CHLORAMPHENICOL

History

- Chloramphenicol was discovered after being isolated from *Streptomyces venezuelae* in 1947.

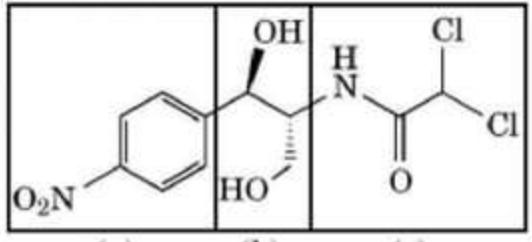
- Scientists at Parke-Davis including Mildred Rebstock published identification of the chemical structure and synthesis in 1949 (first antibiotic to be made instead of extracted from a microorganism).

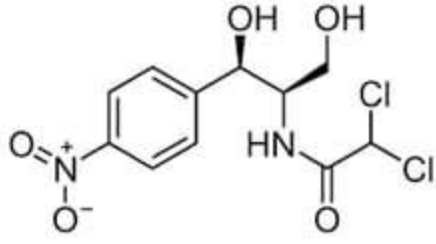
- Subsequently, a large number of chloramphenicol derivatives were synthesized (more than 500 compounds till 1961).

- In 2007, the accumulation of reports associated with aplastic anemia and blood dyscrasis with chloramphenicol eye drops led to the classification of "probable human carcinoma" according to the WHO criteria.

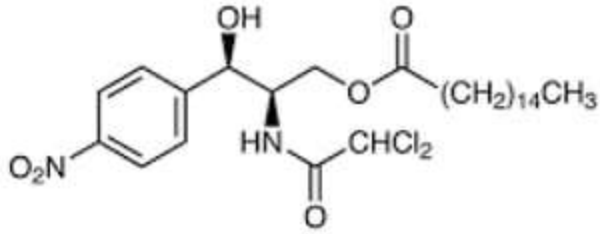
Chemistry

The chemical structure of chloramphenicol can be portioned into aromatic ring system (a), propandiol moiety (b) and acyl side chain (c).

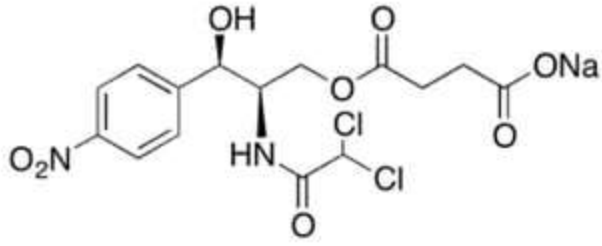




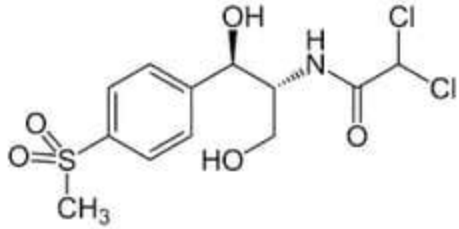
Chloramphenicol



Chloramphenicol palmitate

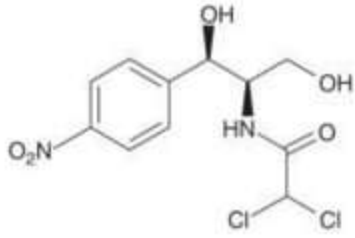


Chloramphenicol sodium succinate



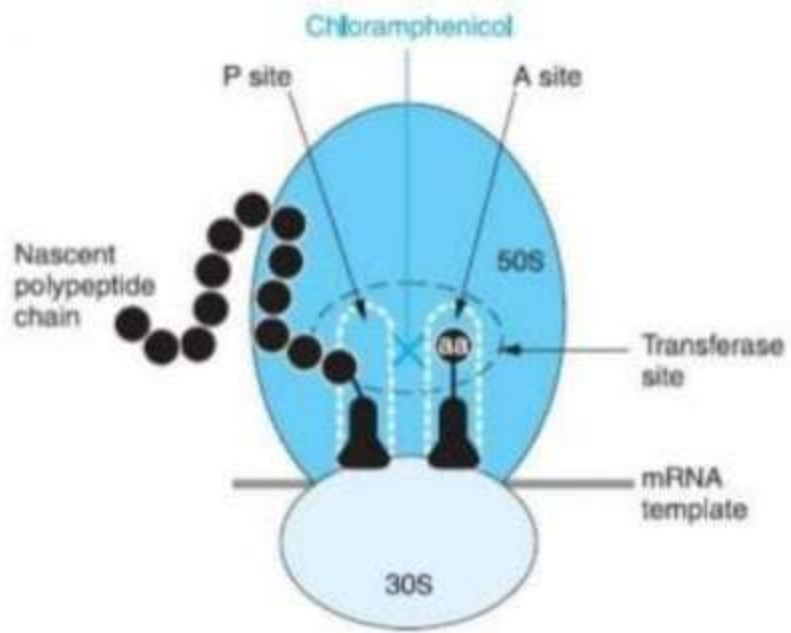
Thiamphenicol

Two asymmetric centers are present in this molecule; only the (1R,2R) natural diastereoisomer displays a significant antibacterial activity.



Mechanism of action

Chloramphenicol binds reversibly to 50s subunit of the bacterial ribosome and inhibits bacterial protein synthesis by preventing transfer of amino-acyl tRNA to its acceptor site on ribosome and as such prevent peptide bond formation (by inhibiting the peptidyl transferase activity of the bacterial ribosome). It specifically binds to A2451 and A2452 residues in the 23S rRNA of the 50S ribosomal subunit. The inhibition of protein synthesis leads to bacteriostatic action.


Chloramphenicol
P site
A site
Nascent
polypeptide
chain
50S
Transferase
site
mRNA
template
30S

Videos

https://www.youtube.com/watch?v=OVIg2x4iGWo

https://www.youtube.com/watch?v=Rnhk57WlDkM&t=21s

https://www.youtube.com/watch?v=b-ymYxca_1A

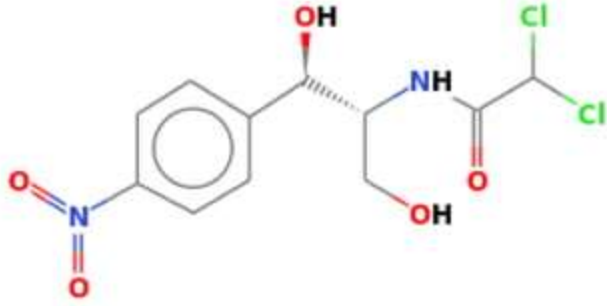
Therapeutic uses

Chloramphenicol is not safe and it should not be used for treatment of minor infections. Some of the uses of chloramphenicol are:

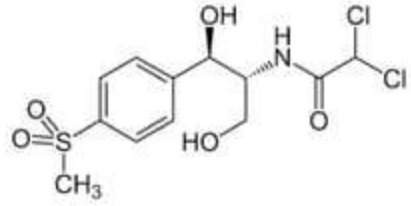
- Intraocular infection
- Euteric fever (typhoid fever)
- Pyogenic meningitis

- Anaerobic infection, e.g., pelvic and brain abscess, etc
- Urinary tract infection (as 2nd choice drug)
- Whooping cough (as 2nd choice drug)
- Conjunctivitis
- Cholera

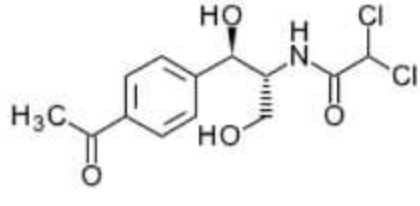
SAR



- Replacement of nitro group with other electron withdrawing groups gives active compounds, e.g., $-SO_2CH_3$ grouop and $-COCH_3$ group in thiamphenicol and cetophenicol, respectively.



Thiamphenicol



Cetophenicol

- Shifting nitro group from para position to other positions (ortho or meta positions) resulted in reduced activity.

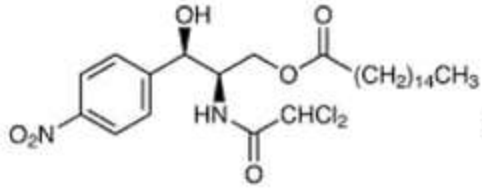
- Replacement of phenyl ring of chloramphenicol with cyclohexyl ring resulted in decreased activity.

- Replacement of dichloroacetamide group of chloramphenicol with trihalo derivatives (e.g., -$NHCOCF_3$) resulted in more activity.

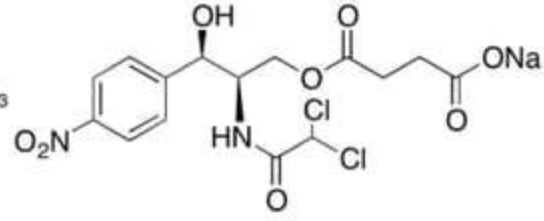
- Addition of one or more alkyl or alkoxy substituents on the phenyl ring resulted in decreased activity.

- Replacement of nitro group of chloramphenicol with chloro (-Cl) resulted in decreased activity.

- Conversion of C-3, hydroxyl group to ester resulted in decreased water solubility (masking of bitter taste), e.g., palmitate and succinate esters.



Chloramphenicol palmitate



Chloramphenicol sodium succinate

- Conversion of C-1, hydroxyl group to carbonyl (>C=O group) resulted in loss of antibacterial activity.

- Replacement of the phenyl ring with furyl, naphthyl or xenyl rings resulted in reduced activity.

Chemical Degradation

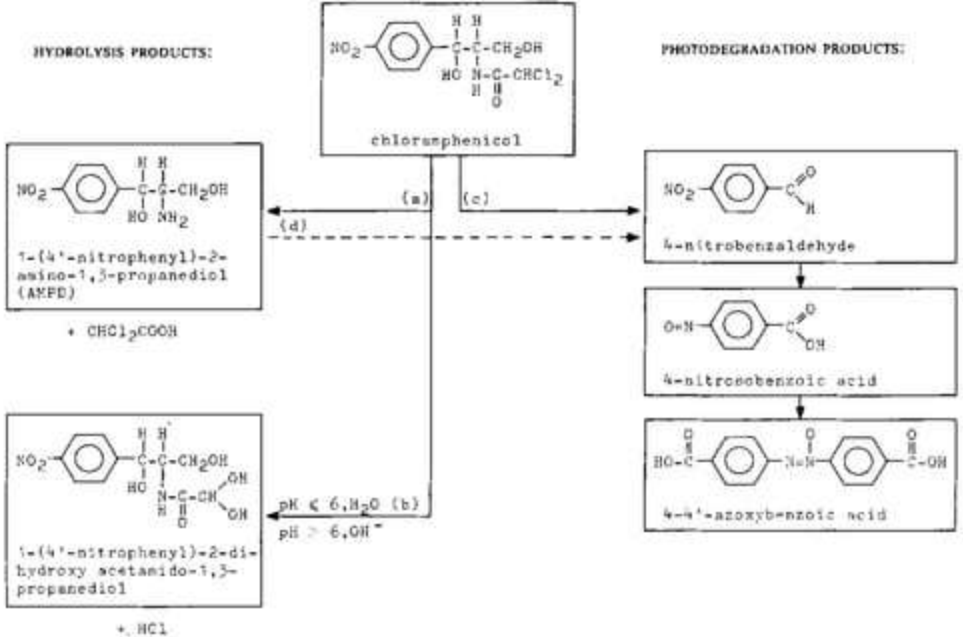
Hydrolysis:

(1) Amide hydrolysis occurs in pH < 7 results in formation of 4-nitrobenzaldehyde.

(2) At pH > 6, catalytic action of OH^- ions leads to the hydrolysis of covalent bonded chlorine atom of dichloroacetamide moiety.

Photochemical degradation:

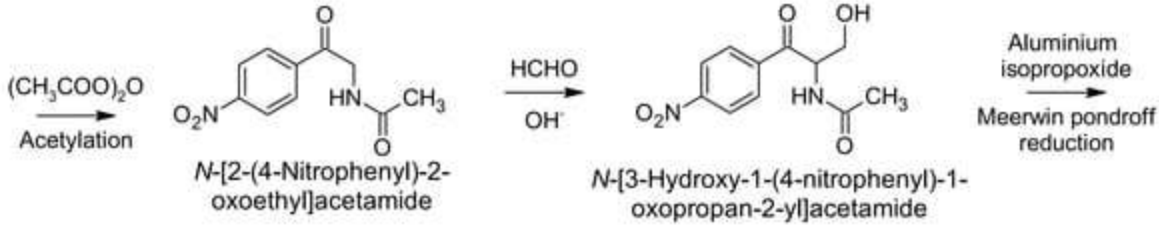
At light exposure during several hours the aqueous solution slowly turns yellow to yellowish brown due to oxidation, reduction and condensation reactions.


HYDROLYSIS PRODUCTS:
PHOTODEGRADATION PRODUCTS:
chloramphenicol
(a)
(c)
(d)
1-(4'-nitrophenyl)-2-amino-1,3-propanediol (AMPD)
+ $CHCl_2COOH$
4-nitrobenzaldehyde
4-nitrosobenzoic acid
4-4'-azoxybenzoic acid
pH ≤ 6, H_2O (b)
pH > 6, OH^-
1-(4'-nitrophenyl)-2-dihydroxy acetamido-1,3-propanediol
+ HCl

Synthesis

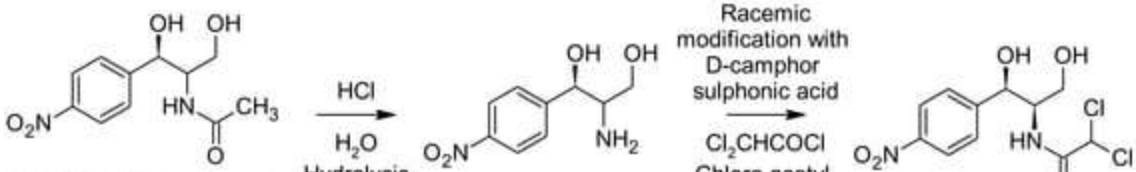
Due to the relative simplicity of the chloramphenicol molecule, the chemical production rapidly supplanted the production via fermentation. Several routes have been used, all started from readily available materials, the main difficulty was the syn relationship between the hydroxyl and dichloroacetamido groups. The optically pure material was obtained by chemical resolution. One of the first routes used industrially was the synthesis of the racemic syn-isomer which was prepared by using a Meerwein-Verley-Pondorff reduction. After deacetylation, the aminodiol was resolved by formation of the camphosulfonate salt or by using the seeding method.


O
CH3
O2N
4-Nitro
acetophenone
Br2
CH3COOH
Bromination
O
Br
O2N
4-Nitro
phenacylbromide
(CH2)6N4
(Hexamine)
HCl
Delepine reaction
O
NH2
O2N
2-Amino-1-(4-nitro
phenyl)ethan-1-one



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

N-[3-Hydroxy-1-(4-nitrophenyl)-1-oxopropan-2-yl]acetamide



N-[(1*S*)-1,3-Dihydroxy-1
-(4-nitrophenyl)propan-
2-yl]acetamide

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

Chloramphenicol

Thank You