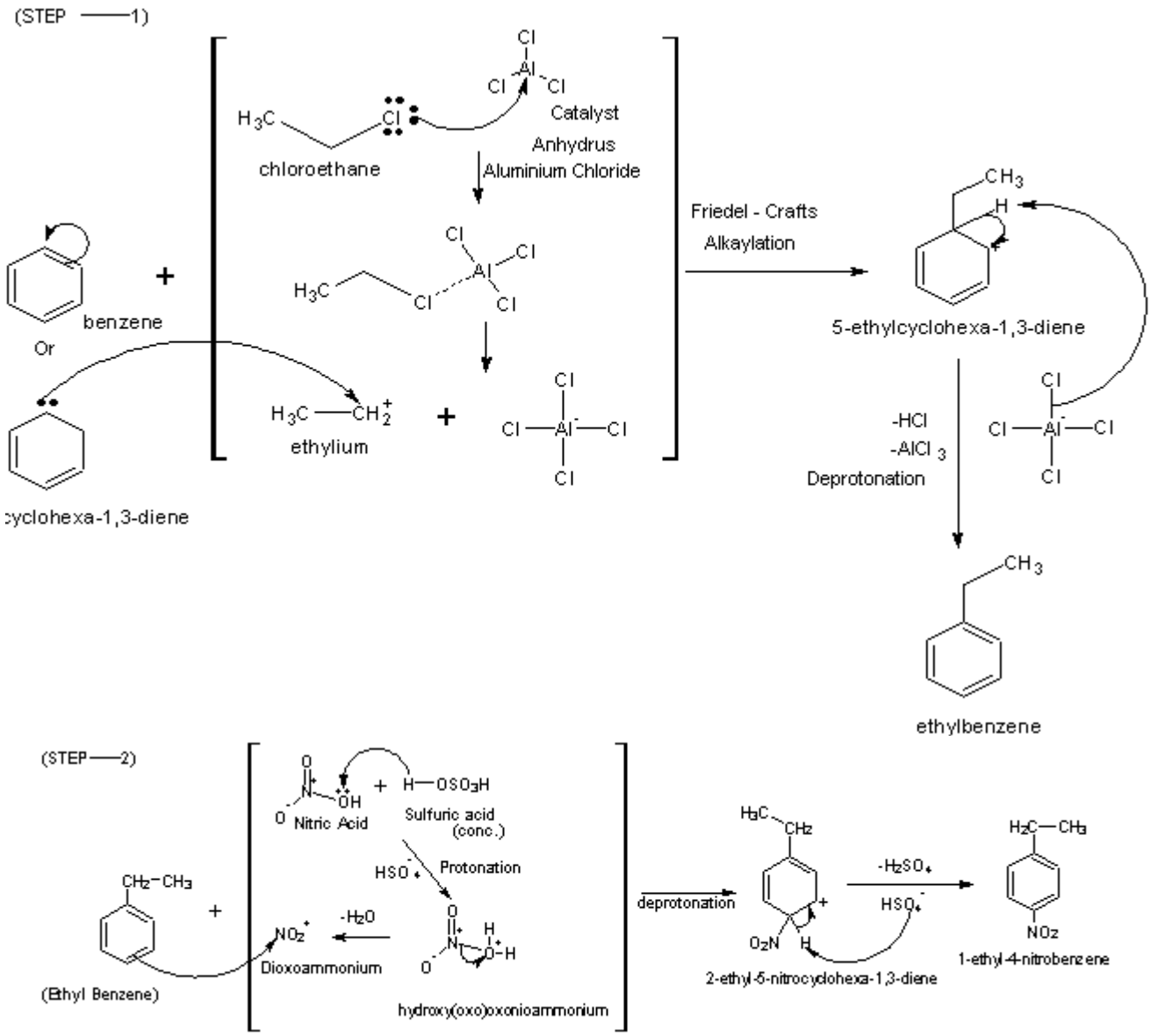
Chloramphenicol Palmitate: are soluble in ether, very slightly soluble in hexane, in chloroform, in acetone, in alcohol. Chloramphenicol Palmitate is insoluble in water.1[3]

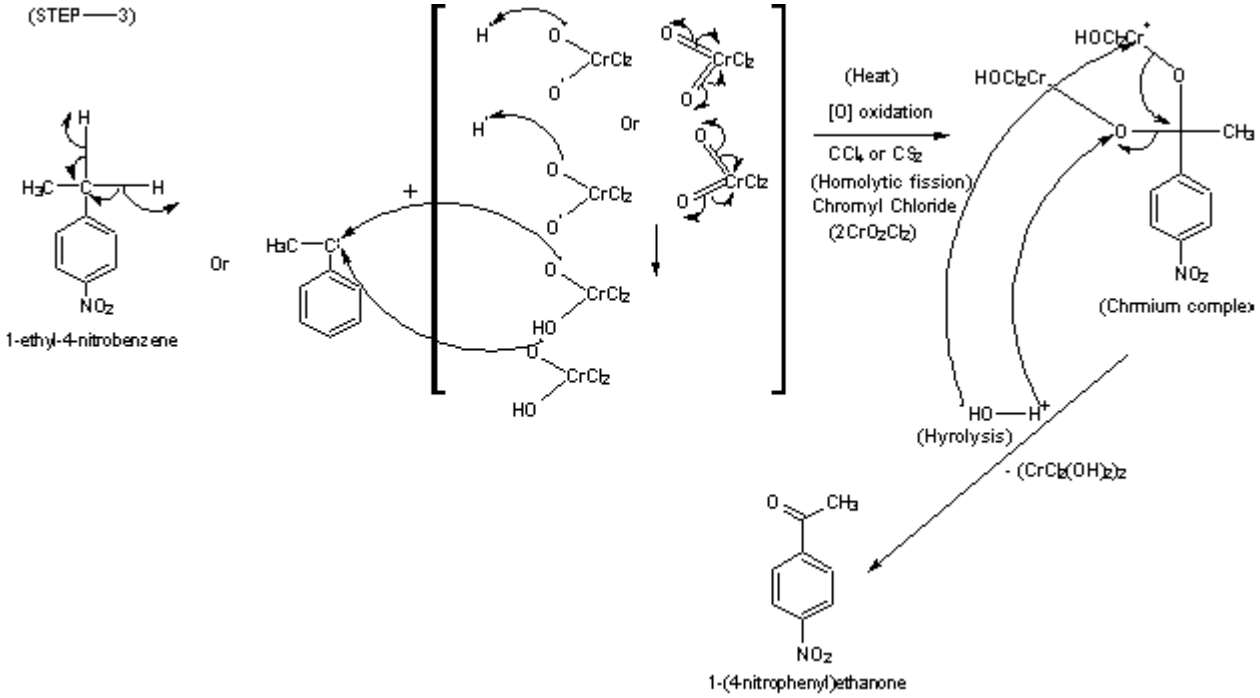
Veterinary Use of Chloramphenicol

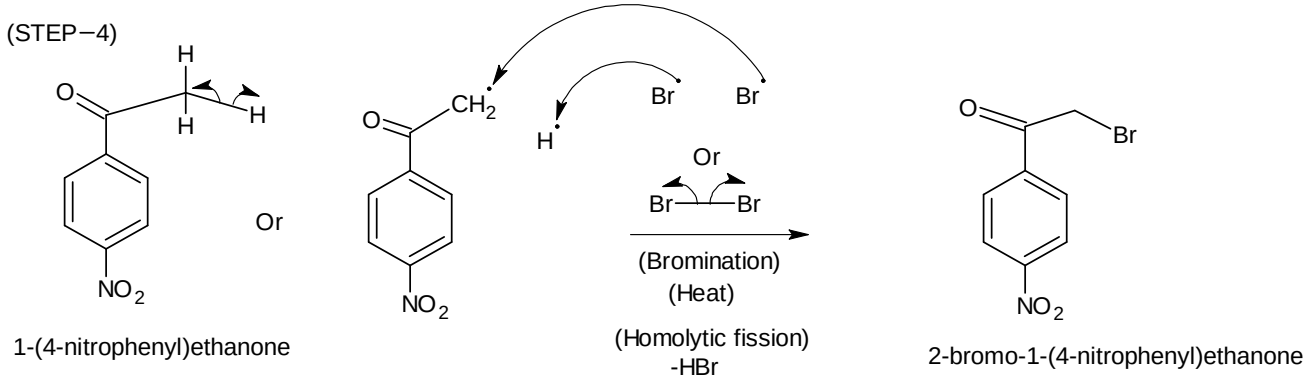
Chloramphenicol is also be used for animal treatment. Chlamydial (sexually transmitted) disease in Koalas is cured by Chloramphenicol. Chytridiomycosis (fungal) disease in amphibians is also be treated by Chloramphenicol. Chloramphenical antibiotics can also be used for the treatment of dogs, cats, horses for their bacterial infections.1[4]

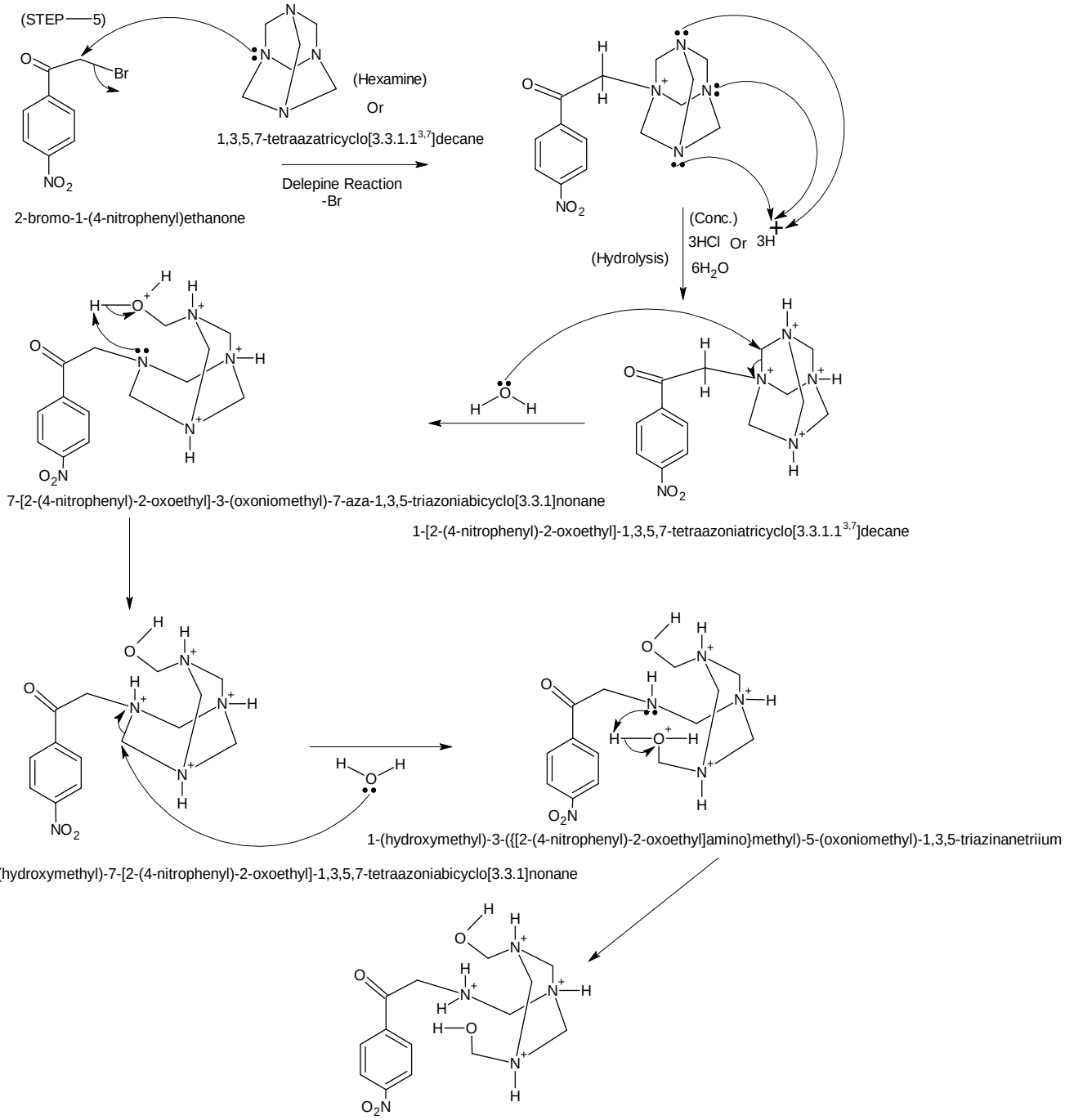
Synthesis of Chloramphenicol Palmitate

There is a various method to synthesis of Chloramphenicol or Chloramphenicol Palmitate. One of them in which ethylbenzene is used as starting material and the chain or order of reaction forward to the formation of Chloramphenicol Palmitate are as given below: [15]









2-bromo-1-(4-nitrophenyl)ethanone

7-[2-(4-nitrophenyl)-2-oxoethyl]-3-(oxoniomethyl)-7-aza-1,3,5-triazoniabicyclo[3.3.1]nonane

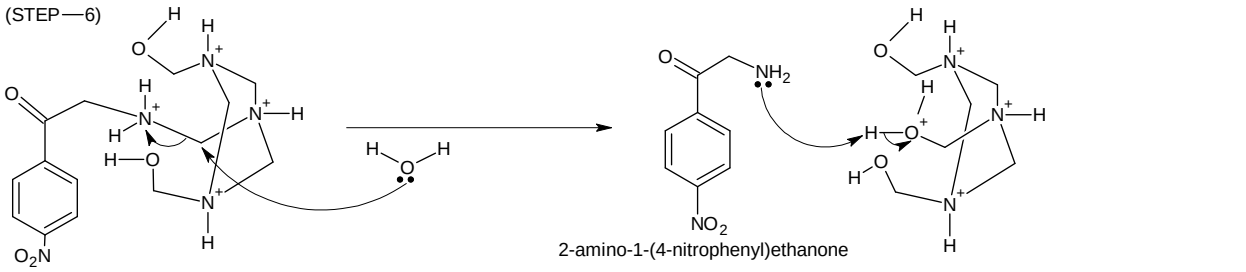
1-[2-(4-nitrophenyl)-2-oxoethyl]-1,3,5,7-tetraazoniatricyclo[3.3.1.1^{3,7}]decane

3-(hydroxymethyl)-7-[2-(4-nitrophenyl)-2-oxoethyl]-1,3,5,7-tetraazoniabicyclo[3.3.1]nonane

1-(hydroxymethyl)-3-({[2-(4-nitrophenyl)-2-oxoethyl]amino}methyl)-5-(oxoniomethyl)-1,3,5-triazinanetriium

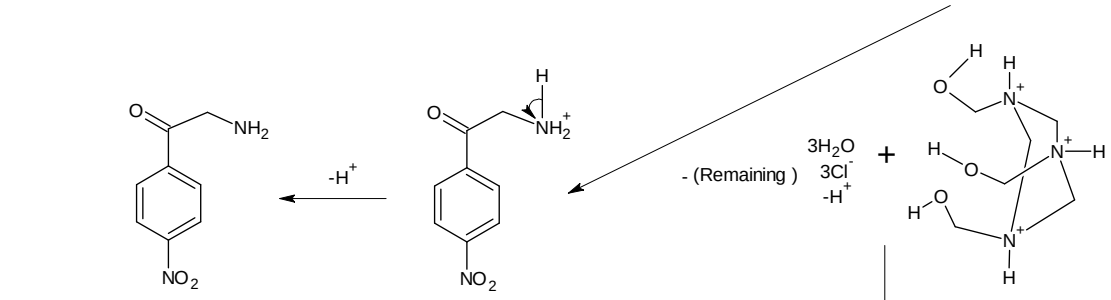
1,3-bis(hydroxymethyl)-5-({[2-(4-nitrophenyl)-2-oxoethyl]ammonio}methyl)-1,3,5-triazinanetriium

(STEP—6)



2-amino-1-(4-nitrophenyl)ethanone

1,3-bis(hydroxymethyl)-5-(oxoniomethyl)-1,3,5-triazinanetriium



2-amino-1-(4-nitrophenyl)ethanone

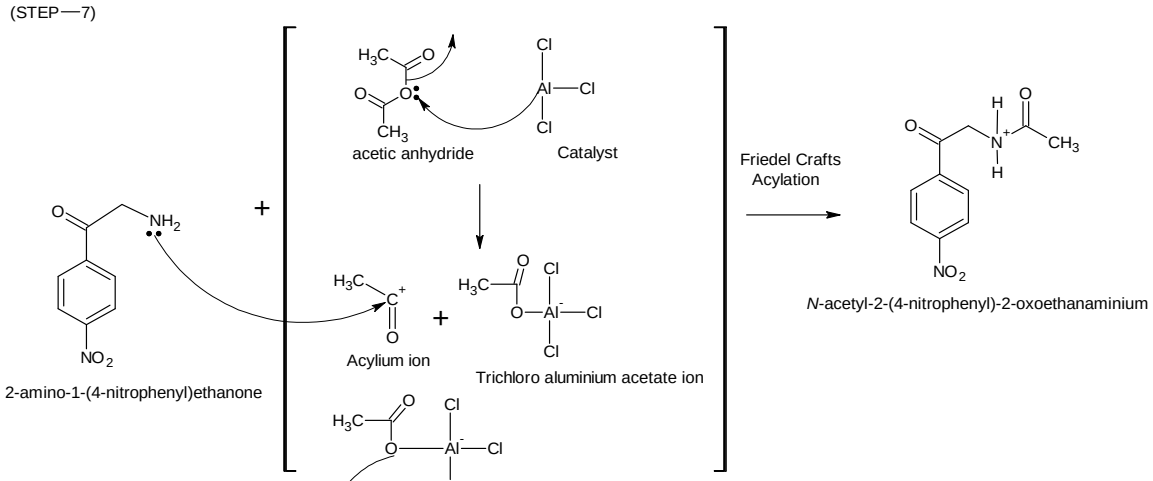
2-(4-nitrophenyl)-2-oxoethanaminium

- (Remaining)

Ammonium Chloride

Formaldehyde

(STEP—7)



acetic anhydride

Catalyst

2-amino-1-(4-nitrophenyl)ethanone

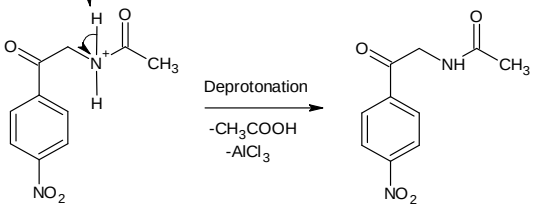
Acylium ion

Trichloro aluminium acetate ion

Friedel Crafts Acylation

N-acetyl-2-(4-nitrophenyl)-2-oxoethanaminium

(STEP——7.1)

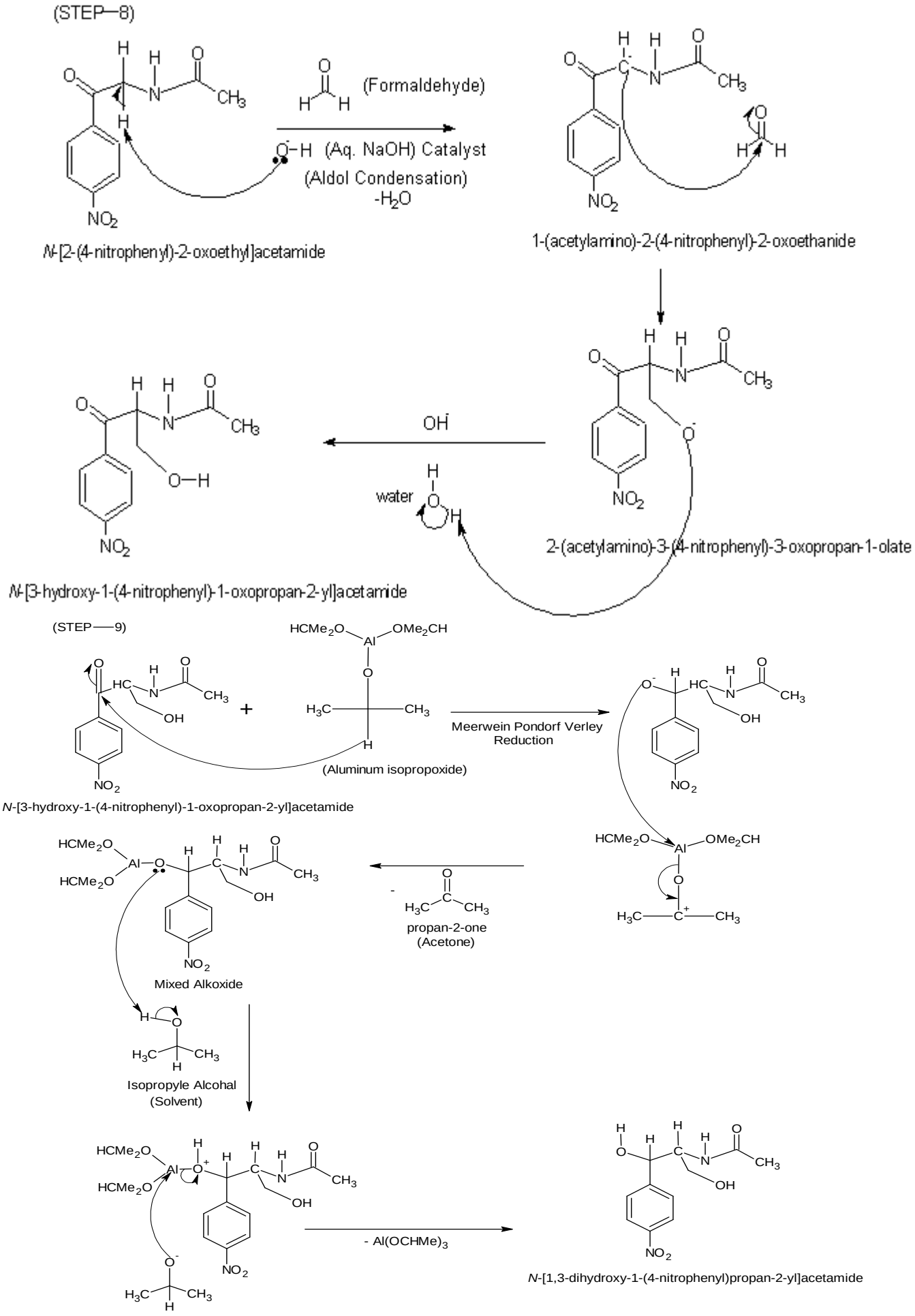


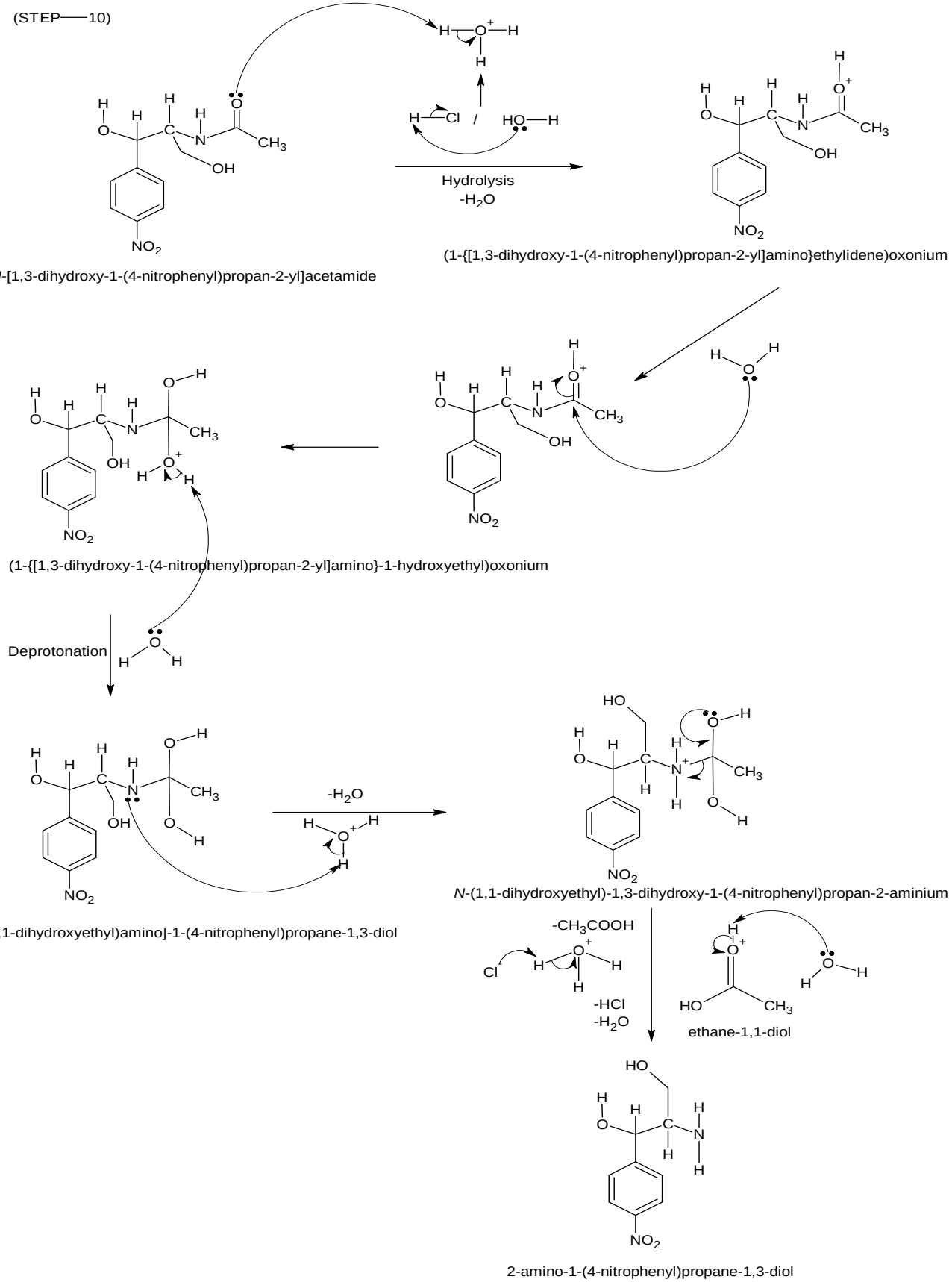
Deprotonation

$-CH_3COOH$

$-AlCl_3$

N-[2-(4-nitrophenyl)-2-oxoethyl]acetamide





N-[1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide

(1-{[1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]amino}ethylidene)oxonium

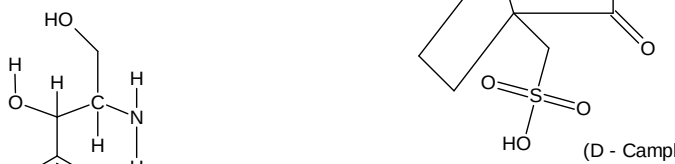
(1-{[1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]amino}-1-hydroxyethyl)oxonium

2-[(1,1-dihydroxyethyl)amino]-1-(4-nitrophenyl)propane-1,3-diol

N-(1,1-dihydroxyethyl)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-aminium

2-amino-1-(4-nitrophenyl)propane-1,3-diol

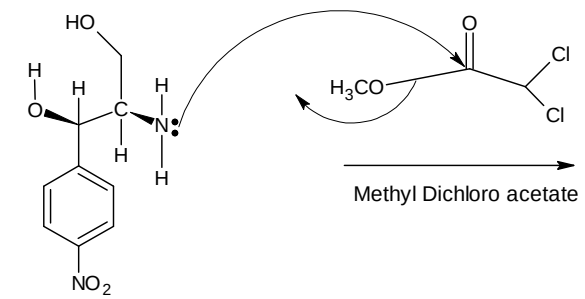
(STEP——11)



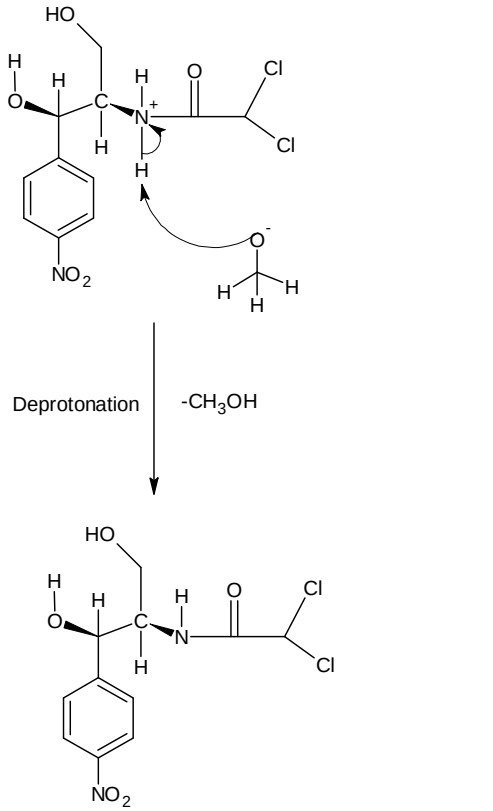
Racemic mixture or Racemic amine and alcohal
Dexo and levo form (±)
2-amino-1-(4-nitrophenyl)propane-1,3-diol

(1*R*,2*R*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol
D - threo form

(STEP——12)

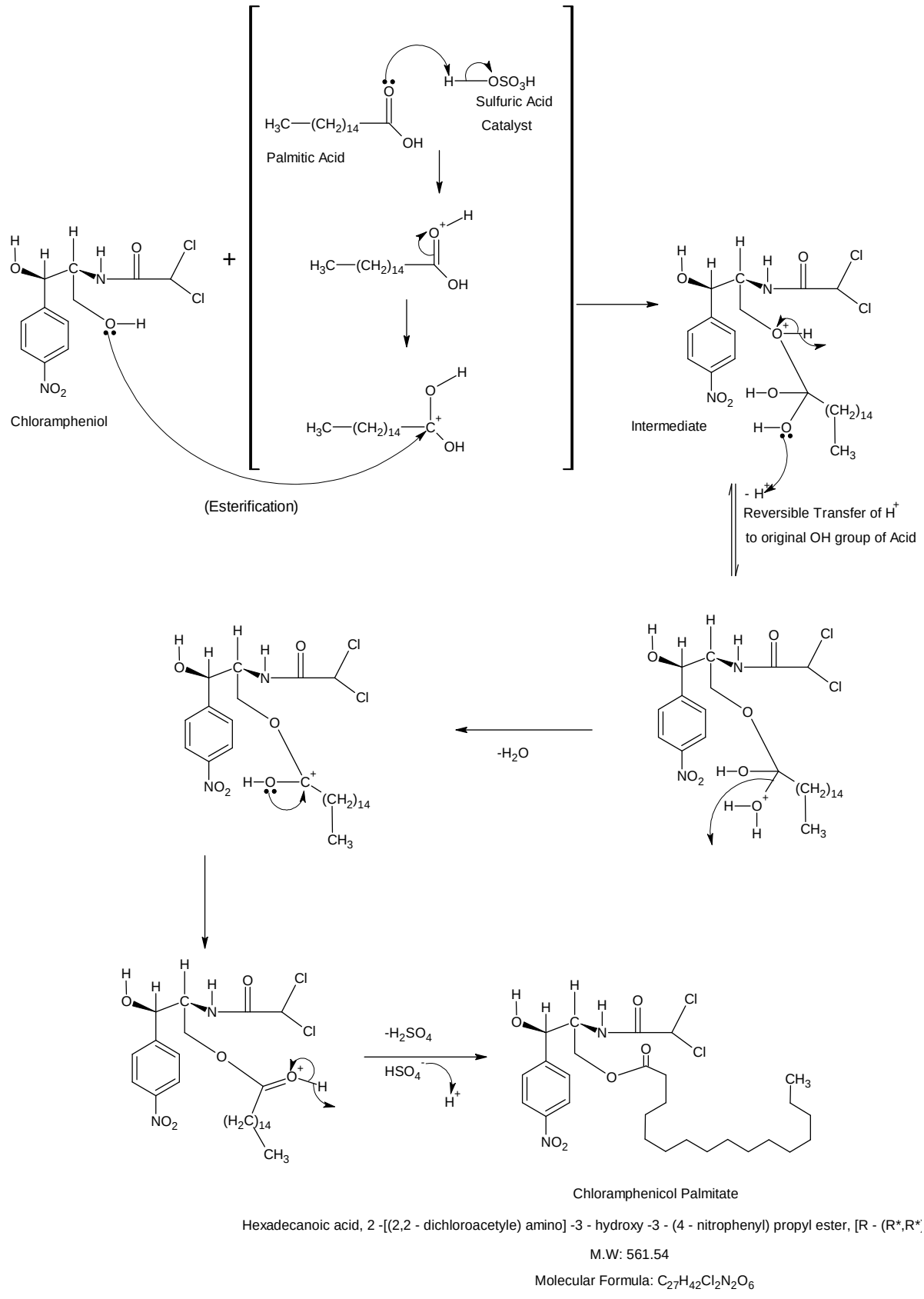


(1*R*,2*R*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol



2,2-dichloro-*N*-[(1*R*,2*R*)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl]acetamide
(Chloroampheniol)
Molecular Formula: $C_{11}H_{12}Cl_2N_2O_5$
M.W: 323.13

(STEP—13)



Hexadecanoic acid, 2 -[(2,2 - dichloroacetyle) amino] -3 - hydroxy -3 - (4 - nitrophenyl) propyl ester, [R - (R*,R*)

M.W: 561.54

Molecular Formula: $C_{27}H_{42}Cl_2N_2O_6$

Setwise Explanation of Chloramphenicol Palmitate Synthesis:

Step - 1:

In step -: 1 Friedel crafts alkylation reaction is taken place. Benzene is treated with chloroethane in the presence of anhydrous aluminium chloride (catalyst). Initially, the generation of electrophile is taken place. The Lewis acid anhydrous aluminium chloride which is an electron - deficient species, to complete its deficiency the chlorine atom of chloroethane is donated its lone pair electron in form of coordinate bond to anhydrous aluminium chloride.

The pull of anhydrous aluminium chloride is most on chlorine and the bond break and the formation of ethylium ion which is act as electrophile and $AlCl_4^-$ is taken place.
Now benzene pi - electron is attacked on electrophile and it becomes 5 - ethylcyclohexa - 1, 3 - diene. After that, deprotonation of benzene is taken place. The hydrogen atom of benzene donates its electron to benzene and H^+ will take electron from the chlorine atom of $AlCl_4^-$ and the formation of byproduct will be taken place in form of HCl. Hence ethylbenzene will be formed.1[6, 17, 18]

Step - 2:
In step - 2: Nitration of ethylbenzene is taken place. Ethylbenzene is treated with nitric acid in presence of sulfuric acid (catalyst). Sulfuric acid acts as a strong acid, so the H^+ atom of sulfuric acid will attack on OH group of nitric acid and the H^+ atom of sulfuric acid is attached with OH group of nitric acid via coordination bond. Hence protonation of OH molecules is taken place. After the protonation of OH molecule, hydroxy (oxo) oxonio - ammonium compound will be formed. The oxygen atom which is bonded with coordination bond will take an electron from nitrogen atom and will be leaved as a water molecule and hence dioxoammonium ion will be formed. The para pi - electron of ethylbenzene is attacked on dioxoammonium ion and 2 - ethyl - 5 - nitrocyclohexa - 1, 3 - diene will be formed. After this, deprotonation of ethylbenzene will take place. The hydrogen sulfate ion of sulfuric acid will attack on para proton of 2 - ethyl - 5 - nitrocyclohexa - 1, 3 - diene and hydrogen will donate its electron to benzene ring and hence 1 - ethyl - 4 - nitrobenzene will be formed.1[9, 20, 21]

Step - 3:
In step - 3: 1 - ethyl - 4 - nitrobenzene is treated with oxidizing agent chromyl chloride in presence of CS_2 or CCl_4 (catalyst). In this, homolytic fission will be taken place. The methyl group hydrogen of 1 - ethyl - 4 - nitrobenzene will be shattered by homolytic fission and free radical will be formed. Similarly, the pi - electron of chromyl chloride oxygen will be shattered by homolytic fission and free radical will be formed. The chromyl chloride free radical is gotten bonded with free radical of 1 - ethyl - 4 - nitrobenzene and hence chromium complex will be formed. After this, hydrolysis of chromium complex is taken place. And hence 1 - (4 - nitrophenyl) ethanone is formed. Thus the oxidation of 1 - ethyl - 4 - nitrobenzene is done.2[2, 23]

Step - 4:
In step - 4: 1 - (4 - nitrophenyl) ethanone is treated with diatomic bromine. In this, homolytic fission will be taken place. The methyl group hydrogen of 1 - (4 - nitrophenyl) ethanone will be shattered by homolytic fission and free radical formation will take place. Similarly, diatomic bromine will be shattered by homolytic fission and free radical formation will take place. The diatomic bromine free radical is gotten bonded with free radical of 1 - (4 - nitrophenyl) ethanone. And hence 2 - bromo - 1 - (4 - nitrophenyl) ethanone will be formed.2[4, 25, 26]

Step - 5, 6:
In step - 5, 6: 2 - bromo - 1 - (4 - nitrophenyl) ethanone is treated with hexamethylenetetramine. Initially, lone pair of nitrogen atom of hexamethylenetetramine will attack on R - CH_2Br and resulting bromine will be leaved. After this, lone pair of remaining three nitrogen atom of hexamethylenetetramine will attack on concentrated 3HCl and resulting one - one hydrogen will be attached with nitrogen. After this, hydrolysis is taken place. The oxygen lone pair of water will attack on carbon and carbon donates its electron to nitrogen and resulting nitrogen will be neutral from positive charge and bond will be shattered between nitrogen and carbon. The oxygen atom of water will be received positive charge when it attached with shattered carbon. To neutralized positive charge on oxygen atom of water, nitrogen lone pair will attack on hydrogen of water and resulting hydrogen will donates its electron to oxygen and itself hydrogen attached with nitrogen and hence hydroxyl group will be formed which is attached with carbon. Similarly, this all process will be done frequently till primary amine formation. And hence at last our 2 - amino - 1 - (4 - nitropheny) ethanone is formed. These all process is done via delepine reaction.2[7, 28, 29]

Step - 7, 7.1:
In step - 7: Friedel crafts acylation is taken place. The 2 - amino - 1 - (4 - nitropheny) ethanone is treated with acetic anhydride in the presence of anhydrous aluminium chloride (catalyst). $AlCl_3$ acting as a lewis acid and it need electron so it will attack on acetic anhydride and resulting acylium ion and trichloro aluminium acetate ion will be formed. After this, nitrogen lone pair of 4 - nitrobenzamide will attack on acylium ion and resulting N - acetyl - 2 - (4 - nitrophenyl) - 2 - oxoethanaminium is formed. After this to neutralize positive charge on nitrogen atom of N - acetyl - 2 - (4 - nitrophenyl) - 2 - oxoethanaminium deprotonation is taken place by trichloro aluminium acetate ion. And hence N - [2 - (4 - nitrophenyl) - 2 - oxoethyl] actamide is formed.3[0]

Step - 8:
In step - 8: Aldol condensation is taken place. The N - [2 - (4 - nitrophenyl) - 2 - oxoethyl] actamide is treated with formaldehyde in the presence of aq. NaOH (catalyst). Initally, base will attack on alpha carbon hydrogen which more acidic due to the presence of electron withdrawing group C=O. When base will attack on alpha hydrogen then alpha hydrogen donates its electron to alpha carbon and carbanion formation is taken place. Now carbanion which is act as a nucleophile will attack on formaldehyde carbon and hence formation of 2 - (acetylamino) - 3 - (4 - nitrophenyl) - 3 - oxopropan - 1 - olate is taken place. After this, the oxygen of 2 - (acetylamino) - 3 - (4 - nitrophenyl) - 3 - oxopropan - 1 - olate act as nucleophile which will attack on hydrogen of water and hence *N* - [3 - hydroxy - 1 - (4 - nitrophenyl) - 1 - oxopropan - 2 - yl]acetamide formation is taken place.3[1]

Step - 9:
In step - 9: Meerwein pondorf verley reduction is taken place. The *N* - [3 - hydroxy - 1 - (4 - nitrophenyl) - 1 - oxopropan - 2 - yl] acetamide is treated with aluminium isopropoxide. As we know aldehyde and ketones generally shows nucleophilic addition reaction. In this reduction process the hydride of aluminium isopropoxide will act as nucleophile. The hydride will attack on carbonyl carbon and the formation of *N* - [1, 3 - dihydroxy - 1 - (4 - nitrophenyl)

propan - 2 - yl] acetamide is taken place. Now the oxygen atom of *N* - [1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl] acetamide becomes nucleophile and will attack on aluminium and the formation of mixed alkoxide is taken place as well as acetone will be byproduct. After this, Mixed alkoxide oxygen will act as nucleophile and will attack on oxygen hydrogen of isopropyle alcohol (solvent), therefore hydrogen gives its electron to isopropyle alcohol oxygen and itself will be attached with mixed alkoxide. Now isopropyle alcohol oxygen will act as nucleophile and will attack on mixed alkooxide aluminium and aluminium will give its electron to electrophile. And hence the reduction of *N* - [3 - hydroxy - 1 - (4 - nitrophenyl) - 1 - oxopropan - 2 - yl] acetamide is done. The aluminium isopropoxide will be as byproduct.3[2, 33]

Step - 10:
In step - 10: Hydrolysis of N - [1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl] acetamide is taken place. The N - [1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl] acetamide is treated with aq. HCl and the formation of (1 - { [1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl]amino}ethylidene) oxonium is taken place. After this, oxygen atom of water will attack on carbonyl carbon and hence positive charge on hydroxyl group of (1 - { [1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl]amino}ethylidene) oxonium is neutralized and the formation of (1 - { [1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl]amino} - 1 - hydroxyethyl) oxonium is taken place. Now the deprotonation of (1 - { [1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl]amino} - 1 - hydroxyethyl) oxonium is taken place. After deprotonation, the formation of 2 - [(1, 1 - dihydroxyethyl) amino] - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is taken place. After this, protonation of 2 - [(1, 1 - dihydroxyethyl) amino] - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is taken place and water will be as byproduct and the formation of *N* - (1, 1 - dihydroxyethyl) - 1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - aminium is taken place. At last the rearrangement of *N* - (1, 1 - dihydroxyethyl) - 1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - aminium is taken place and acetic acid, HCl, water will be as byproduct and hence the formation of 2 - amino - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is taken place.3[4, 35]

Step - 11:
In step - 11: Resolution of an enantiomer is taken place. The 2 - amino - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is existed in both dexo and levo form (amine and alcohol) i. e 50% (R) and 50% (S). The racemic mixture of amine and alcohal cannot be separated by physical change. To separate these dexo and levo form the chiral acid is used. Chiral acid can be tartaric acid, mandelic acid, camphor sulphonic acid. Therefore, 2 - amino - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is treated with camphor sulphonic acid and resulting we get four different form of stereoisomers such as D - erythro, L - erythro, D - threo, and L - threo. D - threo is an active form of 2 - amino - 1 - (4 - nitrophenyl) propane - 1, 3 - diol racemic mixture. And hence the formation of (1*R*, 2*R*) - 2 - amino - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is taken place.3[6, 37]

Step - 12:
In step - 12: The (1*R*, 2*R*) - 2 - amino - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is treated with methyl dichloro acetate. The nitrogen atom of (1*R*, 2*R*) - 2 - amino - 1 - (4 - nitrophenyl) propane - 1, 3 - diol is acted as nucleophile and will attack on carbonyl carbon of methyl dichloro acetate and resulting methoxy group will be shattered. And hence the formation of (1*R*, 2*R*) - *N* - (dichloroacetyl) - 1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - aminium is taken place. After this, deprotonation of nitrogen atom of (1*R*, 2*R*) - *N* - (dichloroacetyl) - 1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - aminium is taken place. And hence the formation of chloramphenicol antibiotic medicine (2, 2 - dichloro - *N* - [(1*R*, 2*R*) - 1, 3 - dihydroxy - 1 - (4 - nitrophenyl) propan - 2 - yl]acetamide) is taken place which is in their active form (D - threo).3[8]

Step - 13:
In step - 13: The formation of chloramphenicol palmitate is taken place. The chloramphenicol is treated with palmitic acid in the presence of concentrated sulfuric acid (catalyst) via esterification. The palmitic acid is stronger acid than sulfuric acid so the oxygen atom of palmitic acid will attack on hydrogen of sulfuric acid and hydrogen will be attached with oxygen by coordination bond. Now after the rearrangement palmitic cation formation is taken place. Now the oxygen atom of chloramphenicol is attacked on palmitic cation and the formation of intermediate is taken place. After this reversible transfer of H^+ to original OH group of acid is taken place and water will be removed. And after the rearrangement sulfuric acid will be byproduct and the formation of chloramphenicol palmitate is taken place.3[9, 40, 41]

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