Damietta University
Faculty of Science
Department of Chemistry

التدريب الصيفى للطالب المنقول الى الفرقة الرابعة
العام الدراسى ٢٠٢٠-٢٠٢١م

أستاذ المادة : أ.د. محمد محمد عبد الهادى مشالى
أستاذ الكيمياء العضوية المتفرغ

فترة التدريب : أغسطس ٢٠٢٠م

مقدمة مبسطة ومختصرة للتوافق مع التخصصات المختلفة
للطلاب تحت عنوان:

Design, protection, deprotection and synthesis of simple target organic molecule (the sulfanilamide) of potential biological activity.

The aim

The aim is to train the students on the basic principles of design, protection, deprotection and synthesis in the field of organic chemistry.

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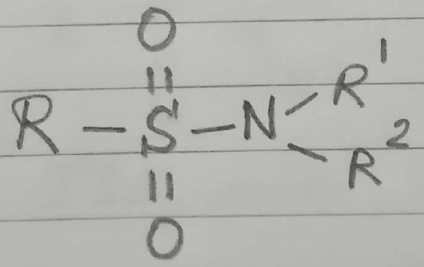
Sulfonamides and Sulfa Drugs

Sulfonamides are synthetic (man-made) organic compounds. The sulfonamide molecule is, essentially, composed of the elements: C, H; N, O & S. All the sulfonamides must contain the sulfonamido moiety ($-\overset{\overset{O}{\|}}{\underset{\underset{O}{\|}}{S}}-N<$).



The general structure of a sulfonamide

R represent any carbon-based side chain. It could be cyclic or acyclic. It could be: aliphatic; aromatic or heterocyclic. It could be parent or substituted. R^1 and R^2 may be the same or different. R^1 and R^2 may be: H; aliphatic; aromatic or heterocyclic.

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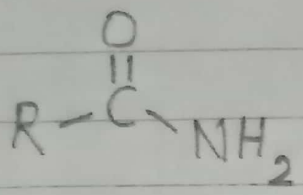
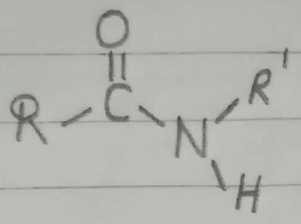
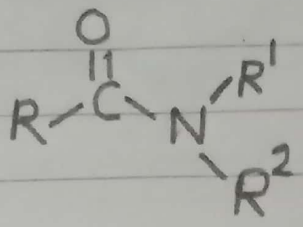
Types of sulfonamides



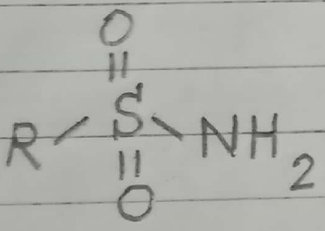
primary (1°) amide (two H on N)



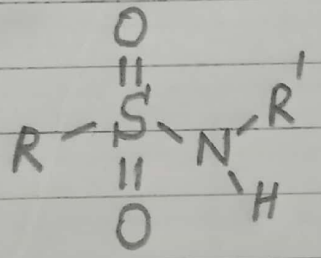
secondary (2°) amide (one H on N)



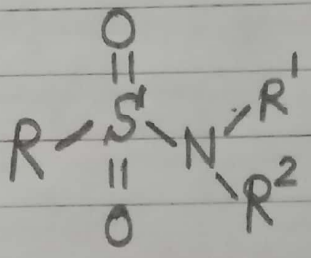
tertiary (3°) amide (no H on N)



1° Sulfonamide



2° Sulfonamide



3° Sulfonamide

R, R' & R^2 = any carbon – based organic group.

Most biologically active sulfonamides (e.g., sulfa drugs) belong to the classes of 1° & 2° sulfonamides. Biologically active 3° sulfonamides are much less common.

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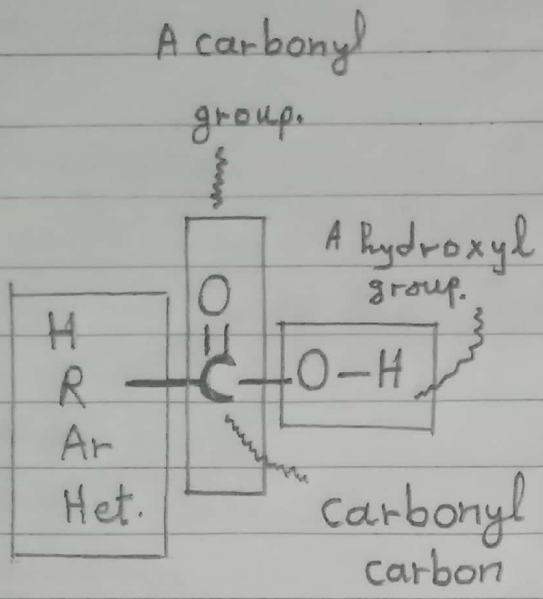
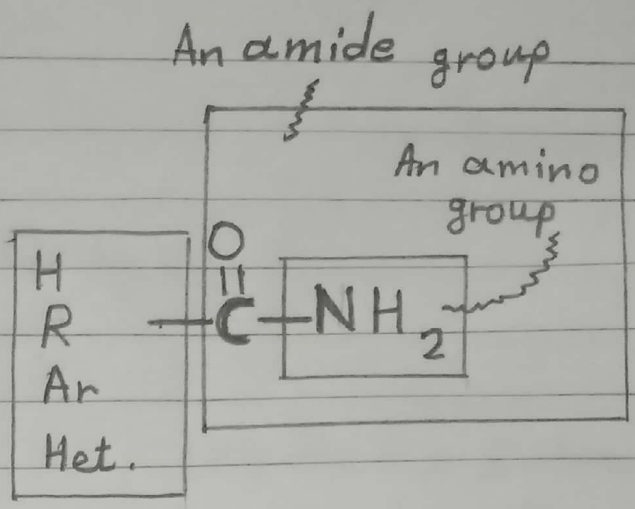
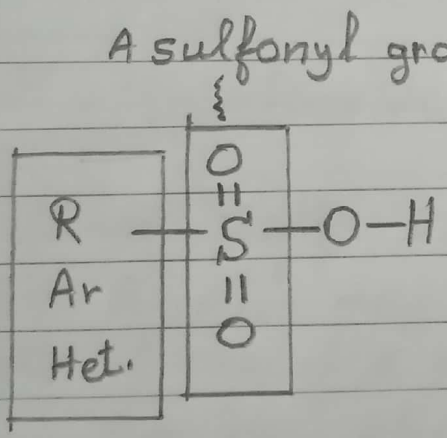


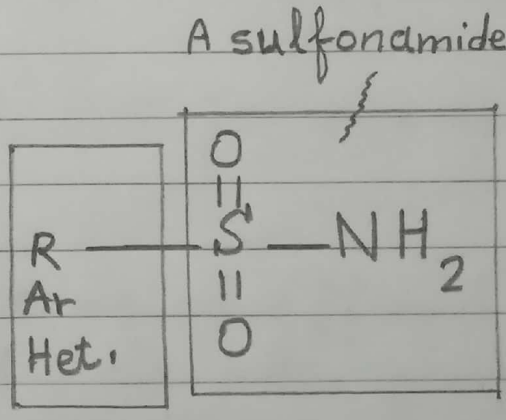
A general structure of a carboxylic acid
R = aliphatic ; Ar = aromatic
Het. = heterocyclic.



A general structure of a carboxylic acid amide



A general structure of a sulfonic acid



A general structure of a sulfonic acid amide.
A Sulfonamide

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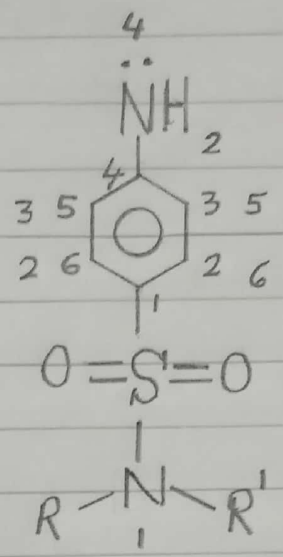
Preparation of Sulfanilamide as an Example of the Sulfa Drugs

Always :

(i) $\overset{4}{N}H_2$ is free.

(ii) positions 2, 3, 5 & 6 are free (unsubstituted).



(iii) the $\overset{4}{N}$ & S atoms are para to each other.

(iv) the only variable is R and R'.

(v) biologically active sulfa drugs usually have R or R' as H atom.

Sulfanilamide : R = R' = H (comp. No. 14).

Other Sulfa Drugs:

(1) R , R' may be the same or different.

(2) if one of R or R' = H , the other group may be ; aliphatic ; aromatic or heterocyclic (either aromatic or nonaromatic)

(3) each of R & R' may not be hydrogen ; and they may not be the same (R ≠ R' ≠ H). They may be aliphatic ; aromatic ; heterocyclic (either aromatic or non aromatic).

(4) R or R' may be a monovalent metal.

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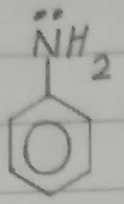
6/15

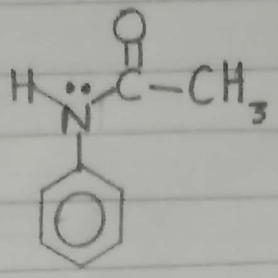
1

Benzene



2

Aniline



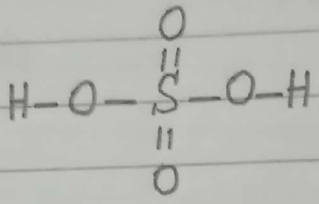
3

Acetanilide
(N-Acetylaniline)

H_2SO_4

4

Sulfuric acid

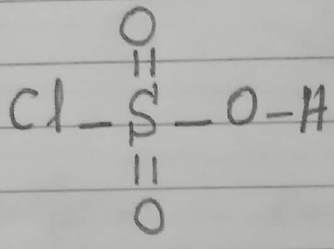


4

$ClSO_3H$

5

Chlorosulfonic acid



5

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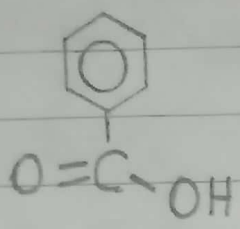
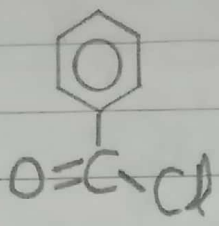


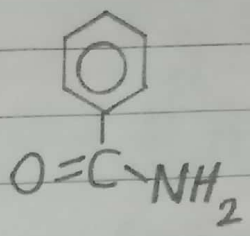
6

Benzoic acid



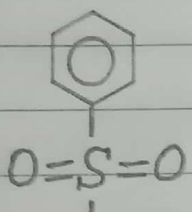
7

Benzoyl chloride



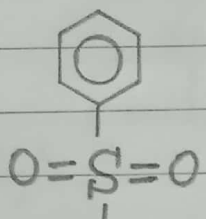
8

Benzamide



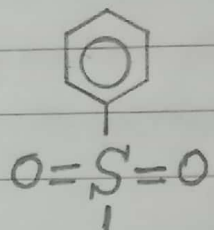
9

Benzenesulfonic acid



10

Benzenesulfonyl chloride



11

Benzenesulfonamide

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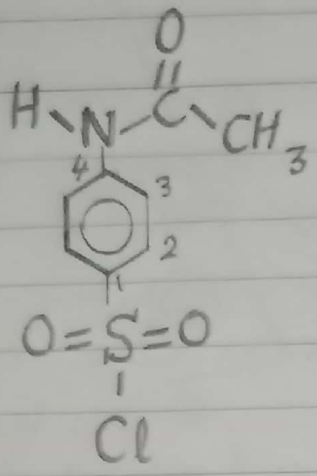
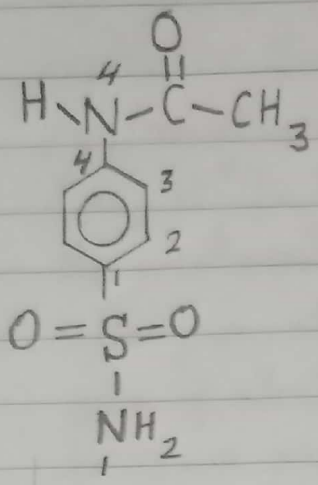


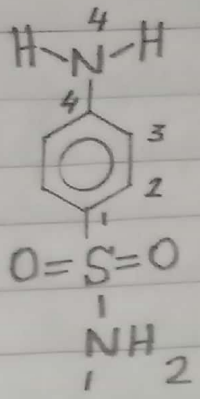
12

4-Acetamido-benzenesulfonyl chloride (N-Acetylsulfanilyl chloride)



13

N^4-Acetyl-sulfanilamide



14

Sulfanilamide (4-Aminobenzene-sulfonamide)

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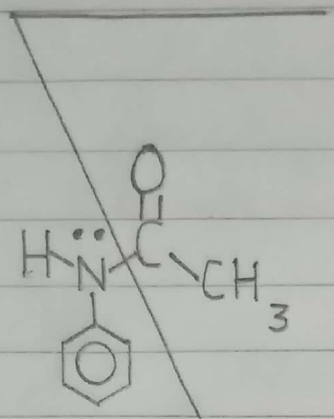
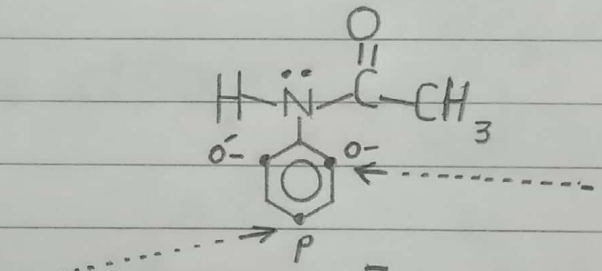


3

N-Acetylaniline
Acetanilide

Protection

the acetyl group, $-\overset{O}{\overset{\|}{C}}-CH_3$, protectes the $H\ddot{N}$ group from protonation (accepting hydrogen ion, H^+). Thus, it helps keeping the unshared pair of electrons on the nitrogen atom, $-\ddot{N}-$. This unshared pair of electrons activates the benzene ring to receive substitution at positions 2 (= ortho, o-) and/or 4 (= para, p-). After achieving the target molecule, deprotection takes place.



3

the 2 position (o- = o'-) is sterically hindered (crowded).

the 4 position (p-) is not sterically hindered (not crowded).

So, in case of mono-substitution, especially with bulky groups, e.g., the sulfonyl chloride group, $-SO_2Cl$, the substitution takes place at the uncrowded position 4 (= p-) only.

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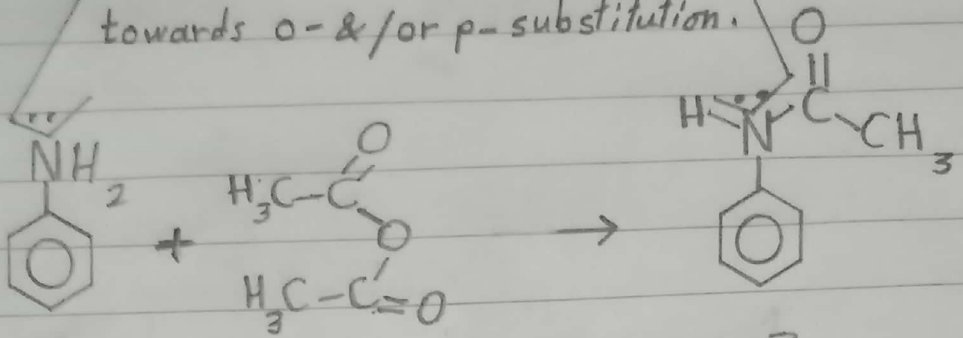
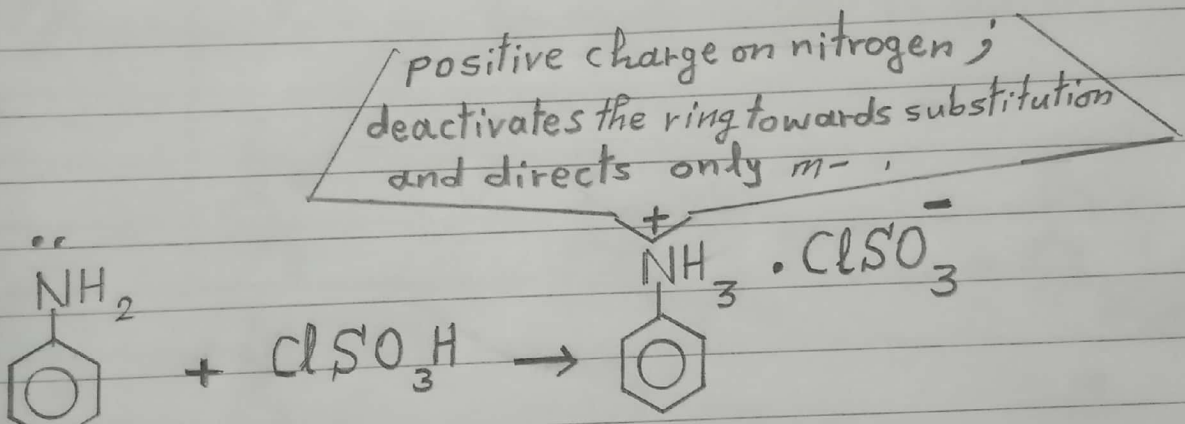
Protection and unprotection effects

unshared pair of electrons on nitrogen; activates the ring towards o- & /or p- substitution.

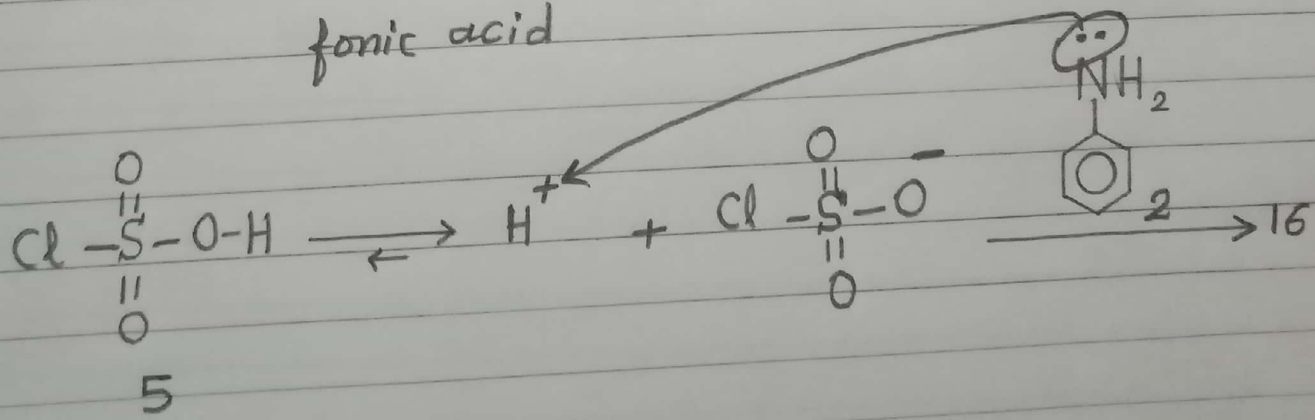


2 Aniline + 15 Acetic anhydride → 3 Acetanilide

positive charge on nitrogen; deactivates the ring towards substitution and directs only m- .

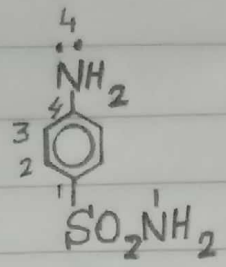


2 + 5 Chlorosulfonic acid → 16 Anilinium salt.



5

Sulfanilamide is the target molecule.



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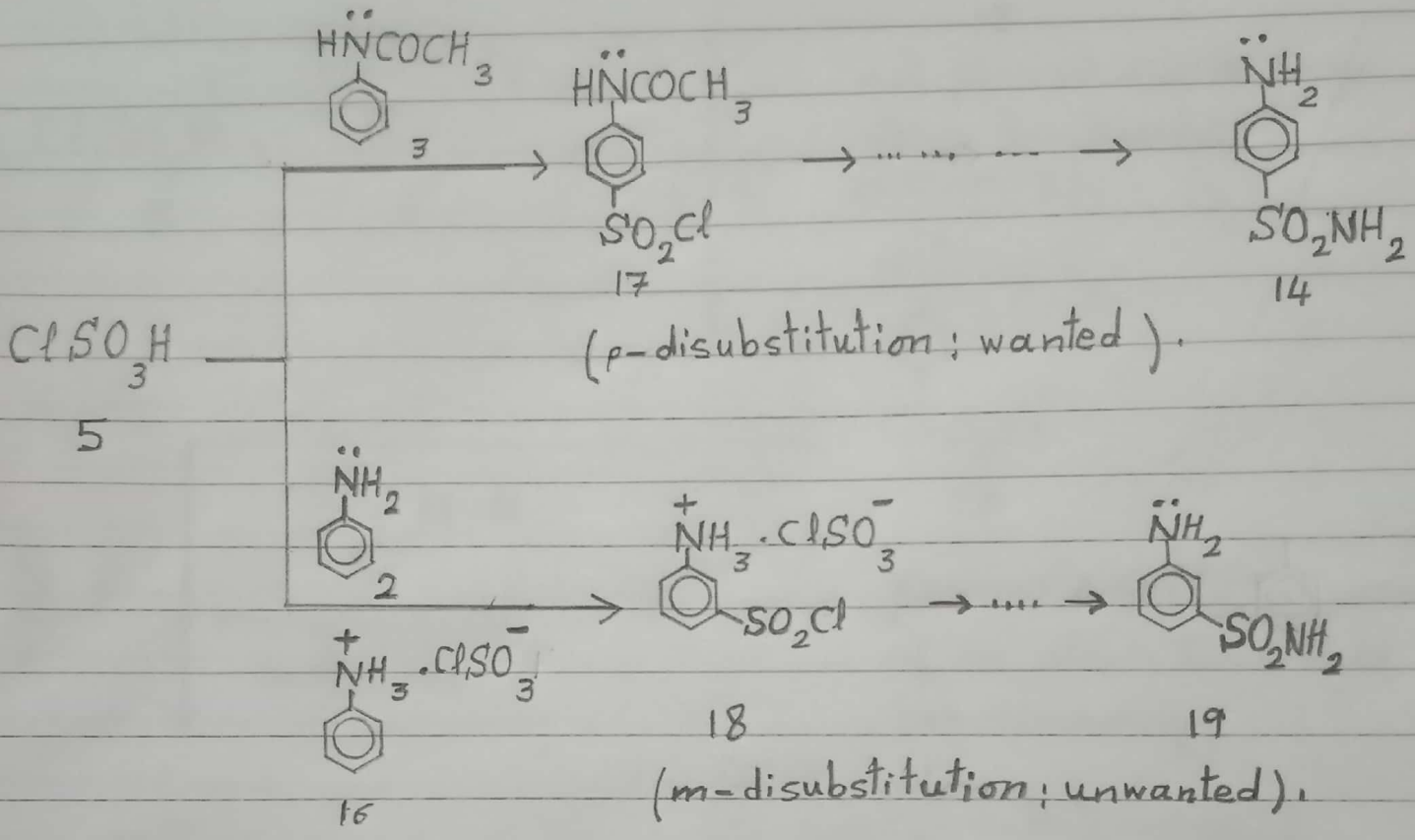

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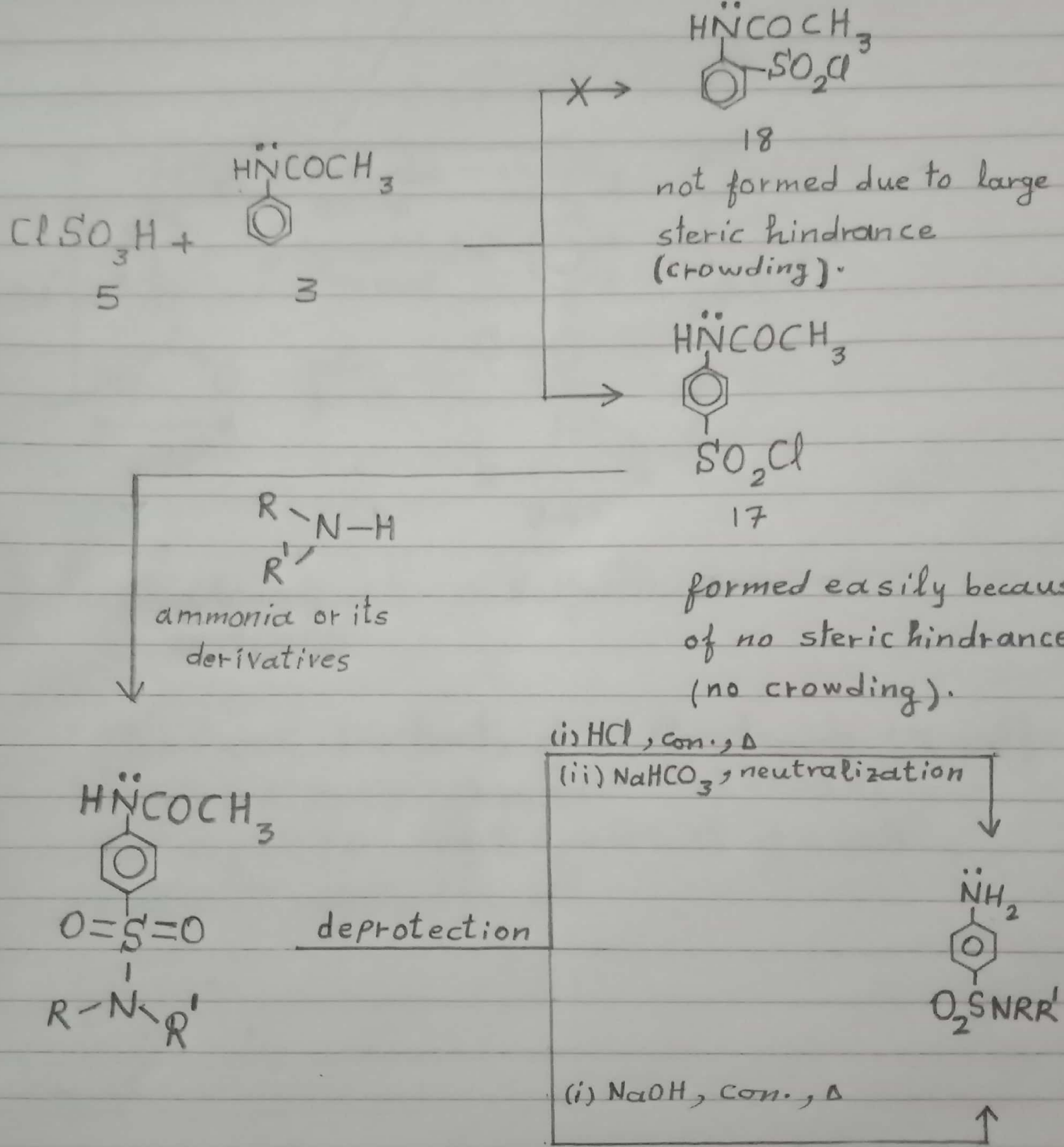

R, R' can be any of:-
H; alkyl; aryl; heteryl functional groups.

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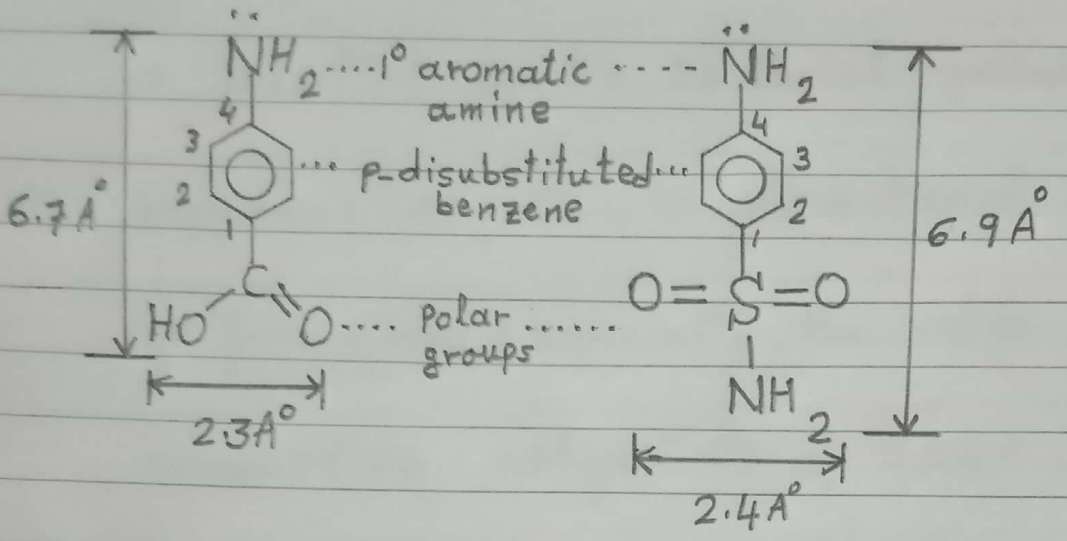
Why bacteria take(s) sulfonamides ?



p-Aminobenzoic acid (PABA)

Sulfanilamide

Structural similarity of sulfanilamide (a sulfa drug) and p-aminobenzoic acid (PABA).

A° = angstrom = one ten-billionth of a meter.

$1A^\circ = 10^{-10}$ meter.

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Mechanism of the sulfonamide action against bacteria :

Very simply, feeding on p-aminobenzoic acid (PABA) is essential for the bacterial growth and reproduction. Due to structural similarity, sulfonamides (especially, the sulfa drugs) are competitive antagonists of PABA. When bacteria take sulfonamides – in place of PABA –, the sulfonamides inhibit the processes of the bacterial growth and reproduction, leading – at the end – to the death of bacteria.

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Conclusion

The sulfonamides constitute a large and important synthetic chemical class of C, H, N, O & S containing organic compounds. They, all, contain the sulfonamido moiety ($-SO_2N<$) in their structures. They may be cyclic or acyclic aliphatic or aromatic compounds. Heterocyclic sulfonamides are also very common and show remarkable biological activity.

Many sulfonamides are known as drugs possing not only antibacterial activity, but also, anticancer, diuretic and hypoglycemic activity among others.

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