SYNOPSIS

The thesis entitled " Synthesis and Study of Cyanuric Chloride Derivatiives of β-Lactam Antibiotics and Synthetic Uses of Silazanes ", is divided into two parts ; Part A and Part B.

Part - A comprises of three chapters.

Chapter -I gives a review of classical β-lactam antibiotics i.e. penicillins and cephalosporins. It starts with definition of the word " antibiotic" itself and ends with the common methods used in the synthesis of semi-synthetic penicillins and cephalosporins. It includes the developmental history of antibiotics; penicillins and cephalosporins in details alongwith their structural and chemical properties and their biosynthesis; biological activity of β-lactam antibiotics explained under various points such as 1] Spectrum of activity 2] Factors affecting antibacterial activity 3] Methods of assay 4] Bacterial resistance to antibiotics 5] Mode of action and 6] Structure-activity relatioship.

Chapter-II gives an account of cyanuric chloride derivatives. In its introduction, the synthesis of cyanuric chloride , its physical and chemical properties , the derivatives of cyanuric chloride used in chemotherapy and other industrial fields such as furniture, crockery, textiles, paper etc. have been described. The most important property which attracted us was that sequential replacement of its chlorine atoms, its selective reactions with amines, its thermal stability due to the structural symmetry. Thus, synthesis of seventeen different types of mono-substituted cyanuric chloride derivatives has been described as shown in Scheme - I-V.

Chapter III gives an account of synthesis of cyanuric chloride derivatives of penicillins and cephalosporins , which starts with a brief introduction explaining the aim of the research undertaken; the possibility that β-lactam antibiotics with the original mode of action could be devised by introduction of non-amidic C-6 & C-7 substituents in penicillins and cephalosporins; the structural features and properties of cyanuric chloride applicable in synthesis of such antibiotics and the possibility of increase in activity to avoid the bacterial resistance caused due to their overuse.

This Chapter describes the following :

i> Synthesis of cyanuric chloride derivatives of penicillins by the reaction of mono-substituted cyanuric chloride derivatives with 6-aminopenicillanic acid (6-APA) has been described (Scheme-VI). By knowing the fact that functionalization of α-amino group in ampicillin (α-aminobenzyl penicillin) leads to the penicillin derivatives having expanded spectrum of antibacterial activity , the above method was extended to synthesize ampicillin derivatives (Scheme- VII);

ii> Synthesis of cyanuric chloride derivatives of cephalosporins by reaction of mono-substituted cyanuric chloride derivatives with 7-aminodeacetoxycephalosporanic acid (7-ADCA) (Scheme-VIII). The fact that 3-deacetoxycephalosporanic acid derivatives are orally active, and one such widely used cephalosporin is cephalexin (α-aminobenzyldeacetoxycephalosporanic acid), tempted us to use the above method to functionalize the α-amino group in cephalexin (Scheme- IX);

iii> Determination of in vitro antibacterial activity of the derivatives mentioned above. The activity is determined in

terms of minimum inhibitory concentration (MIC,ug/ml) against one gram-positive bacteria viz.Staphylococcus aureus (penicillin sensitive) and five gram-negative bacteria viz. Eschirichia coli, Pseudomonas aeruginosa, Salmonella typhimerum, Klebsiella pneumoniae and Shiegella flexneri.

Initially, ten fold dilutions of the compounds were used to determine the concentration range within which the compound showed activity. Then the range was expanded using two-fold serial dilutions. Finally, serial dilutions e.g.5,6,7,..... .....10 ug/ml were prepared to expand the range between 5-10 ug/ml.

PART- B comprises of two chapters.

Chapter-I gives a brief review on silylation reaction.It includes mechanism of silylation; use of hexamethyldisilazane (HMDS) and hexamethylcyclotrisilazane(HMCTS) in organic chemistry.

Chapter-II gives an introduction of catalytic silylation of hydroxy compounds i.e. phenols,alcohols,hydroxy acids and amino acids using HMDS.

HMCTS has been utilized in silylation of phenols, diols and oximes. Lead nitrate is itself an oxidizer and lead being electro-positive makes the nitrate group comparatively electro-negative which in turn, may try to abstract a proton from -COOH or -OH group and thus facilitates the silylation reaction.Hence, lead nitrate was used here as a catalyst.

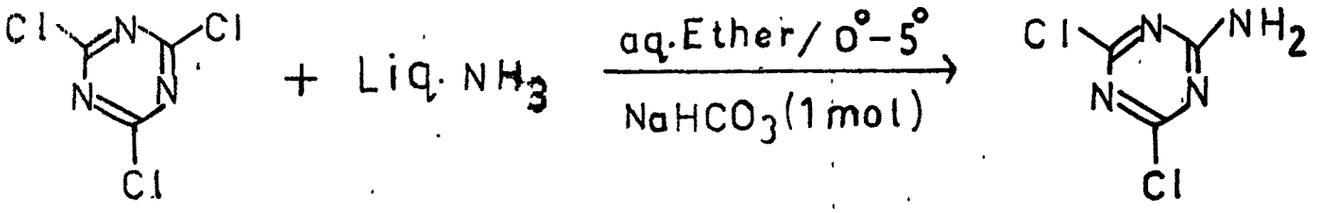
This Chapter describes the following :

i> Protection of -OH group in amino phenols using HMDS catalysed by lead nitrate and -COOH group in amino acids (Scheme- X).

A method for reaction of these silylated compounds with cyanuric chloride has been described (Scheme-XII) .

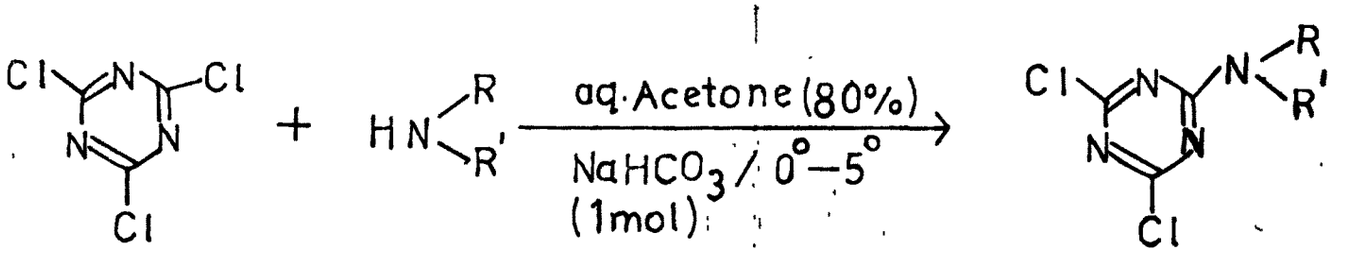
ii> HMCTS is a cyclic silazane which reacts slowly due to steric hindrance and may be selective in its reactions. The use of HMCTS as a divalent silylation agent for aminophenols and aminoacids in presence of lead nitrate as a catalyst has been given in (Scheme-XIII). A selective silylation of salicylic acid (a hydroxy acid) to protect -COOH group selectively over -OH group was achieved using HMCTS in presence of lead nitrate as a catalyst. (Scheme-XIV).

Scheme-I



(1) (2)

Scheme-II

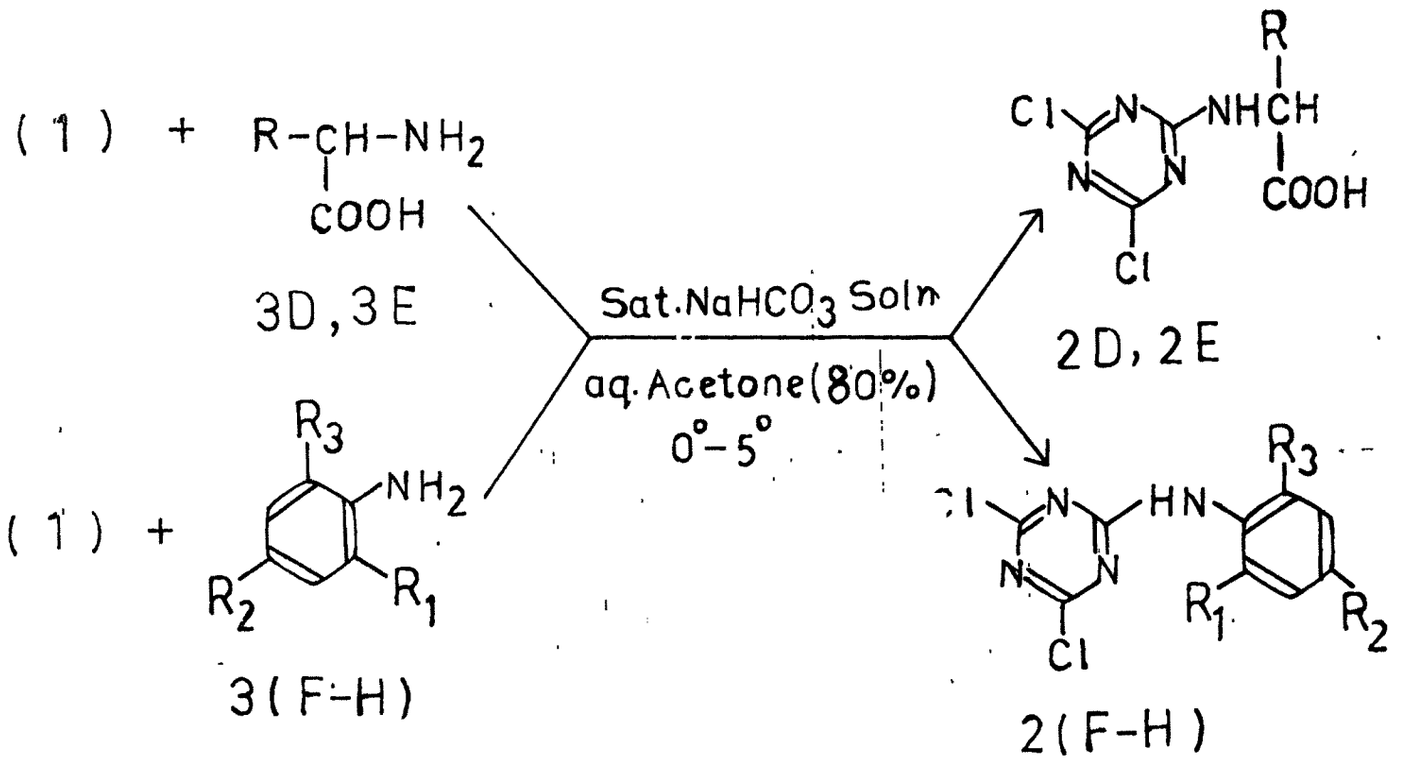


(1) 3(a–c) 2(A–C)

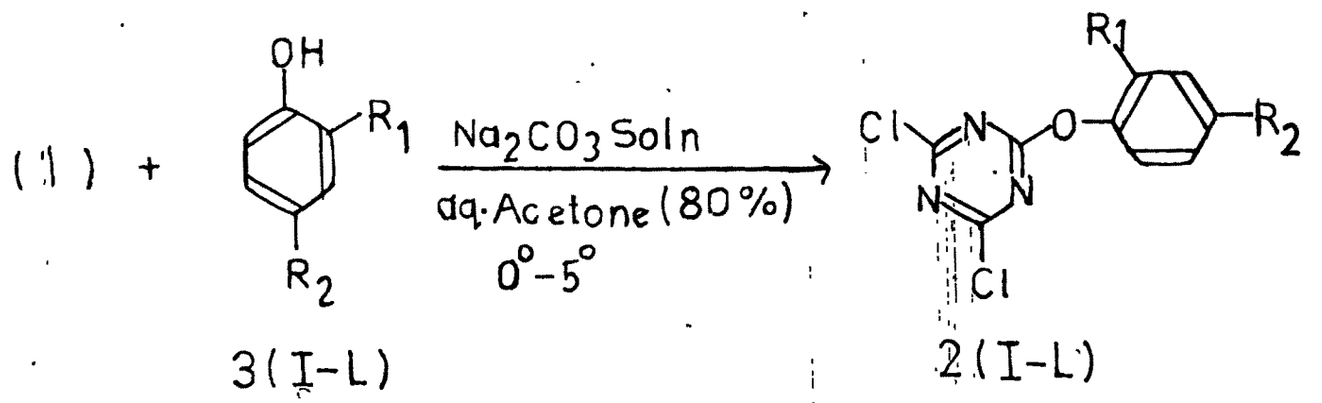
A) $R' = R = CH_2CH_2OH$; B) $R' = H$, $R = o\text{-}MeOOCC_6H_4$;

C) $R' = H$, $R = o\text{-}EtOOCC_6H_4$

Scheme-III



Scheme-IV



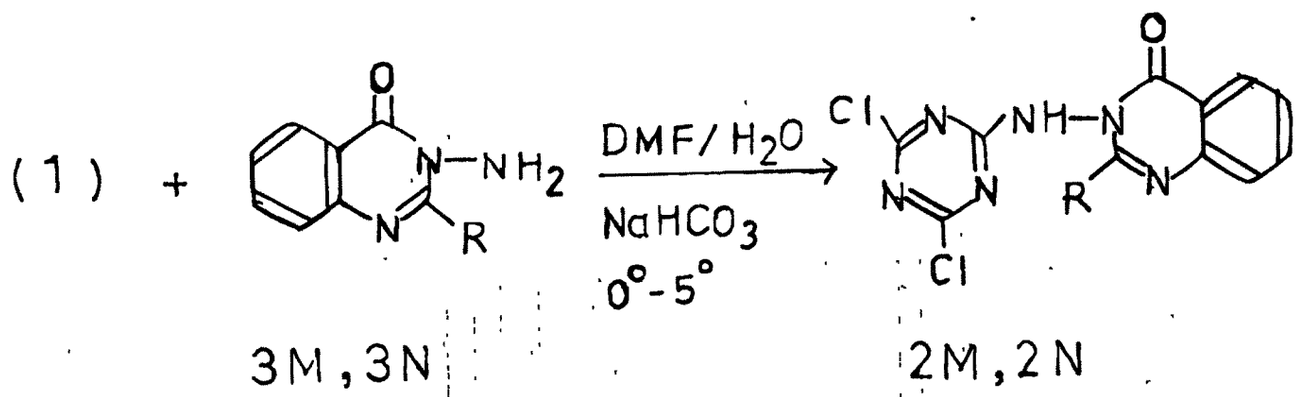
D) $R=C_6H_5$; E) $R=H$; F) $R_1=R_3=H, R_2=COOH$;

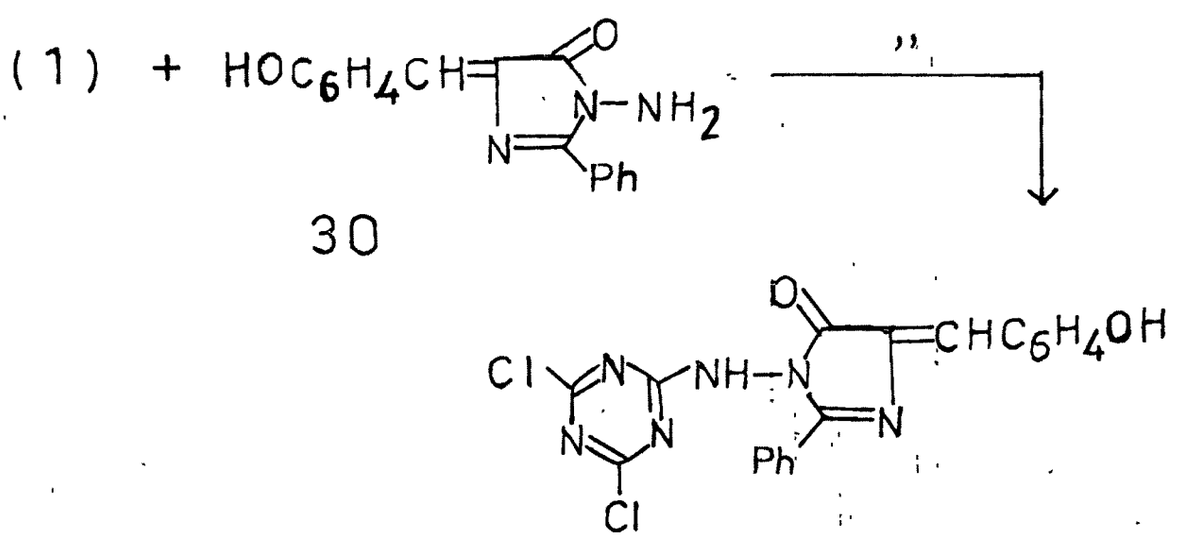
G) $R_2=R_3=H, R_1=COOH$; H) $R_1=COOH, R_2=R_3=Br$;

I) $R_1=R_2=H$; J) $R_1=NO_2, R_2=H$; K) $R_1=H, R_2=NO_2$;

L) $R_1=Cl, R_2=H$

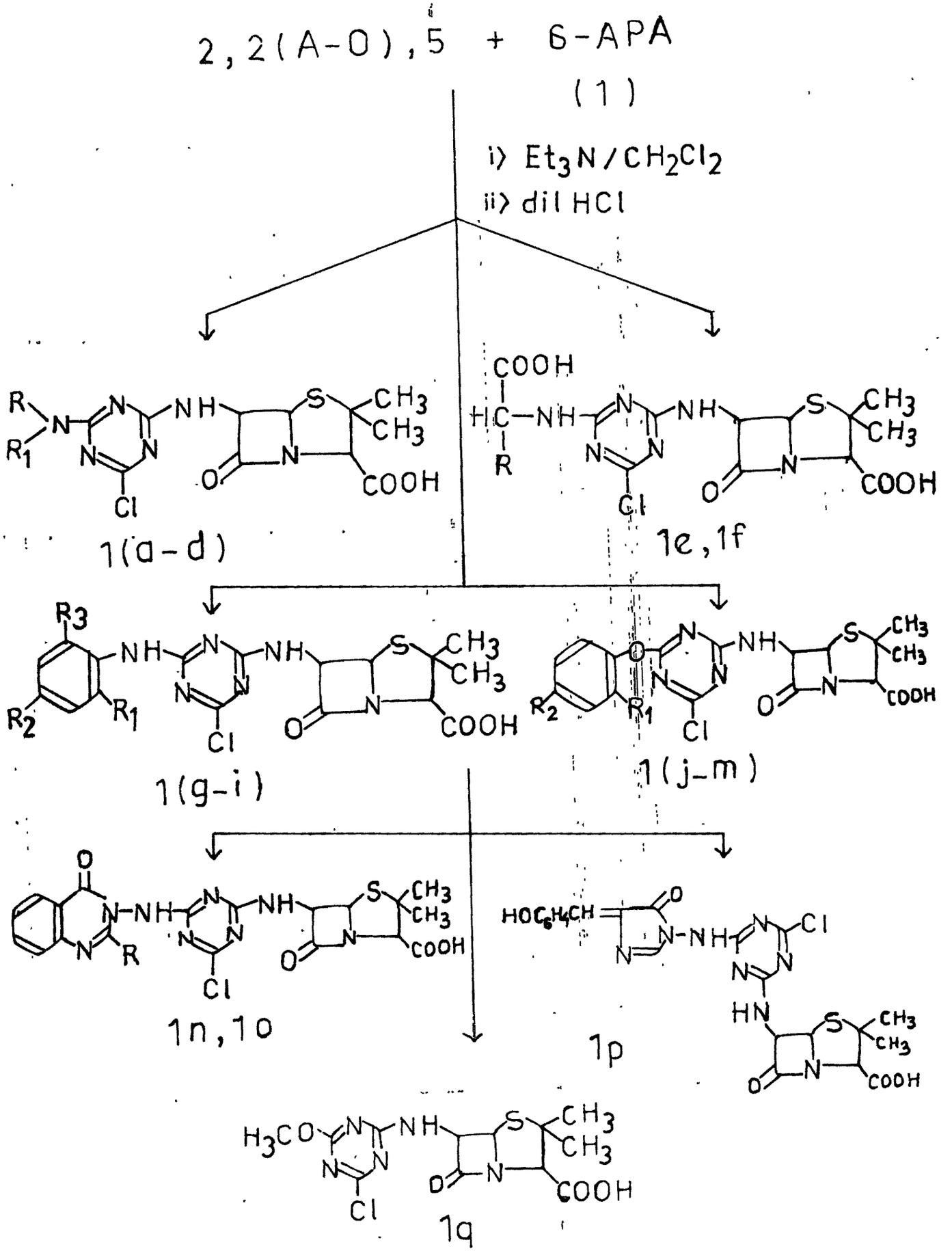
Scheme-V



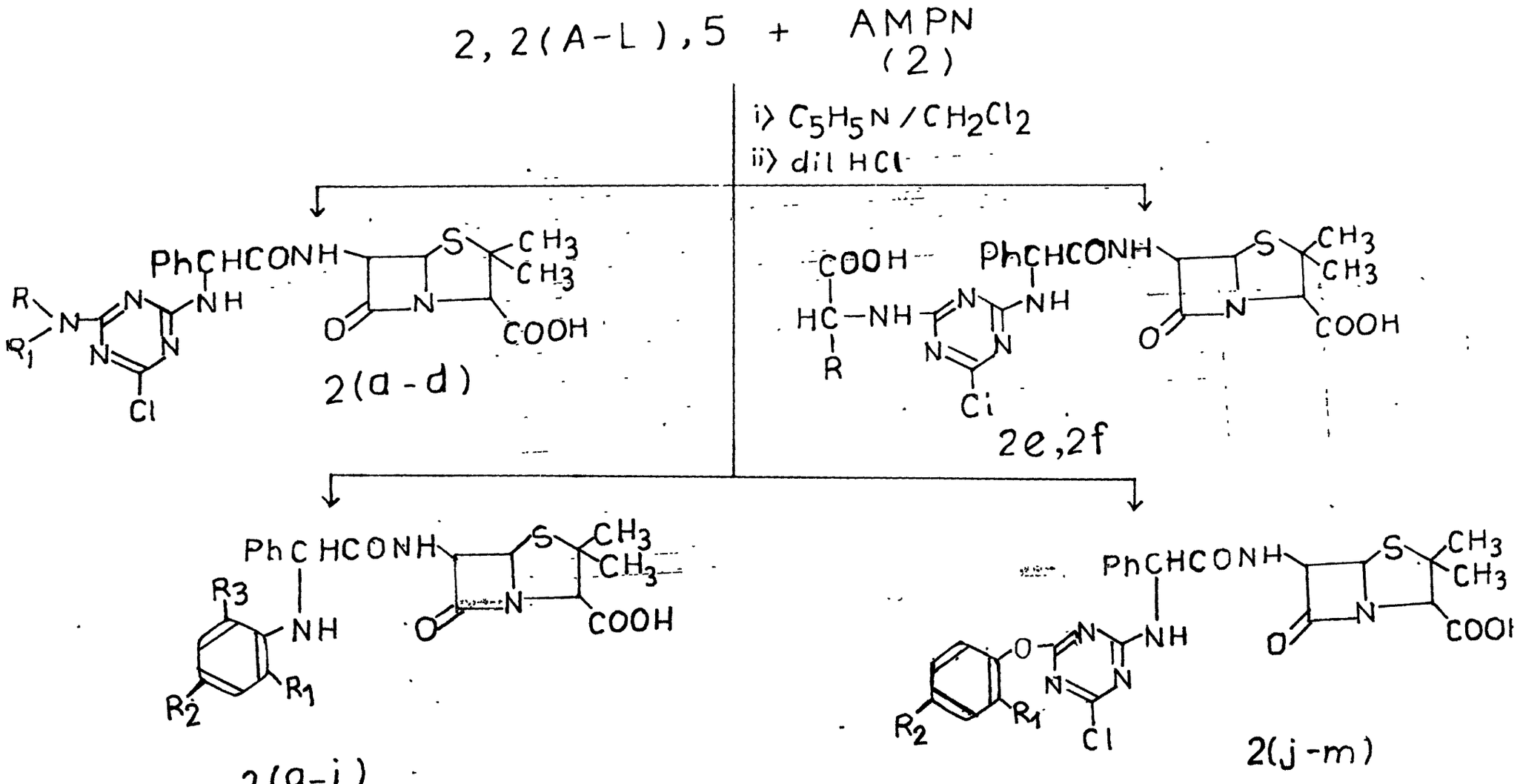


M) $R=CH_3$; N) $R=C_6H_5$

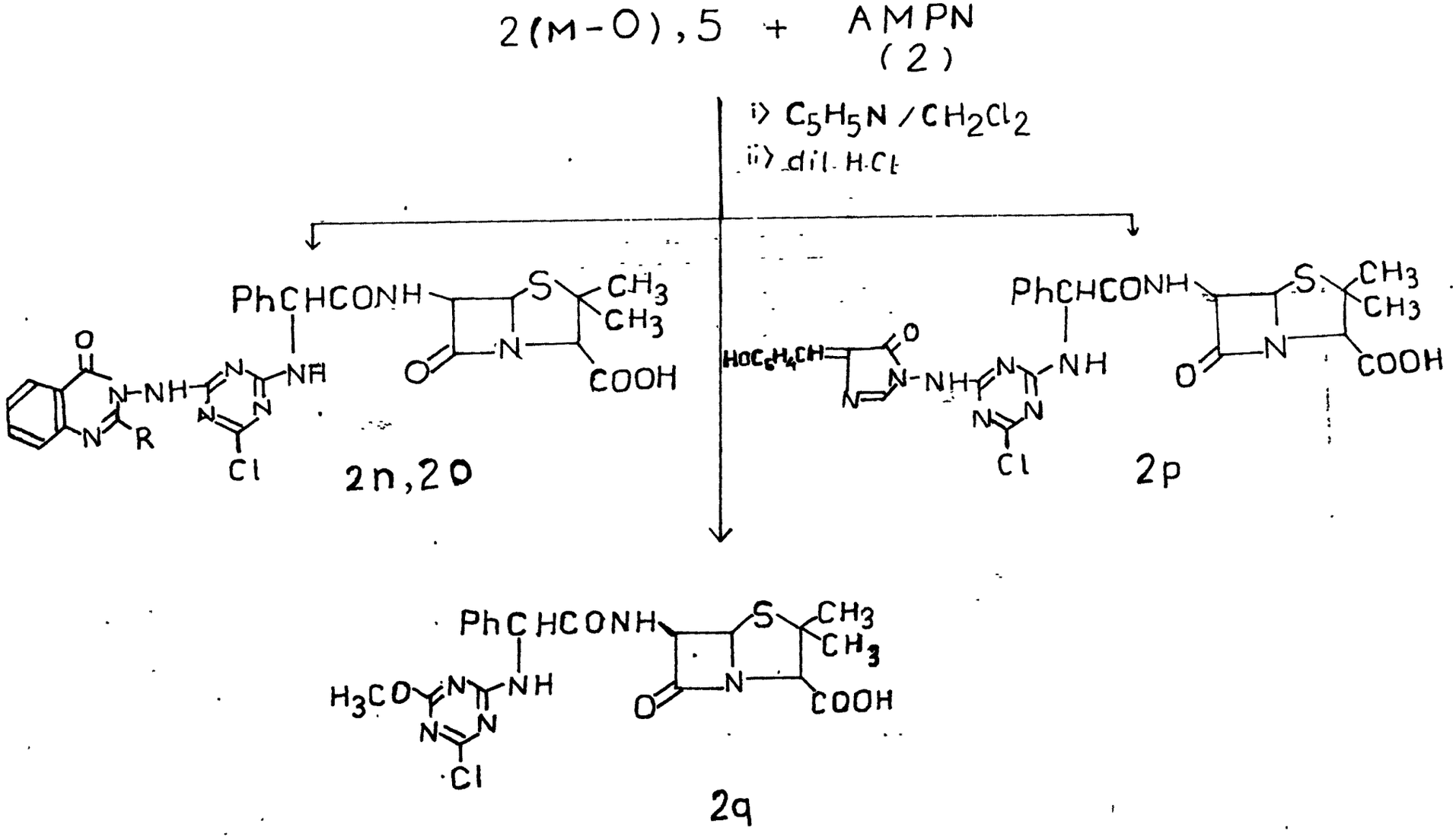
Scheme-VI


2,2(A-O),5 + 6-APA
(1)
i) Et_3N/CH_2Cl_2
ii) dil HCl
1(a-d)
1e,1f
1(g-i)
1(j-m)
1n,1o
1p
1q

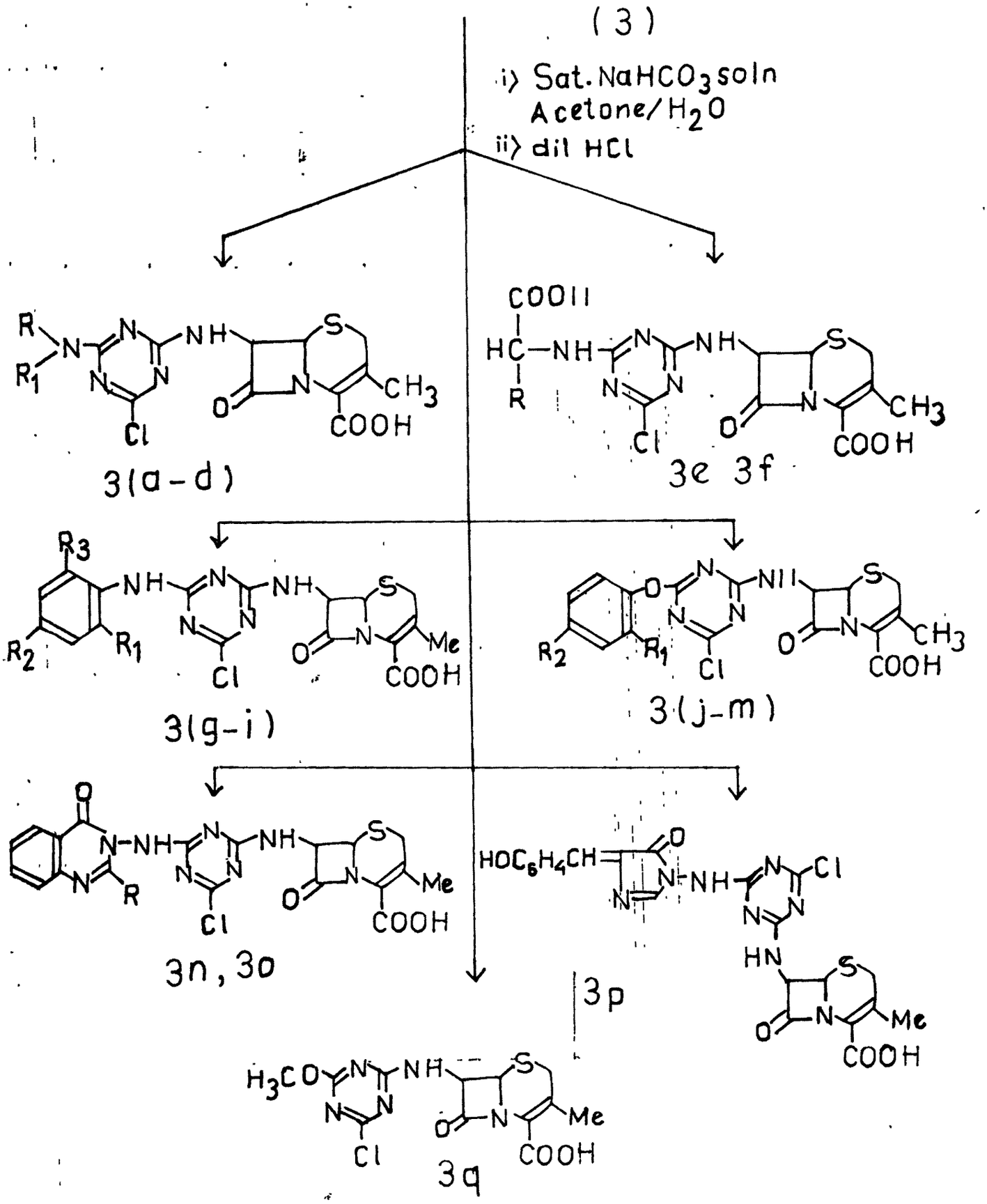
Scheme-VII



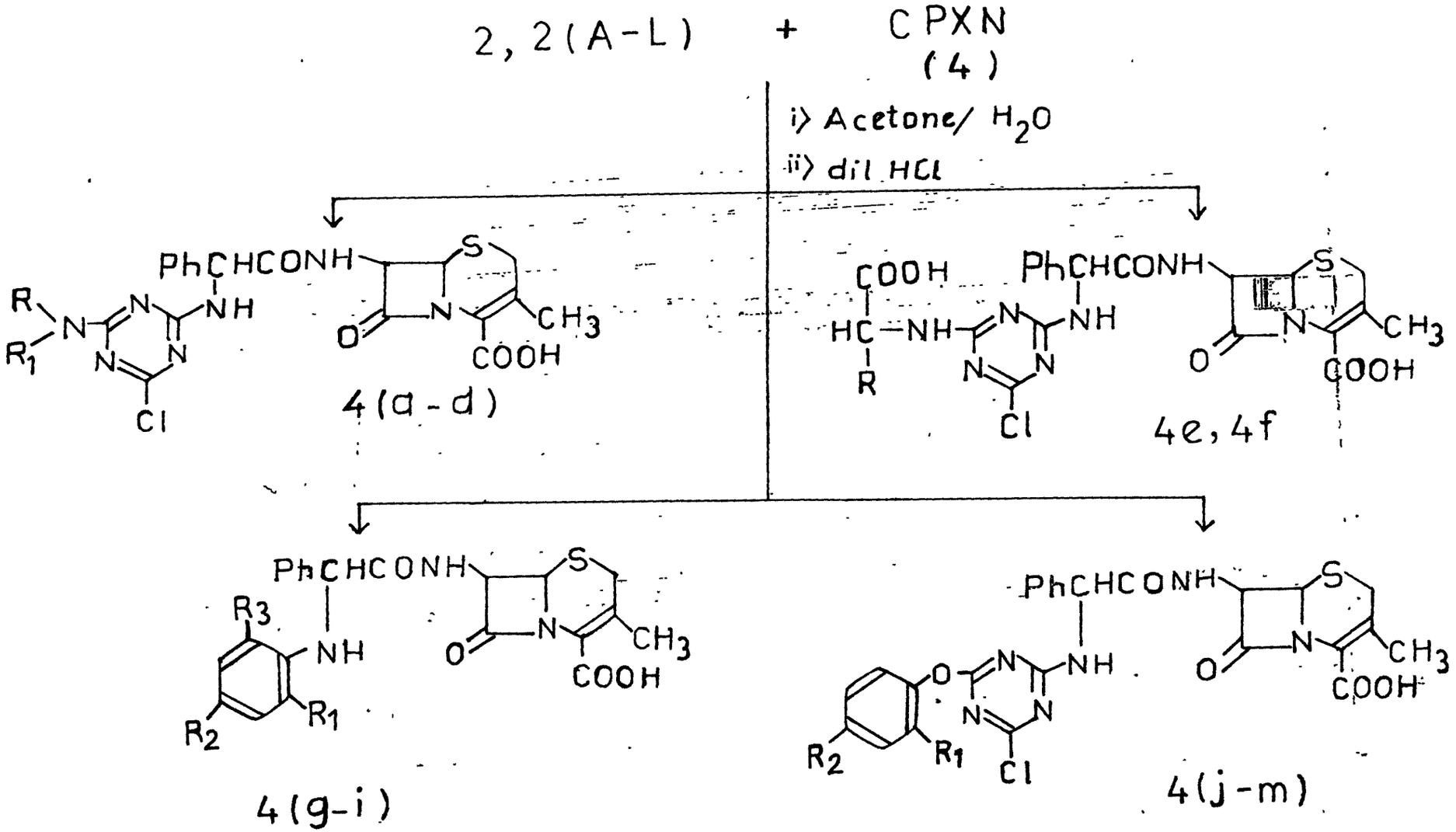
Scheme-VII


2(M-O),5 + AMPN (2)
i) C_5H_5N / CH_2Cl_2
ii) dil. HCl
PhCHCONH
S
CH_3
CH_3
N
COOH
O
NH
NH
N
R
Cl
2n,2o
HOC_6H_4CH
2p
H_3CO
2q

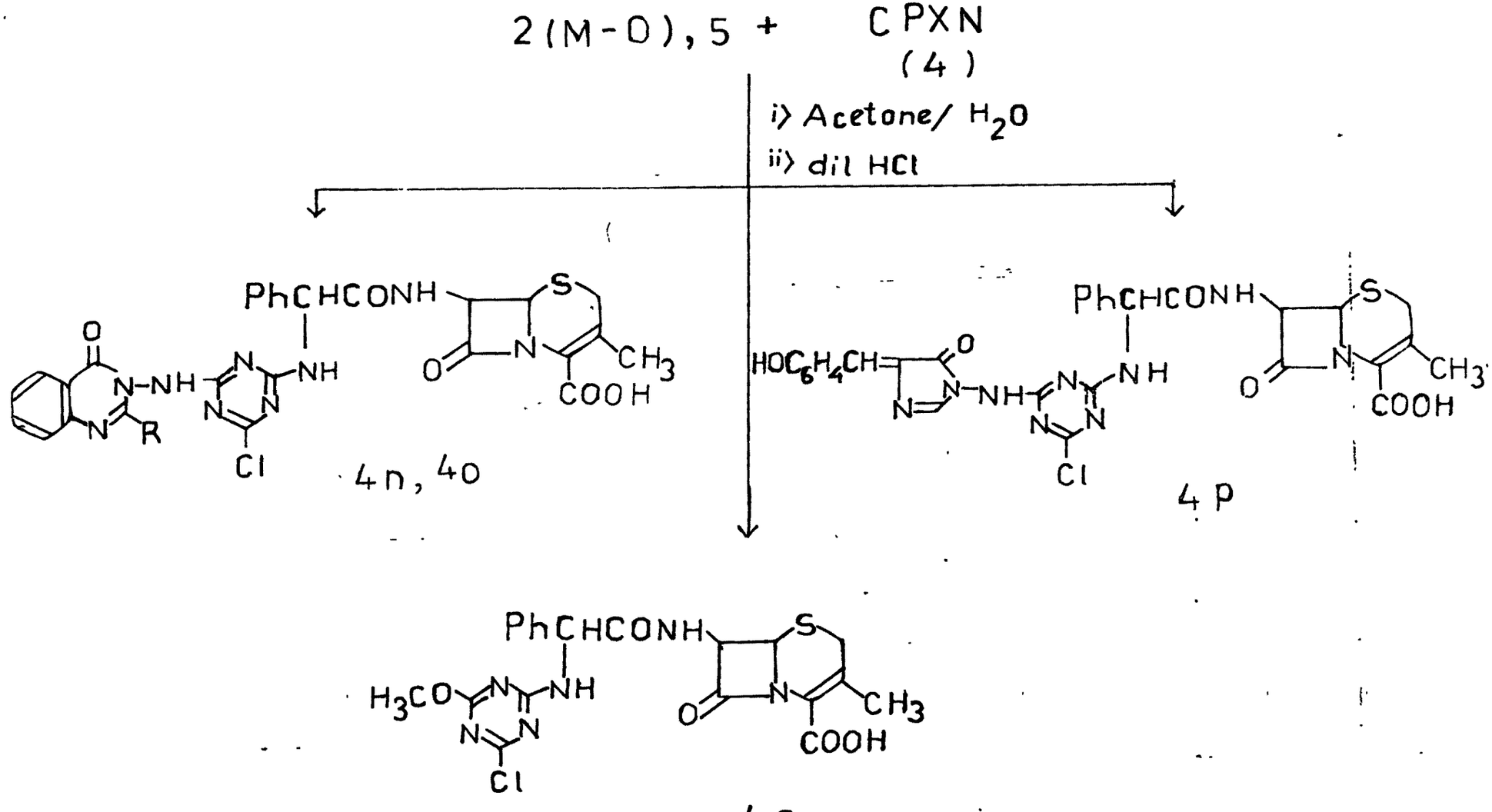
Scheme-VIII


2,2(A-O),5 + 7-ADCA
(3)
i) Sat. NaHCO3 soln
Acetone/H2O
ii) dil HCl
3(a-d)
3e 3f
3(g-i)
3(j-m)
3n, 3o
3p
3q

Scheme-IX


2, 2(A-L)
+
CPXN
(4)
i) Acetone/ H_2O
ii) dil HCl
PhCHCONH
R
R_1
Cl
CH_3
COOH
4(a-d)
HC—NH
4e, 4f
R_3
R_2
R_1
4(g-i)
4(j-m)

Scheme-IX


2(M-O),5 +
CPXN
(4)
i) Acetone/ H_2O
ii) dil HCl
PhCHCONH
S
N
CH_3
COOH
O
N-NH
NH
N
Cl
R
4n, 4o
HOC_6H_4CH
4p
H_3CO
4q

S C H E M E VI - IX

a> R = R_1 = H ; b> R = R_1 = CH_2 CH_2 OH

c> R_1 = H, R = o-MeOOCC_6H_4 ; d> R_1 = H, R = o-EtOOCC_6H_4

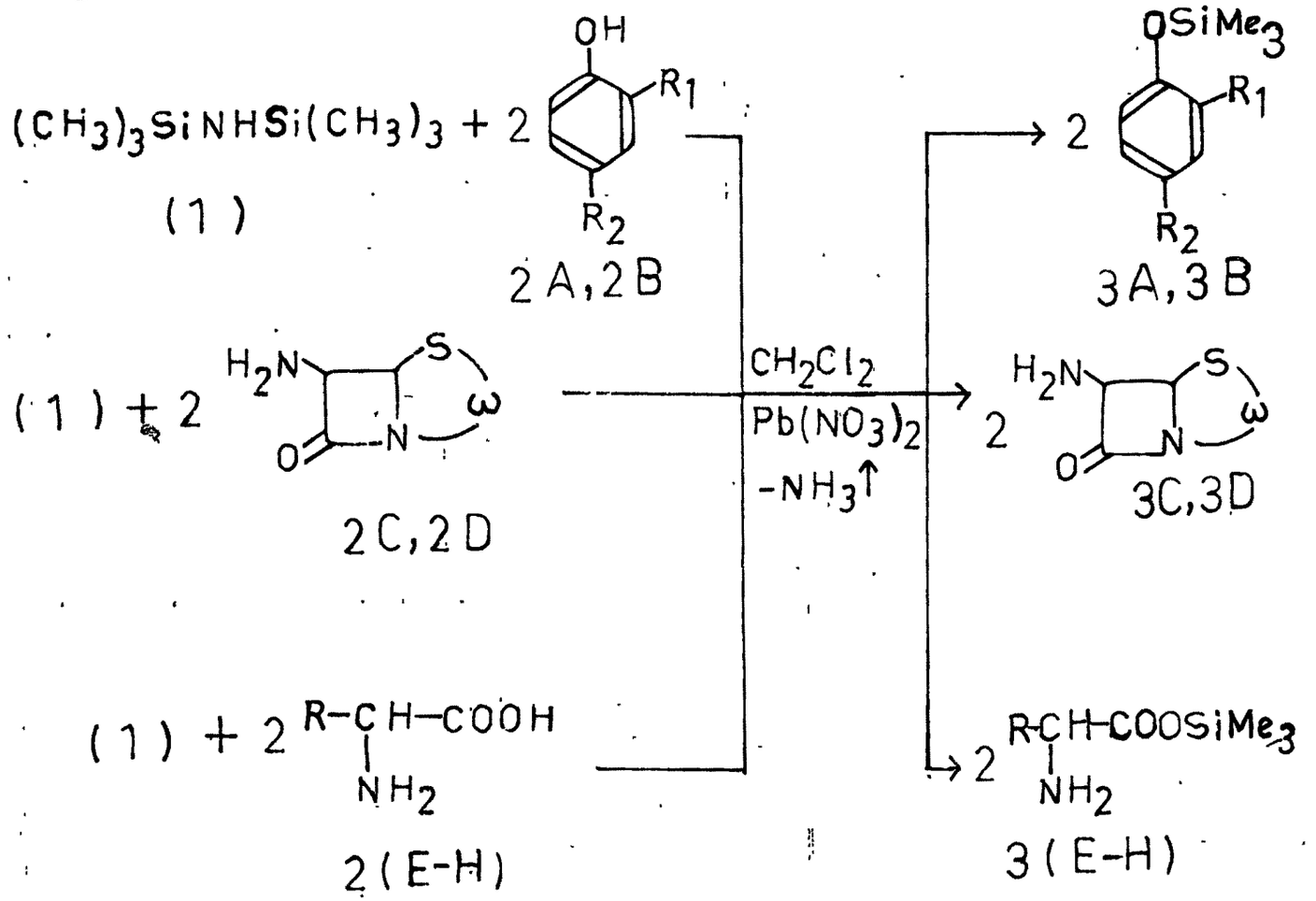
e> R = C_6 H_5 ; f> R = H ; g> R_1 = R_3 = H, R_2 = COOH ;

h> R_2 = R_3 = H, R_1 = COOH ; i> R_1 = COOH, R_2 = R_3 = Br ;

j> R_1 = R_2 = H ; k> R_1 = NO_2 , R_2 = H ; l> R_1 = H, R_2 = NO_2 ;

m> R_1 = Cl, R_2 = H ; n> R = CH_3 ; o> R = C_6H_5.

Scheme-X



SCHEME X - XII

A> $R_1 = NH_2$, $R_2 = H$; B> $R_1 = H$, $R_2 = NH_2$;

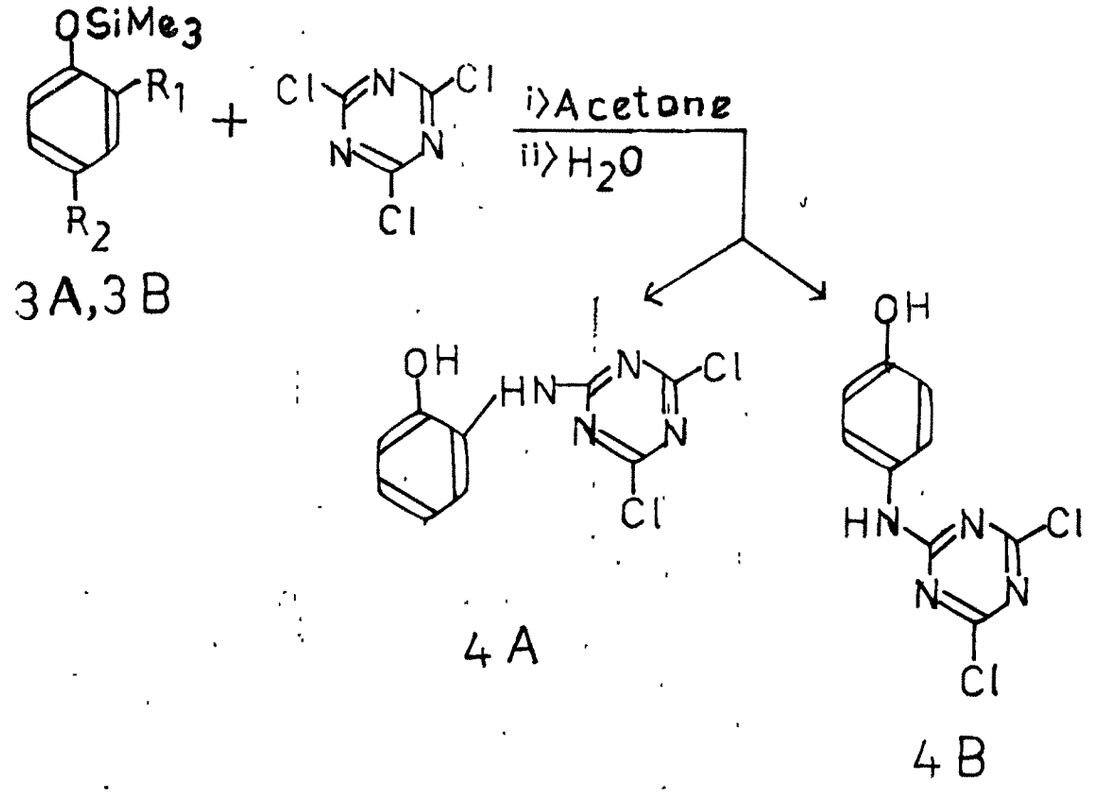
E> $R = C_6H_5$; F> $R = H$; G> $C_6H_5.CH_2$;

H> $R = CH_3$; C> $\omega = C(CH_3)_2CHCOOSiMe_2$;

D> $\omega = CH_2C(CH_3)CCOOSiMe_2$.

Scheme-XI

A)

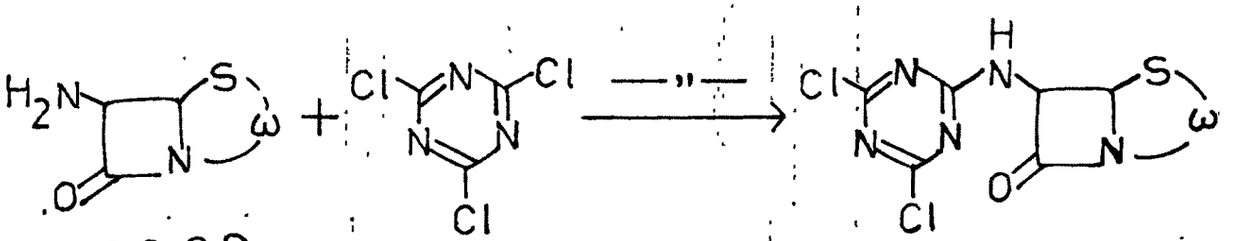


3A, 3B

4A

4B

B)

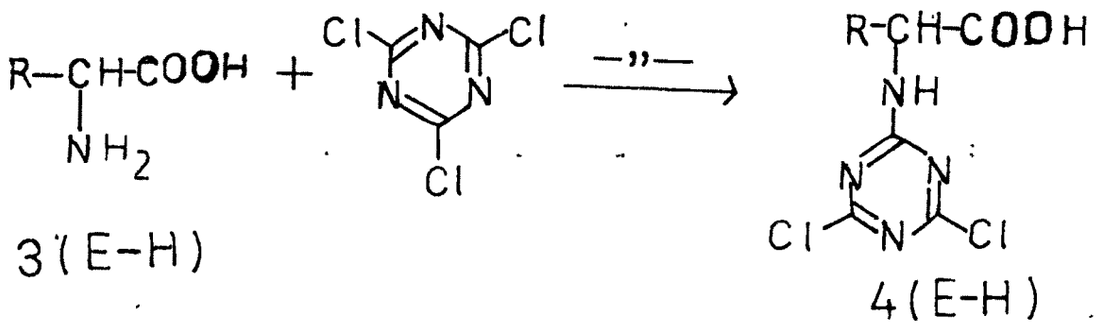


3C, 3D

4C; $\omega = C(CH_3)_2CH(COOH)$

4D) $\omega = CH_2C(CH_3)C(COOH)$

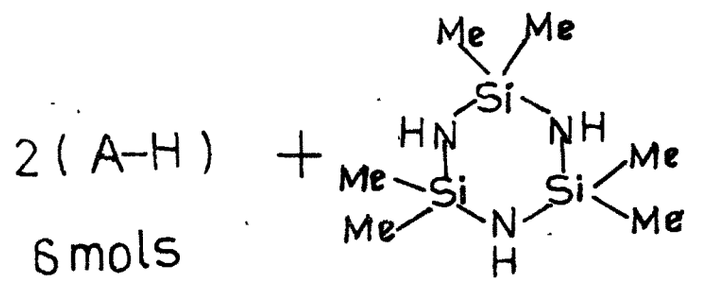
C)



3(E-H)

4(E-H)

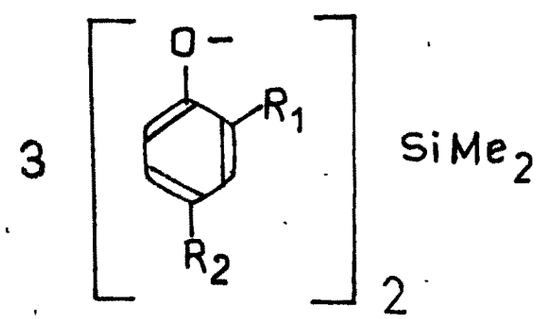
Scheme-III



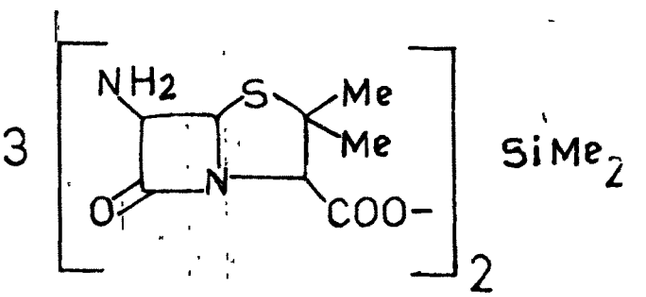
$(NH_4)_2SO_4$

$CH_2Cl_2/Pb(NO_3)_2$

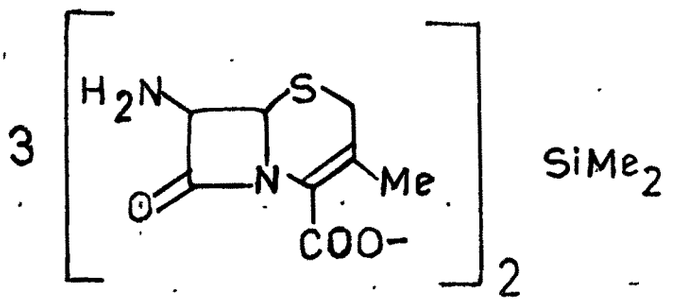
$-3NH_3\uparrow$



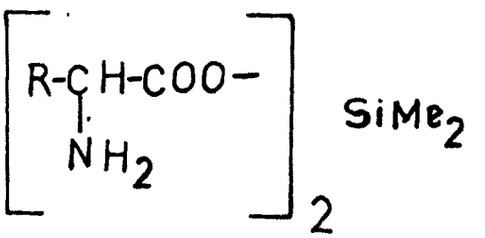
6A, 6B



6C

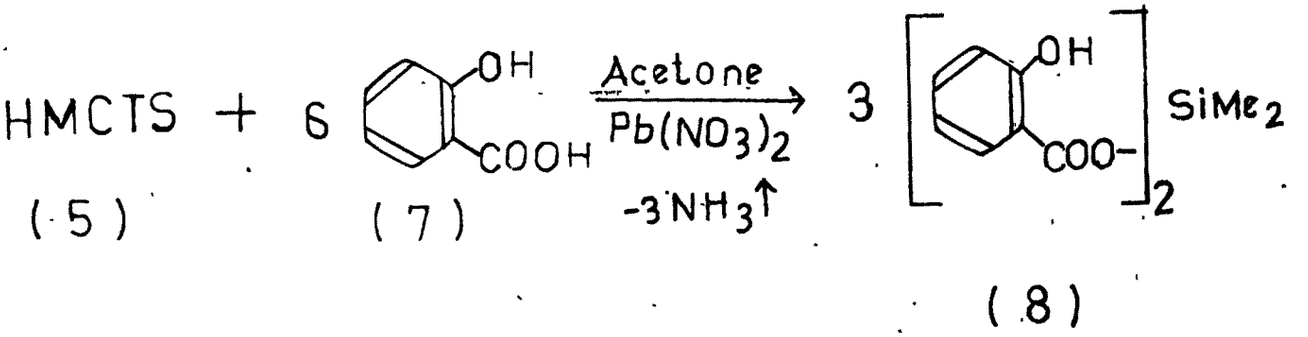


6D

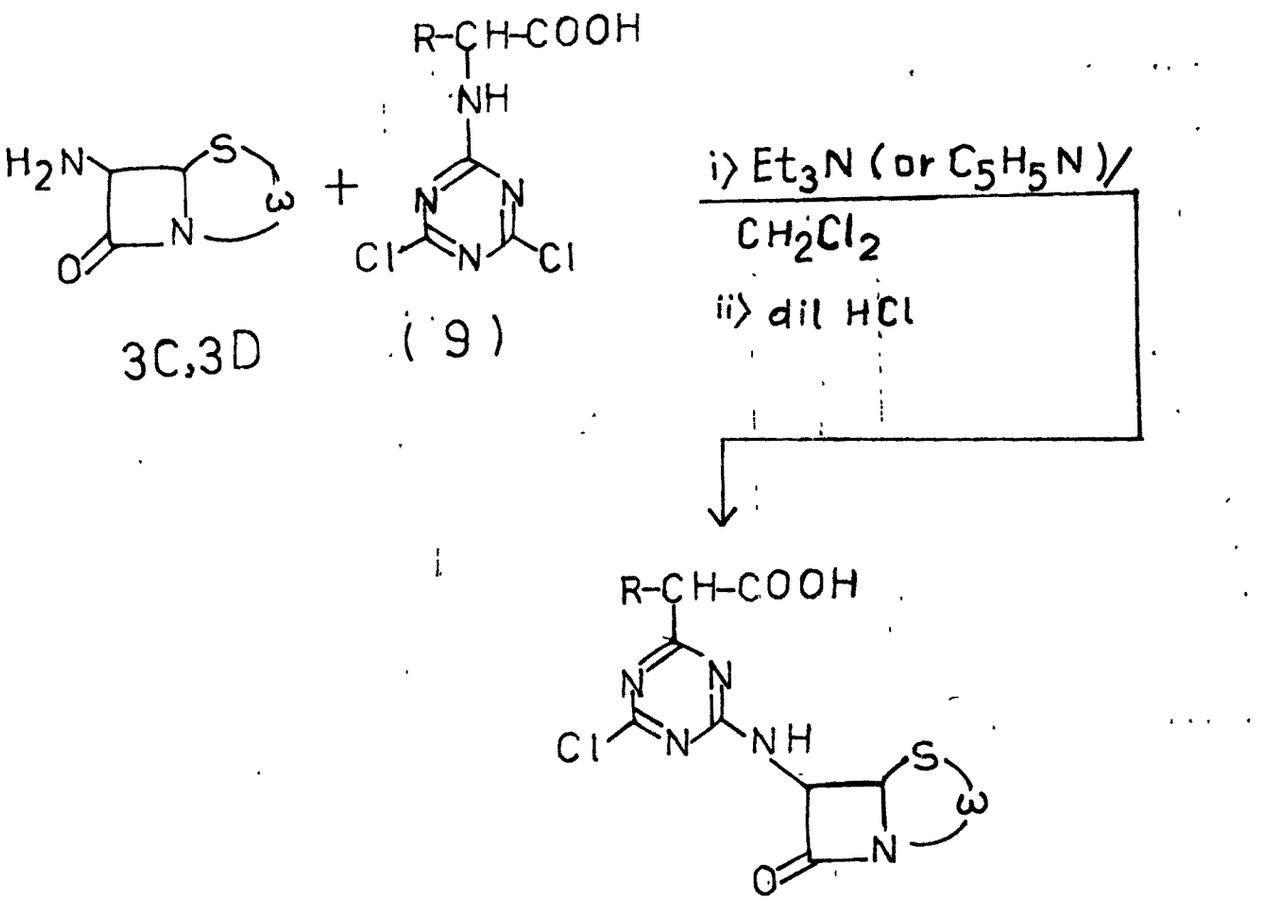


6 (E-H)

Scheme-IV



Scheme-V



a) $R=C_6H_5$; b) $R=H$

$\omega = C(CH_3)_2CHCOOH$

or

$CH_2C(CH_3)CCOOH$