CHAPTER I

HALOQUINOLINES AND THEIR DERIVATIVES AND SULFA DRUGS : A REVIEW

1.1 Haloquinolines and their derivatives - A Review

Many quinoline derivatives are known to exhibit microbial activity, such as 8-hydroxyquinoline and 4-substituted 7-chloroquinoline. These are used as antiamoebic drugs.[1] Quinoline and isoquinoline[2] showed antifilarial properties and were used in the treatment of worm infection.[3,4] All haloquinolines known were prepared using Durbeyshire and Water[5] method. According to this method, dry chlorine is passed at room temperature through the solution of quinoline in conc. sulfuric acid containing silver sulfate, which gives mixture of 5-chloroquinoline and 5,8 chloroquinoline. It was used as antiamoebic[6] in man. 2 or 4 haloquinolines prepared by heating 7-quinolones[7] with PCl_5 or $POCl_3$. Halogenation of quinoline is a complex process. In general, halogenation of quinoline under neutral or weakly acidic condition occurs initially at the pyridine ring at C_3, while in acidic solution substitution takes place at 5 to 8 position.[8]

Earlier, quinoline with dialkylamino group at 4-position showed antimalarial activity.[9] A number of compounds were prepared. German workers[9] first reported the marked antimalarial properties of quinoline bearing the 4-diethylamino-1-Methyl butyl amino side chain. 4 Substituted quinolines show good antimalarial activity.

Substituted 4-aminoquinolines[10] are prepared by reaction of 4-chloroquinoline with primary amines.

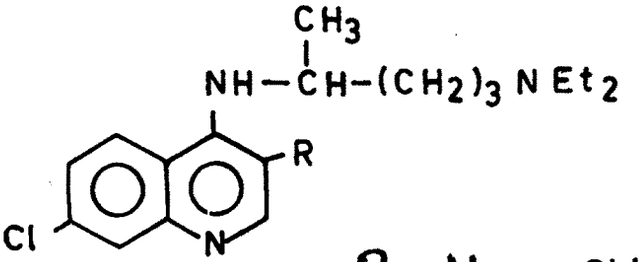
An American researcher[11] prepared 4-substituted aminoquinoline which can show antimalarial activity. 4-Substituted aminoquinolines are highly active antimalarials, e.g. chloroquin and santochin (Fig.1.1). Marvin Carmack and coworkers[12] prepared 4-substituted quinolines having high antimalarial activity and are less toxic. In these compounds tertiary amino group in side chain replaced by primary amino group or various simple aliphatic secondary amino group (Fig. 1.2).

It is also observed that suitably substituted derivative of 4-aminopiperdine and 4-haloquinoline[13] react to form compounds which are useful as antimalarial drugs. (Fig. 1.2).

1.2 George A., Reynold and coworkers[14] synthesised 2-substituted quinoline derivatives. They prepared by treating 2-chloro-4 phenyl quinoline with 1-diethyl aminopentane. These compounds (Fig. 2.1) are similar to certain antimalarial and other drugs. 2-Chloro-4-phenyl quinoline when condensed with sulfonamide derivative gives heterocyclic sulfonamides which showed strong antimicrobial activities. D.V.Ghorpade and B.M.Sawant[15] prepared different heterocyclic sulfonamides (Fig.2.2).

CHART-I

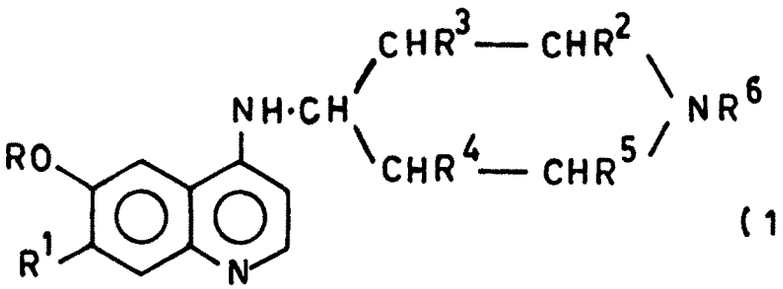
N-4 Substituted amino quinolines .



(1·1)

R = H = Chloroquin

R = CH_3 = Santochin



(1·2)

R_1 = Cl, Br, F, CF_3 or NC .

R_2 = R_3, R_4, R_5 = H, Me, Et .

R_6 = H or Alkyl group of $\angle$ 7 Carbon atom

R = Methyl or Ethyl

2-Chloro-4-Methyl quinoline[16] when condensed with sulfonamide derivatives give heterocyclic sulfonamides (fig.2.3) which show strong antimicrobial activity towards gram positive and gram negative bacteria. In continuation for search of effective antiparasitic agents several 4-dialkylamino-7-haloquinoline derivatives were prepared. Although these have been several papers published recently[17,18,19] on 4-dialkylamino alkylamino 6-methoxy quinoline only the patent literature[20] on synthesis of corresponding-7-substituted compounds is available.

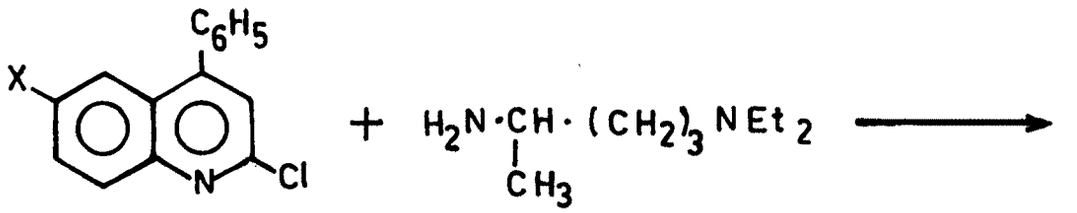
The 4-chloro-7-substituted quinoline were condensed with several primary and tertiary diamines in presence of phenol.

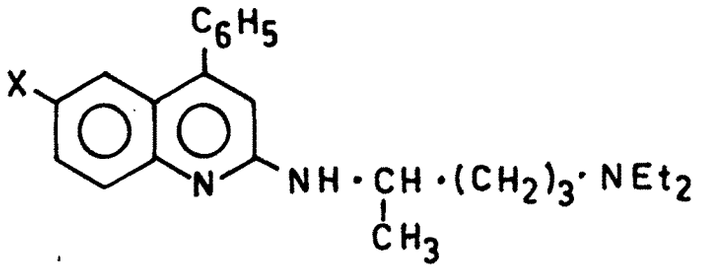
The high antimalarial[21] activity and relatively low toxicity is observed for 4-(4' diethylamino-1-methyl-budyl-amino)-7-chloroquinoline (R = - $N(C_2H_5)$.

The antimalarial drugs of the 4-dialkylamino quinoline series have been reported. The presence of a group especially a chlorine atom in the 7-position gives drugs superior to those having methoxyl group in 6 position.[22] This suggested that preparation of corresponding anologue of pamaquin (plasmachin) with a 7-chlorine rather than 6 methoxyl substituents. 7-chloro-8-hydroxy quinoline and 5-chloro-8-aminoquinoline were submitted to test against avian malaria and found to be devoid of activity.

CHART-II

Synthesis of 2-substituted quinoline derivative

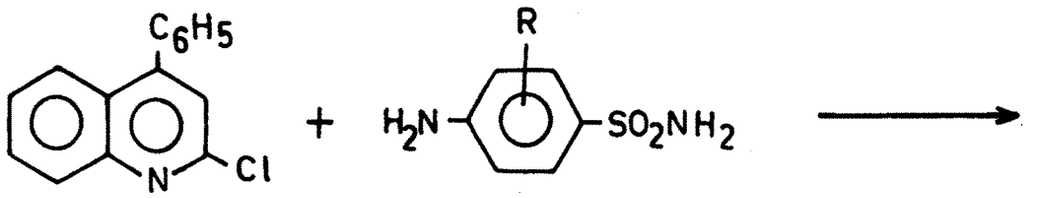


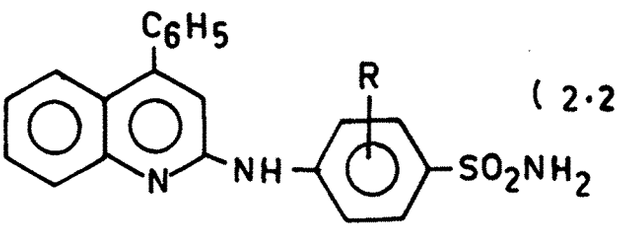


(2·1)

a) X = Cl

b) X = H



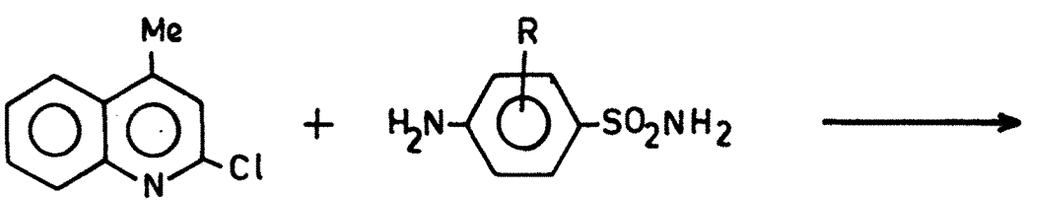


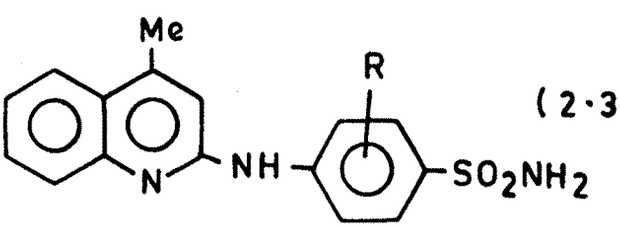
(2·2)

R = H

R = CH_3 ortho to NH_2

R = CH_3 meta to NH_2





(2·3)

R = H

R = CH_3 ortho to NH_2

R = CH_3 meta to NH_2

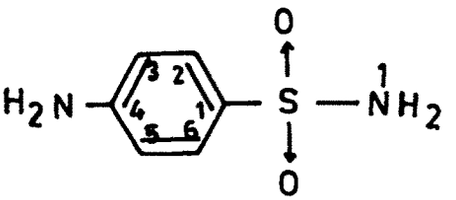
Conflicting report on the value of sulfonamides in the treatment of malaria are to be found in earlier literature.[23] Walker and Van Dyke[24] have shown that sulfathiozole, sulfadiazine and sulfonilamide in this order are most effective against P. Lophurae in ducklings. Coggeshall and coworkers[25] employing sulfadiazine showed to be effective against all form of human malaria.

The recent research on chemotherapy[26] have revealed that dialkylamine chain play considerable part in the development of chemotheraputic activity in quinoline and acridine derivatives. Similarly sulfonilamides and its derivative have been found to possess definite bacteriostatic action against various coccal infection. It was thought of interest to study the class of compounds formed by condensation of sulfonilamides with chloroquinoline. The compounds formed expected to have some therapeutic importance. Since replacement of sulfonamido group of p-amino benzene sulfonamide often wider the range of activity of drugs.

1.3 Sulfanilamide : (3·1)

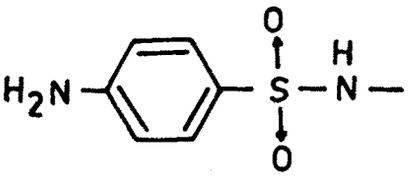
Sulfanilamide[27,28] (p-amino benzene sulfonamide) is the parent compound of this important class of chemotherapeutic agents because it is used as a drug. In 1935 Treufouel, Nitti and Bovel[29] discovered it in "pasteu institute". They prepared and tested different products with help of coupling with diazotised P-amino benzene sulfonamide with mono or poly-

CHART-III

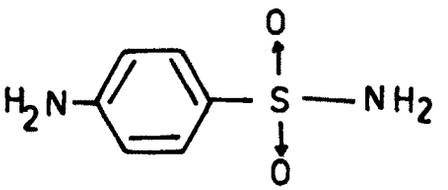


(3·1)

Nomenclature



Sulfanilamido group



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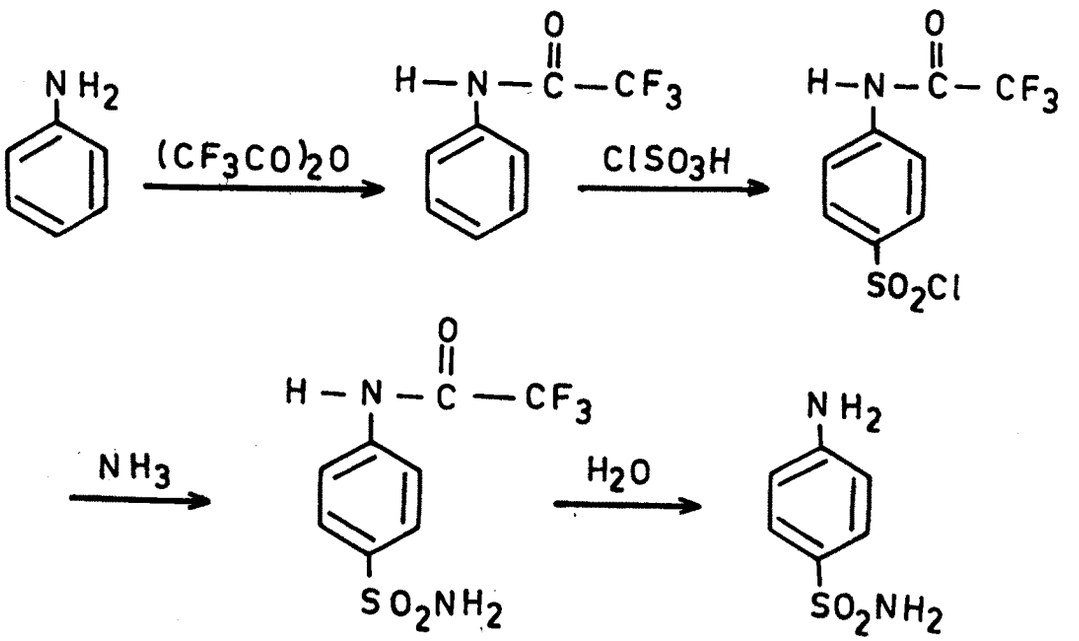
p-aminobenzene sulphonamide



phenols. They showed antistreptococci action. The protective action of p-aminobenzene sulfonamide derivatives may be changed by substitution on the amide by the position of benzene ring of substituted amines, phenols, halogens etc.

Grey and Stephenson suggested the effectiveness of sulfanilamide and its derivatives against streptococal and meingococcal infection in mice. Intensive pharmacological and clinical work rapidly broadened the field of usefulness of parent compounds and its derivatives.

Sulfamethoxy diazine[30,31] (Fig. 4.1)

It should be protected from Light. It is readily absorbed from gastrointestinal tract. It is administered orally as a single daily dose after breakfast.

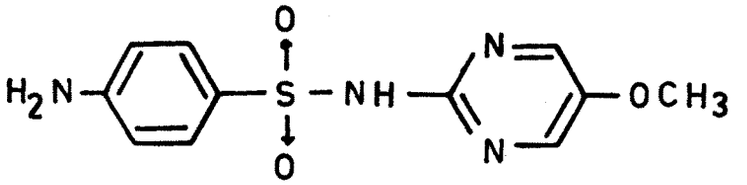
Sulfamethaxazole[32,33] (Fig. 4.2)

Its acetyl derivative is tasteless and therefore suitable for oral administration.

Sulfa-pyridine[34] (Fig. 4.3)

It is prepared by reacting dry acetyl sulfonyl chloride with 2 amido pyridine in presence of pyridine as a solvent and Hydrochloric acid at 60° to 100°. It has outstanding effect in curring pneumonia because of it has high toxicity. The drugs is readily acetylated in the body and it result in kidney damage. It is more potent than sulfonilamide in

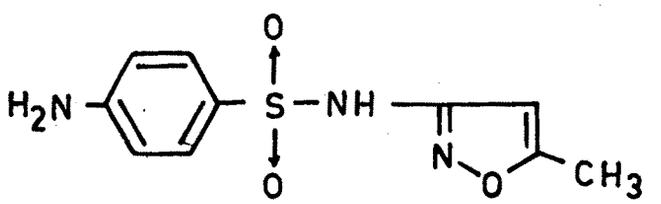
CHART-IV



(4·1)

Sulfamethoxydiazine

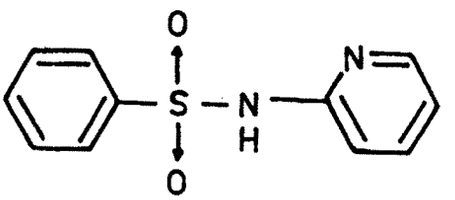
2 (4-aminobenzene sulphonamide) 5 methoxy pyrimidine



(4·2)

Sulphamethoxazole

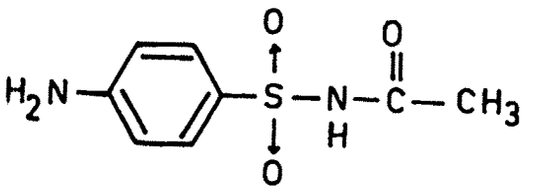
3-(4-aminobenzene sulphonmido)-5-
-methylisoxazolyl sulfonilamide



(4·3)

Sulfapyridine

($\overset{1}{N}$-2-pyridylsulfanilamide)



(4·4)

Sulfacetamide

($\overset{1}{N}$-acetylsulfanilamide)

treatment of streptococcal and gonococcal infection.

Sulfa-acetamide[35,36] (Fig. 4.4)

It is prepared by Dohrn and Diedrich[39] and also independently by Crosseley, Northey and Hutguist.[40] Because of low toxicity, it was found useful in treatment of urinary infections and in the form of its highly soluble neutral sodium salt for ophthalmic and other topical uses.

Sulfaguanidine[37] (Fig. 5.1)

It is prepared by condensation of acetyl sulfonyl chloride with guanidine nitrate in the presence of excess sodium hydroxide in aq. acetone medium[38] gives sulfaguanidine. It is used in treatment of coccidiosis in chicken, and for other veternary purposes.

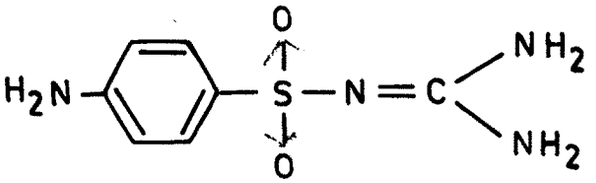
Sulfadiazine[39,40] (Fig. 52)

2-Aminopurimidine is condensed with dry acetyl sulfonyl chloride in pyridine gives 2(N-acetyl sulfanilamide)-pyrimidine it is used in number of infection including pneumococcal meningococcal.

Sulfamerazine[41-44] (Fig. 5.3)

It is prepared by condensing ethyl acetoacetate with guanidine which gives 6-Methyl-iso-cytosine and further procedure of reaction similar to sulfadiazine. It is less toxic and less potent than sulfadiazine.

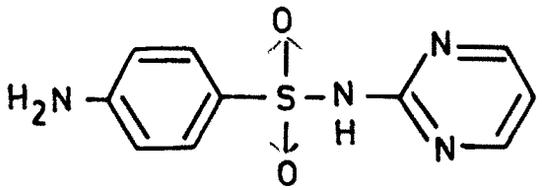
CHART-V



(5·1)

Sulfaguanidine

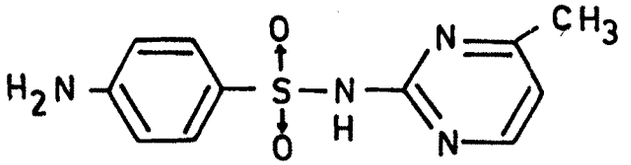
($^{1}_{N}$ – Guanyl sulfanilamide)



(5·2)

Sulfadiazine

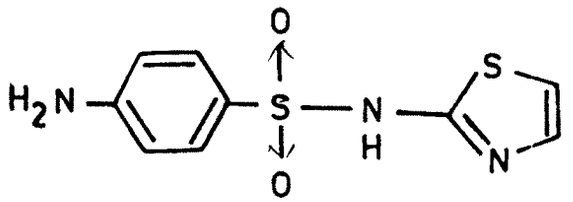
($^{1}_{N}$ – 2 – Pyrimidinyl sulfanilamide)



(5·3)

Sulfamirazine

$^{1}_{N}$ – (4 Methyl – 2 – Pyrimidinyl) sulfanilamide



(5·4)

Sulfathiozole

($^{1}_{N}$ – 2 – thiazolylsulfanilamide)

Sulfathiozole[45-47] Fig. 5.4)

It is synthesised from 2-amino-thiozole with acetyl sulfonyl chloride in dry pyridine and the resulting N^4-acetyl sulfathiozole is hydrolysed with sodium hydroxide. The other process[48] is also known for the preparation of sulfathiozole. It is more potent in staphylococcal, pnemococcal and gonococcal infection.

Sulfisoxasole[49] (Fig. 6.1)

It is synthesised by "Claisen condensation" of propionitril ethylacetate in presence of sodium ethoxide gives cyclobutanone. Further on treatment with hydroxyl amine undergoes cyclization to give isoxazole. Acetylation of isoxazole with sulfonyl chloride gives sulfisoxazole.

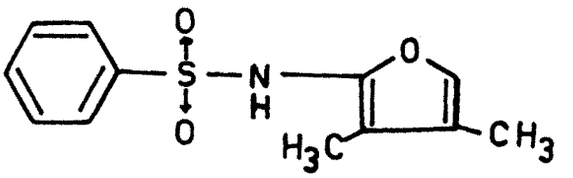
Sulfisomidine[50]

Only 10% of sulfisomidine in the urine is present in the acetylated form. It has similar side effect as those of other sulfonamides.

Sulfadimethaxine[51] :

It is absorbed rapidly and causes kidney damage.[52] It is absorbed from gastro intestinal tract. It is given orally as a single dose after breakfast.[5]

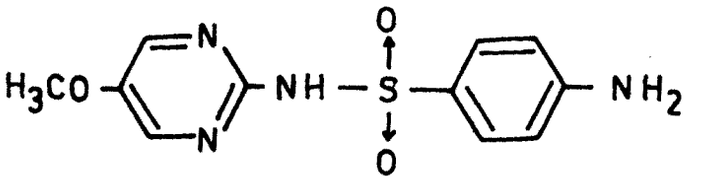
CHART-VI



(6·1)

Sulfisoxazole

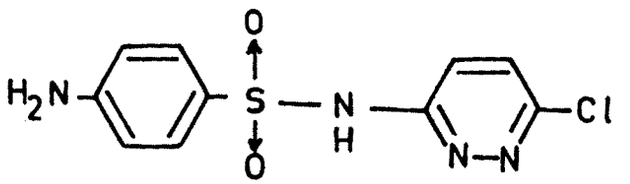
^{1}N-(3-4-Dimethyl-5-isoxalyl) sulfanilamide



(6·2)

Sulfameter

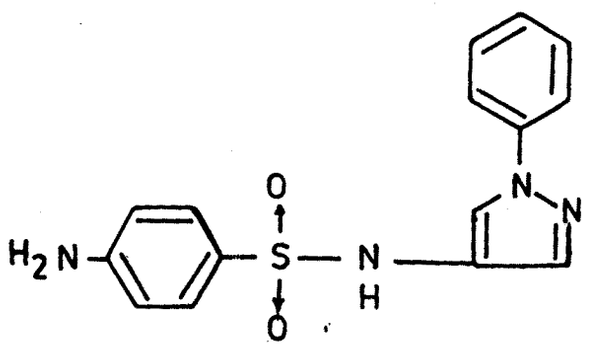
(^{1}N-5-methoxy-2-Pyrimidinyl sulfanilamide)



(6·3)

Sulfachloropyridazine

^{1}N-(6 Chloro-3-Pyridazinyl) sulfanilamide



(6·4)

Sulfaphenazole

(1-Phenyl-5-sulfanilamidopyrazole) sulfanilamide

Sulfa chloro pyridine[53] (Fig. 6.3)

This sulfonamide is well tolerated, absorbed and excreted rapidly in urine. It is valuable in chronic infection which involves only the urinay tract.

Sulfa phenazole[54-57] (Fig.6.4)

It is readily absorbed from gastro intestinal tract. It is used in treatment of urinary tract infection which is caused by susceptible organisms.

Sulfamethiozole[58-61] (Fig. 7.1)

It is useful for treatment of urinary tract infection.

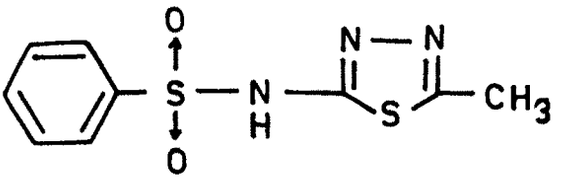
1.4 (A) N^4 substituted sulfonamides

N^4-Methyl and dimethyl sulfonamides are active in men and mice as dealkylation gives aryl amines.[62] N-4 Benzyl and 4-Nitro benzyl derivative are active in vivo. The N-4 glycosyl derivatives of sulfanil-amido heterocyclic are active in vitro and vivo.[63]

Succinyl sulfathiozole[64,65] (7.2)

It is prepared from sulfathiozole with succinic anhydride under vigorous controlled condition. It gives the succinyl sulfathiozole. It is inactive in vitro.

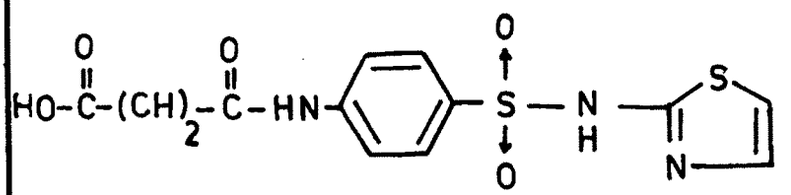
CHART-VII



(7·1)

Sulfamethizole

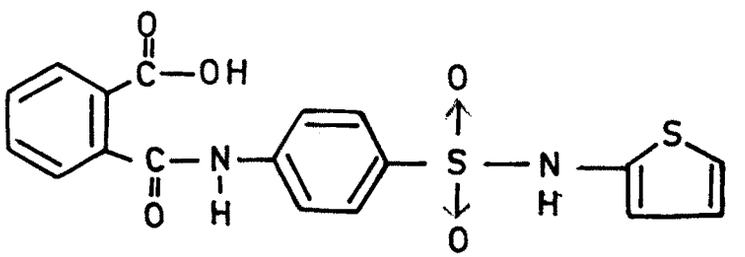
(^{1}N – 5 Methyl – 1,3,4 thiadiazole – 2 yl) Sulphanilamide



(7·2)

Succinyl Sulfathiazole

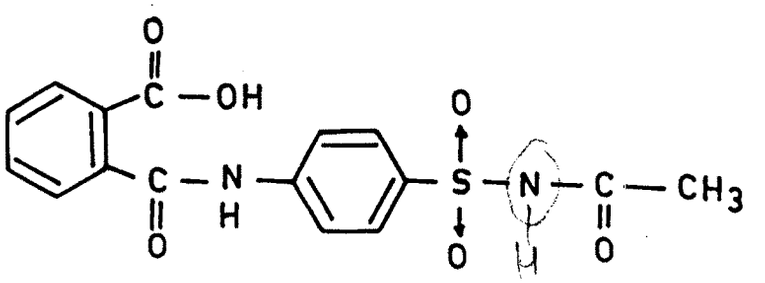
2-(^{4}N-Succinyl sulfanilamido) thiazole



(7·3)

Pthalylsulfathiazole

2-(^{4}N – Pthalyl sulfanilamido) thiozole



(7·4)

Pthalylsulfacetamide

^{1}N — acetyl — ^{4}N — pthaloyl Sulfanilamide

Phthalic sulfacetamide[66] (7.4)

It is synthesised from Phthalic acid sulfanilamide and acetyl chloride under controlled condition. It is used in as intestinal antibacterial agent in gastro intestinal infection and in abdominal surgery.

(B) Some new sulfonamide :

Recently some new sulfonamides have been reported.

1.41. The combination of trimethoprim sulfonamide[67].
This increases the surgical activity of drug.

1.42. N-(amino alkyl)-5-chloro-1-nephthalene sulfonamide:[68]
This is prepared by reaction between (5-chloro-1 nephthelene sulfonyl chloride and diamine in dioxane.

1.43. N-aryloxybenzoyl sulfonamides:[69]
These are prepared from corresponding benzoyl halides and sulfonamide in liquid phase. These sulfonamides are used as herbicidals.[71]

1.44. N-Substituted P-fluorobenzene sulfonamides[70]
There sulfonamides showed the antimicrobial activities against S. aureus, B. substilis etc.

1.45. Combination of sulfonamide and trimethoprim tetroxoprim:[71]
These combinations showed a wide range of inhibiting activities against clinical isolated bacteria.

1.46. Coumarin sulfonamides :

Some cumarin sulfonamides also have been reported. 4-(Sulfonimido Methyl) cumarin[72] (Fig. 8.1) They have been synthesised by a four steps route (8.1 chart). These sulfonamides have been characterised by their spectral data. All these cumarin sulphonilamides showed antimicrobial activity against S. aureus, E. coli.etc.

1.47. Drazotised sulphonomides:[73]

In some cases diazotised sulfonamides were coupled with four new 1:3 diaryl propane, 1:3 dione-1(m/p nitrophenyl 3-p-ethyl phenyl) and 1(m/p nitrophenyl); 30(p-ethoxy phenyl) propane 1:3 dione.[71]

These sulfonamides showed antibacterial properties against S. aureus, E. coli etc.

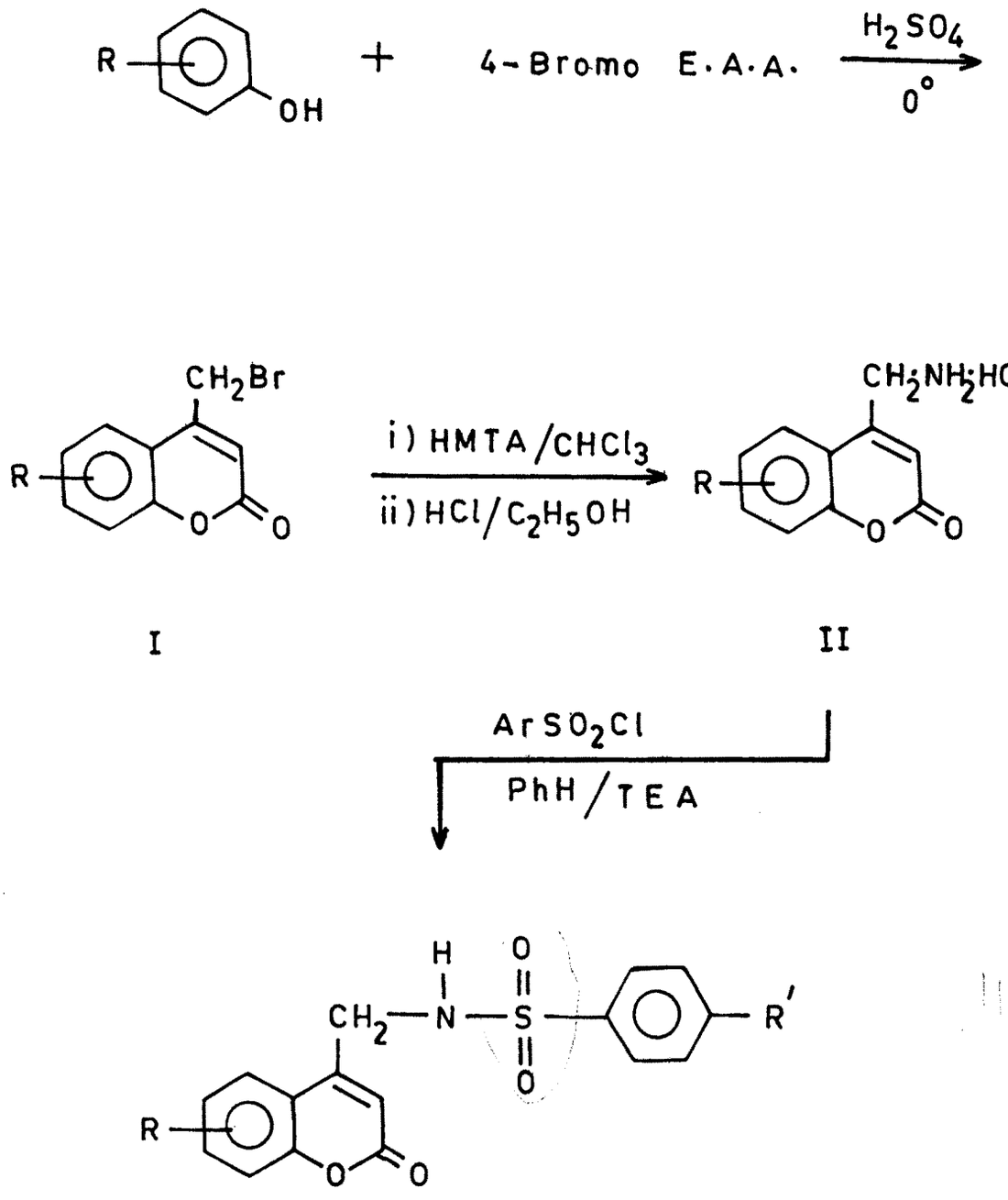
1.5. Some new heterocyclic sulfonamides :

Recently some heterocyclic sulfonamides have been reported.

1.51. 2-(-5-Nitro, 1-Methyl, 2-imadozal, 5-nitro 2-furyl and 5 nitro 2-thienyl venyl) N-aryl sulfonomides and sulfonyl heterocycles;[74] (Fig. 9.1)

In hetero-aryl-vinyl-sulphonamides nitrofuran, nitro thiophene, ring system are present as hetero atomic moiety.

CHART- VIII



4 Aryl sulphanomido methyl coumarin

(8-1)

Steps involved in synthesis are shown (Chart
Some of these sulphenamides possess promising antibacterial, antiamoebitic, antitrichomal activities in vitro.

1.52. A new heterocyclic sulfonamide was prepared by treating 2-acetylamine 4-phenyl thiozole with chlorosulfonic acid followed by condensation[75] with H_2N. CHR.COOme. These sulfonamides are active against various strains of bacterial but these are inactive against fungi (9.2).

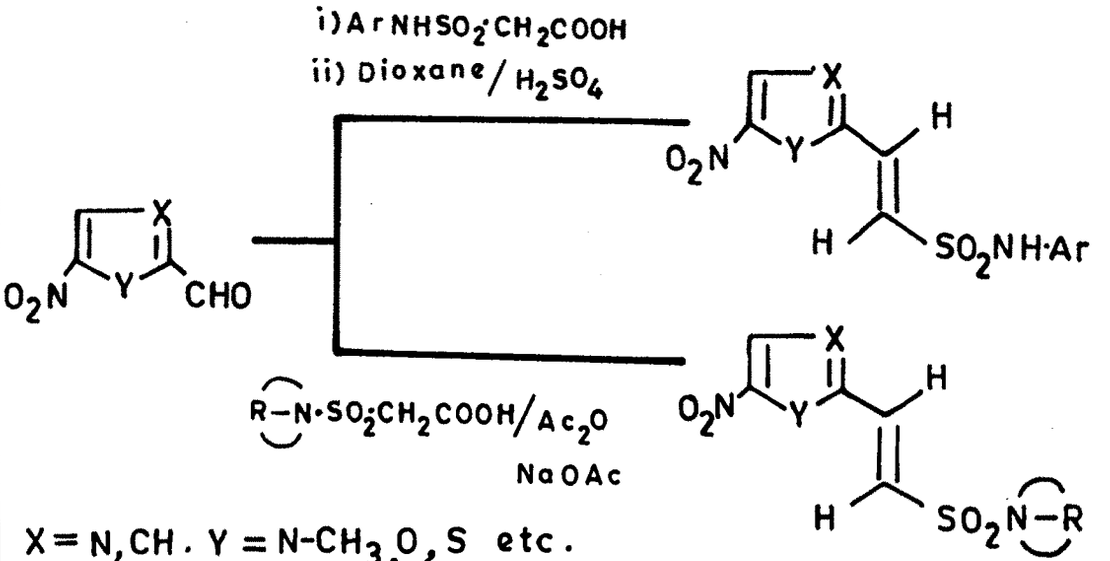
1.53. 2-Sulfanamido and 2-sulfomide 1,3,4,6,7,11 B hexa hydro 2H benzo (a) quinolizine:[76]

The title compound in (9.3) was prepared from corresponding amine. These heterocyclic sulphonamides have antihypertensive activity.

1.54. Some methyl/phenyl-8 Hydroxyquinoline sulfonamides have been reported. 7(α substituted sulfonamido) Methyl and 7-(α substituted sulfonamido) phenyl 8-Hydroxy quinoline:[77]

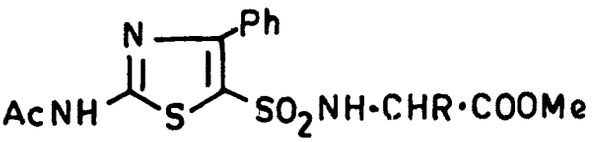
These sulfonamides show antibacterial activities against gram negative bacteria such as solmonella typhi, micrabillis, E. coli etc.

CHART - IX



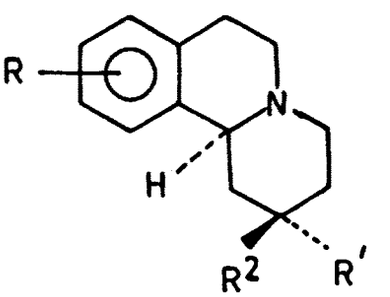
X = N, CH . Y = N-CH_3, O, S etc.

(9·1)



[R = H, Me, $CHMe_2$, Pr, Bu, $CH_2C_6H_4OH$, CH_2-CO-NH_2, $CH_2CH_2CONH_2$]

(9·2)



(9-3)

R = H, 9,10 $(MeO)_2$, -Cl

R' = H, R^2 = $MeSO_2NH$, $PrSO_2N$

R = R^2 = H. R' = $MeSO_2NH$, $PhSO_2NH$

Applications of sulfa drugs:

1) All B. homolytic streptococcal infection of ear, nose, throat and other body organs and blood stream, e.g. mastoditis, sinusitis, streptococcal pnemonia, alcer etc.
2) Meningococcal infection
3) Gonococcal infection
4) Urinary tract infection caused by the above organism or *E. coli*
5) Skin infection such as impetigo and erysipelas.
6) Irachoma and gonacoccal opthalmin.
7) Surgical incisions, reactions, war wounds.

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