CHAPTER III

Studies on 4-bromomethylcarbostyril derivatives

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Section I

Synthesis of Mannich bases from 4-bromomethyl-carbostyril derivatives

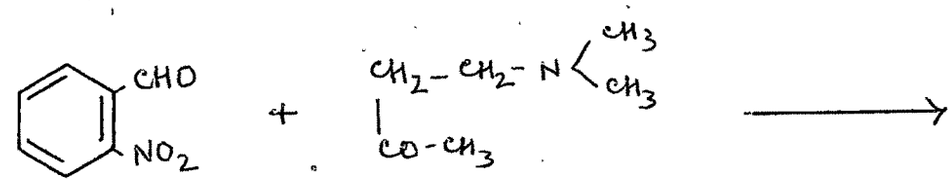
Theoretical

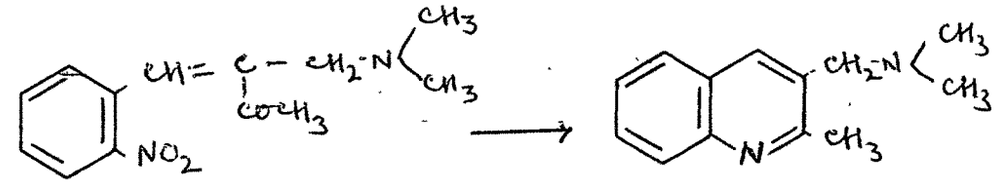
Mannich bases are the products which are obtained by the condensation of a compound containing at least one hydrogen atom of pronounced activity with an aldehyde, usually formaldehyde and ammonia or a primary or a secondary amine.

$$B : H + CH_2O + NHRR' = BCH_2NRR' + H_2O$$

The above reaction which is known as Mannich reaction[1] has been proved to be an important tool in synthetic organic chemistry. The alternate method to prepare Mannich bases is to react a chloromethyl or bromo-methyl derivative with corresponding secondary amines such as piperidine, morpholine etc. This method is used in the present work. Some of the Mannich bases are found to be important medicinal agents. A number of heterocyclic systems containing nitrogen, oxygen or sulphur have been studied. Mannich bases from chromones and flavones[2] possess central nervous stimulant activity. Mannich *et al*.[3] found that β-dimethylaminomethylketone and *o*-nitrobenzaldehyde

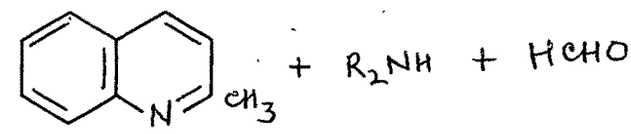
reacted to give a product which upon reduction lost water to form a substituted quinoline (1).

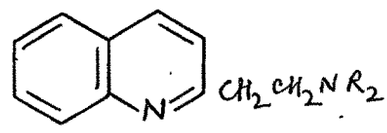




(1)

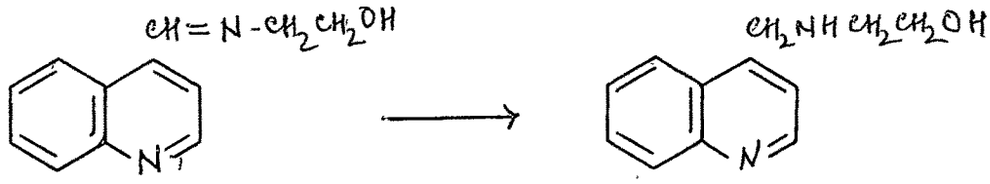
Quinaldine undergoes the Mannich reaction to yield amines of the following type.[4]





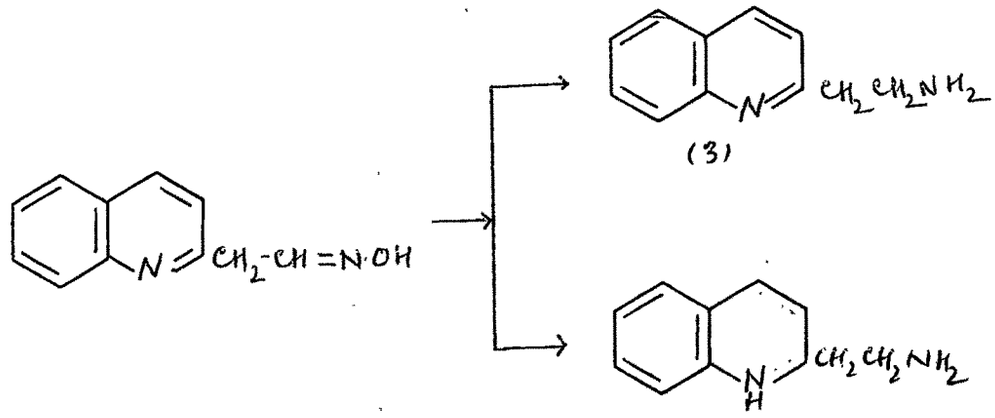
Reduction of Schiff bases derived from

quinoline-4-aldehyde gave lepidylamines[5] (2).



(2)

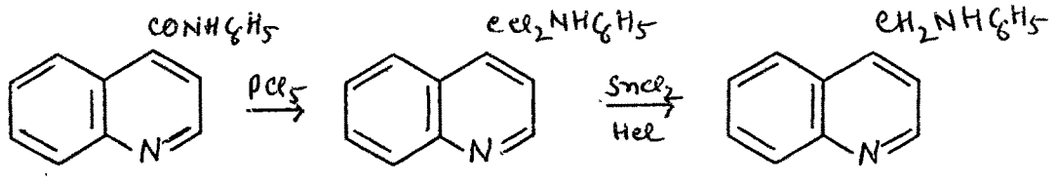
Hupe and Schramme[6] synthesised β-(2-quinolyl) ethylamine (3) and its tetrahydro derivative (4) from the oxime of quinoline-2-acetaldehyde.



(3)

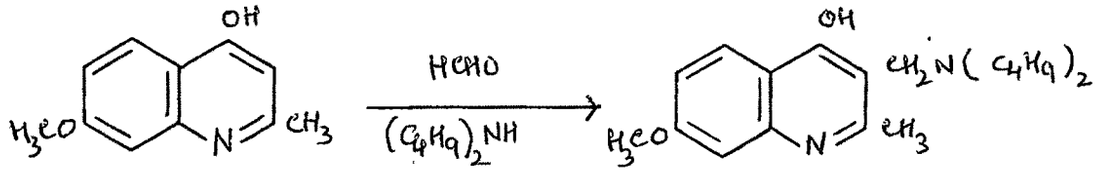
(4)

Work[7] obtained N-phenyl lepidylamine (5) in his attempt to prepare quinoline-4-aldehyde by the Sonn and Muller aldehyde synthesis.



(5)

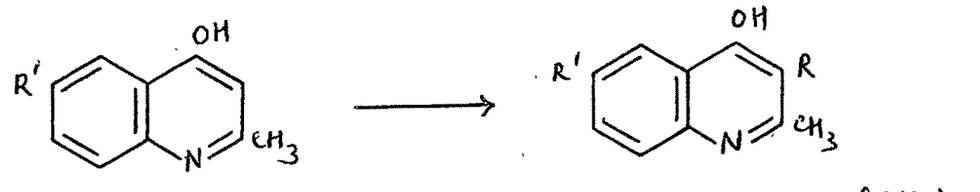
Price and Jackson[8] obtained 3-dibutylaminomethyl-2-methyl-7-methoxy-4-quinolinol (6) by the Mannich reaction on 2-methyl-7-methoxy-4-quinolinol.



(6)

Heou-Feo[9] suggested the mechanism and stated that the Mannich reaction product from quinaldine and diethylamine is quite unstable, but the corresponding compound from lepidine is more stable.

Ghosh and Chaudhuri[10] synthesised 3-diethylaminomethyl (7) and 3-piperidinomethyl (8) derivatives of 2-methyl-, 6-acetoamido-2-methyl- and 6-amino-2-methyl-4-quinolinol by the application of Mannich reaction. 6-(2-Thiazolylamino)-2-methyl-4-quinolinol also underwent the Mannich reaction. These compounds were found to have antispasmodic activity[11].



Saxena and Singh[12] found 3-dibutylaminomethyl-2-methyl-4-quinolinol as an amebicide in rats. Tondon et al.[13] synthesised 3-piperidinomethyl and 3-morpholinomethyl derivatives of 4-hydroxyquinoline and 4-hydroxyquinaldine and tested them as potential amebicides.

Bowman[14] as well as Nabih et al.[15] also synthesised various 3-substituted dialkylaminomethyl quinoline derivatives.

The bromination of acetoacetanilide followed by its cyclisation has given an important method for the synthesis of 4-bromomethyl carbostyril derivatives. These bromomethyl derivatives are now used as starting material for the synthesis of different substituted quinoline derivatives. In the present work the 4-bromomethyl carbostyril derivatives are reacted with different bases such as piperidine,morpholine,dimethylamine and sulphanil-amide to obtain the corresponding Mannich bases, which might be of therapeutic importance. The previous literature on the Mannich bases of quinoline derivatives refer to the synthesis of bases having side chain in the 2- or 3- position. This is the first time that Mannich bases of quinoline derivatives having side chain in the 4-position are prepared.

The following are the Mannich bases prepared by reacting different 4-bromomethylcarbostyril derivatives with piperidine,morpholine etc.

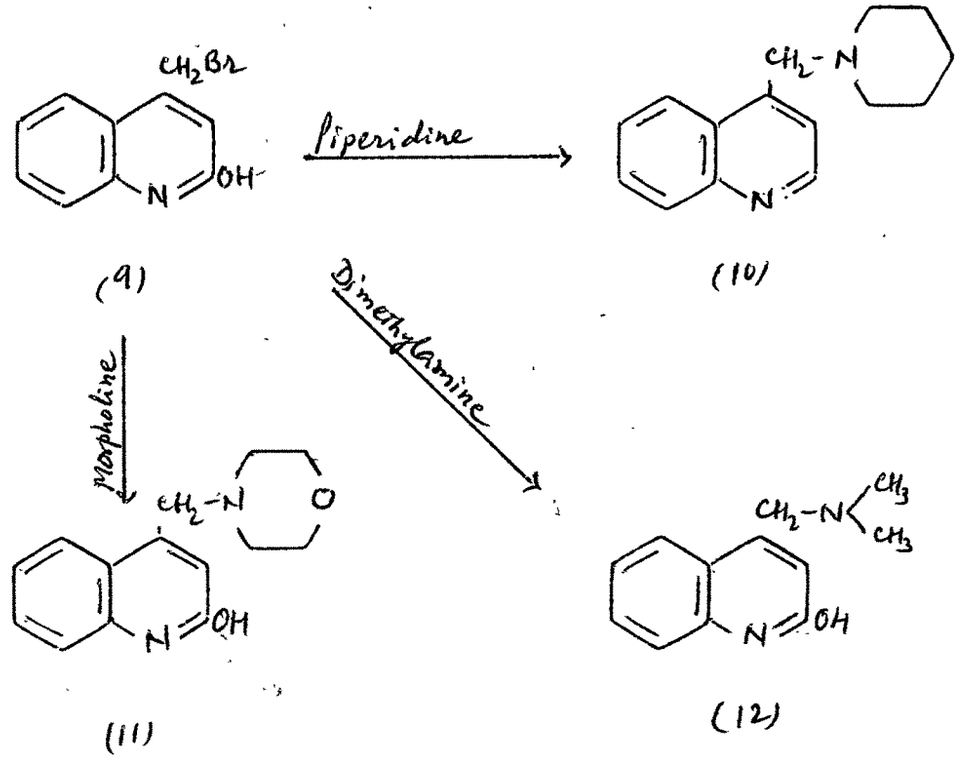
Mannich bases from 4-bromomethylcarbostyril (9) :

(a) with piperidine : The 4-bromomethylcarbostyril (9) as described in the chapter II was reacted with piperidine in alcohol. As the bromine atom was replaced by piperidine molecule the structure was assigned as 4-piperidinomethyl-carbostyril (10).

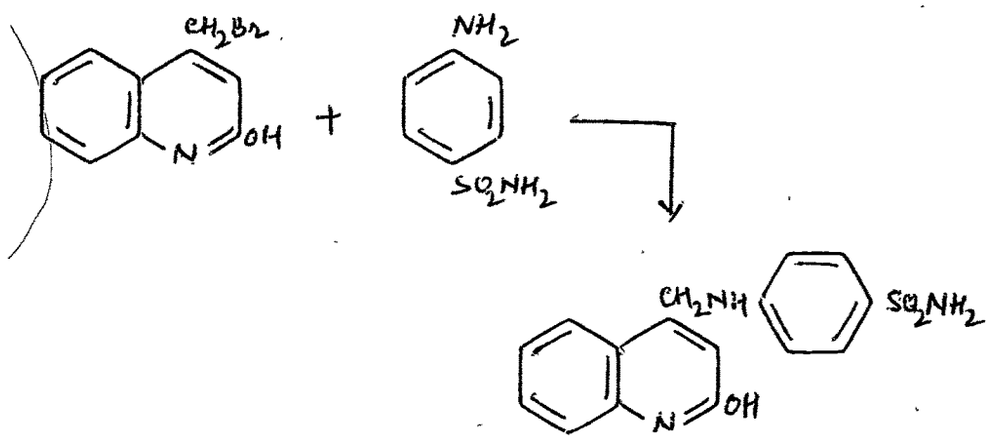
(b) with morpholine : The 4-bromomethylcarbostyril when reacted with morpholine in alcohol gave the 4-morpholino-methylcarbostyril (11).

(c) with dimethylamine : The 4-dimethylaminomethyl-carbostyril (12) was prepared by refluxing 4-bromomethyl-carbostyril (9) with dimethylamine.

(d) with sulphanilamide : The 4-bromomethyl-carbostyril was refluxed with sulphanilamide in alcohol



to give 4-sulphanilamidomethylcarbostyril (13).



(13)

Mannich bases from 8-methyl-4-bromomethyl-carbostyril (14):

(a) with piperidine : 8-Methyl-4-piperidinomethyl-carbostyril (15) was prepared from 8-methyl-4-bromomethyl-carbostyril by refluxing it with piperidine in alcohol.

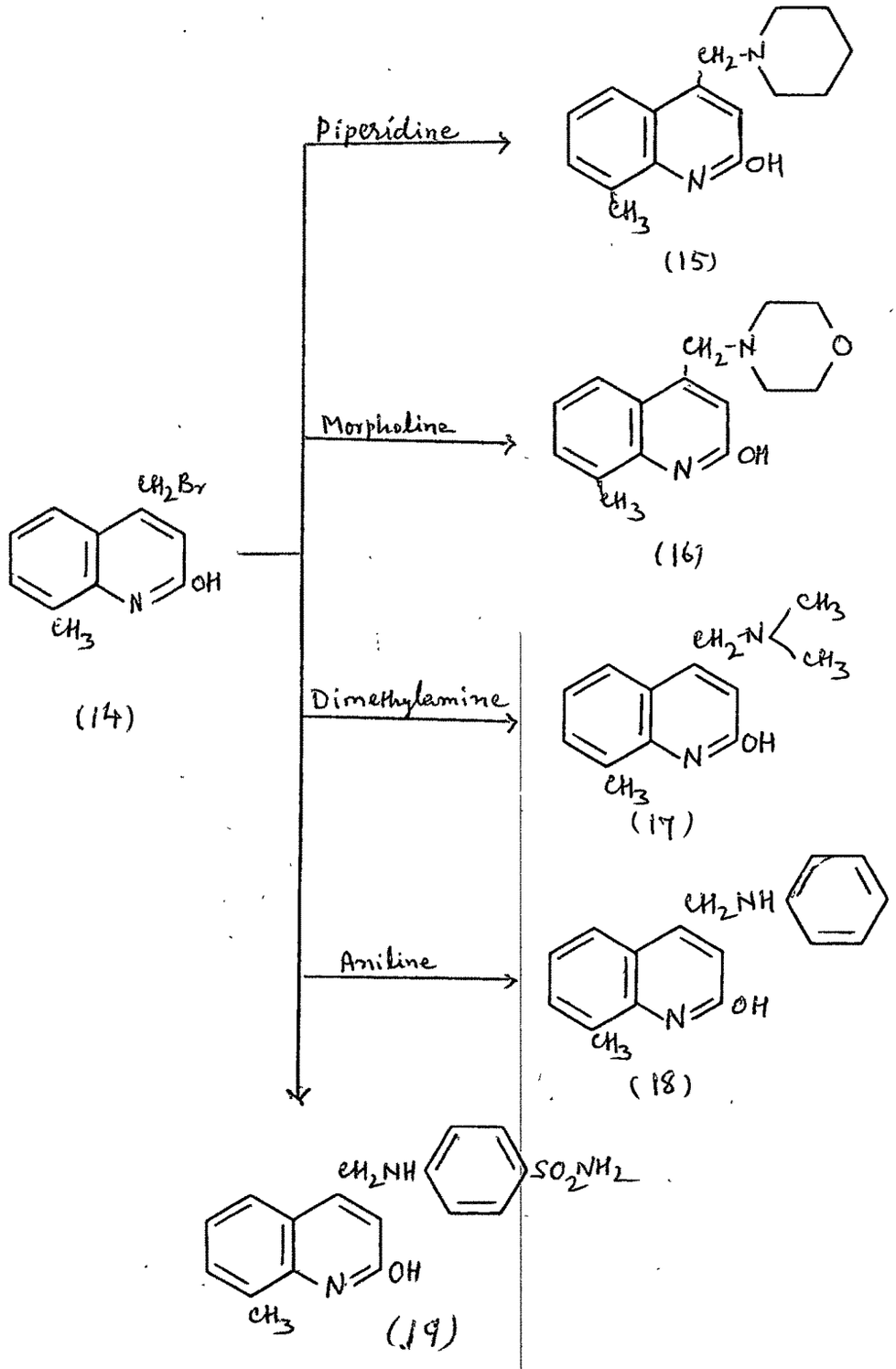
(b) with morpholine : 8-methyl-4-morpholinomethyl-carbostyril (16) was prepared by refluxing 8-methyl-4-bromo-methylcarbostyril (14) with morpholine in alcohol.

(c) with dimethylamine : 8-Methyl-4-bromomethyl-carbostyril gave 8-methyl-4-dimethylaminomethylcarbostyril (17) when it was refluxed with dimethylamine.

(d) with aniline : 8-Methyl-4-anilinomethyl-carbostyril (18) was prepared by refluxing (14) with aniline.

(e) with sulphanilamide : 4-Sulphanilamidomethyl

carbostyril (19) was prepared from the 4-bromomethyl derivative (14) by refluxing it with sulphanilamide in alcohol.

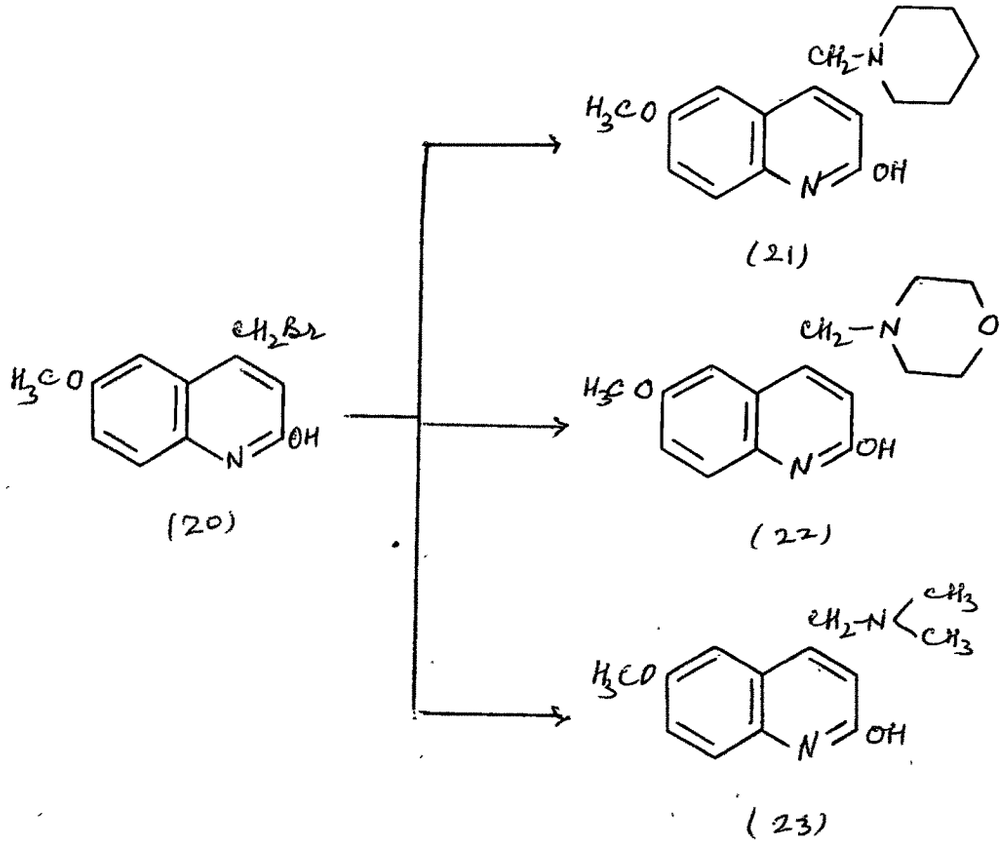


Mannich bases from 6-methoxy-4-bromomethylcarbostyril

(a) with piperidine : 6-Methoxy-4-piperidinomethyl-carbostyril (21) from 6-methoxy-4-bromomethylcarbostyril (20) was obtained by refluxing it with piperidine in alcohol.

(b) with morpholine : The 4-morpholinomethyl derivative (22) of 6-methoxy-4-bromomethylcarbostyril was prepared by refluxing it with morpholine in alcohol.

(c) with dimethylamine : The 4-dimethylaminomethyl derivative (23) of (20) was prepared by refluxing it with dimethylamine.



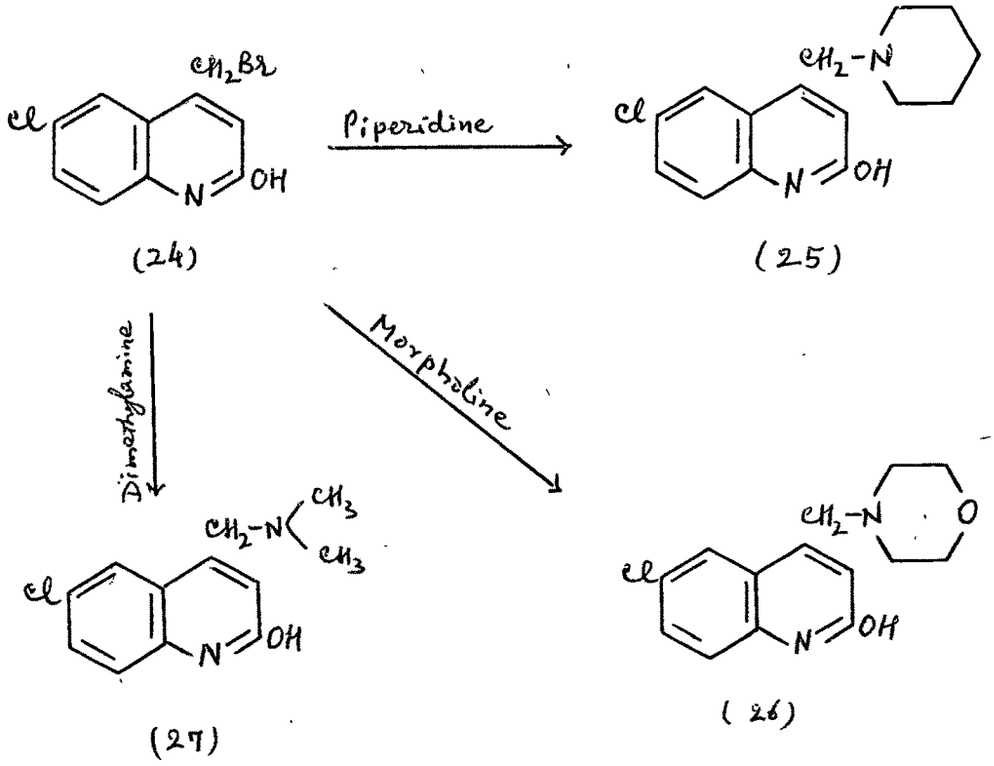
Mannich bases from 6-chloro-4-bromomethylcarbostyril (24):

(a) with piperidine : The 4-piperidinomethyl derivative (25) of 6-chloro-4-bromomethylcarbostyril (24) was prepared by refluxing it with piperidine in alcohol.

(b) with morpholine : The 4-bromomethyl derivative(24) yielded the 4-morpholinomethyl derivative (26) with morpholine in alcohol.

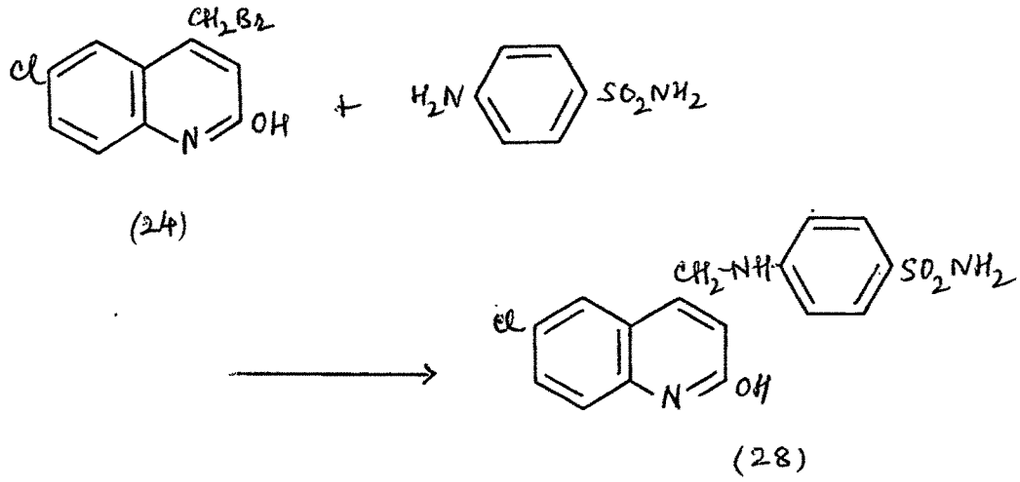
(c) with dimethylamine : The 4-bromomethyl derivative (24) gave the 4-dimethylaminomethyl derivative (27) when it was refluxed with dimethylamine.

(d) with sulphanilamide : The 4-(p-sulphanilamido) methyl derivative (28) of (24) was obtained by refluxing it with sulphanilamide in alcohol.



(24) (25)

(27) (26)

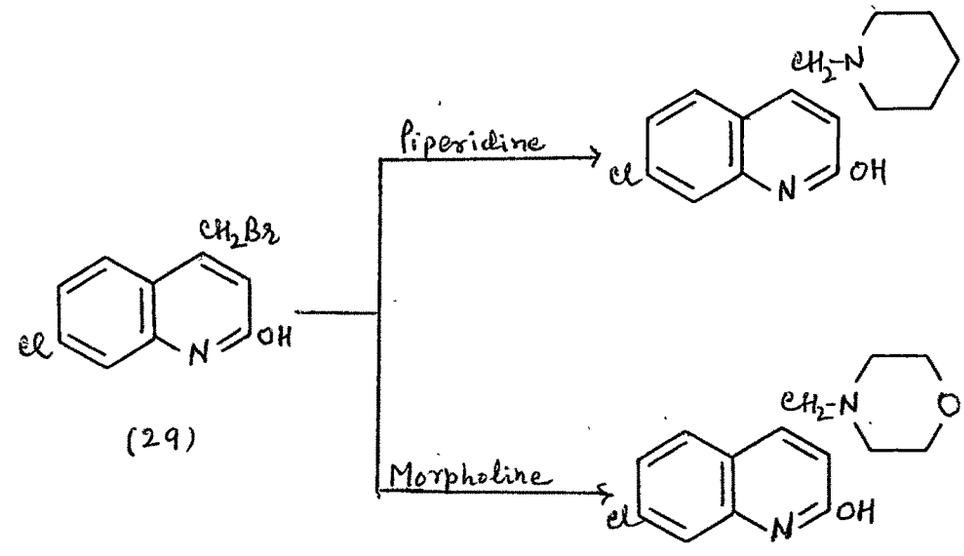


(24) (28)

Mannich bases from 7-chloro-4-bromomethylcarbostyril (29):

(a) with piperidine : 7-Chloro-4-piperidinomethyl carbostyril (30) from 7-chloro-4-bromomethylcarbostyril (29) was obtained by refluxing it with piperidine in alcohol.

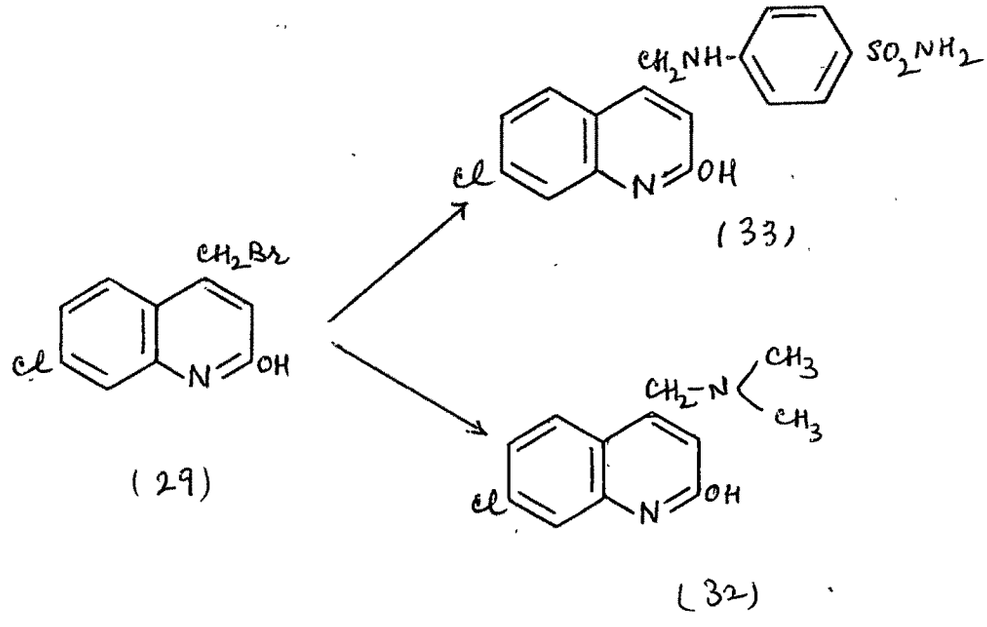
(b) with morpholine : 7-Chloro-4-bromomethylcarbostyril on refluxing with morpholine in alcohol gave the 4-morpholinomethyl derivative (31).



(29)

(c) <u>with dimethylamine</u> : The dimethylaminomethyl derivative (32) of (29) was prepared by refluxing it with dimethylamine.

(d) <u>with sulphanilamide</u> : The bromomethyl derivative (29) on refluxing with sulphanilamide in alcohol gave the sulphanilamidomethyl derivative (33).

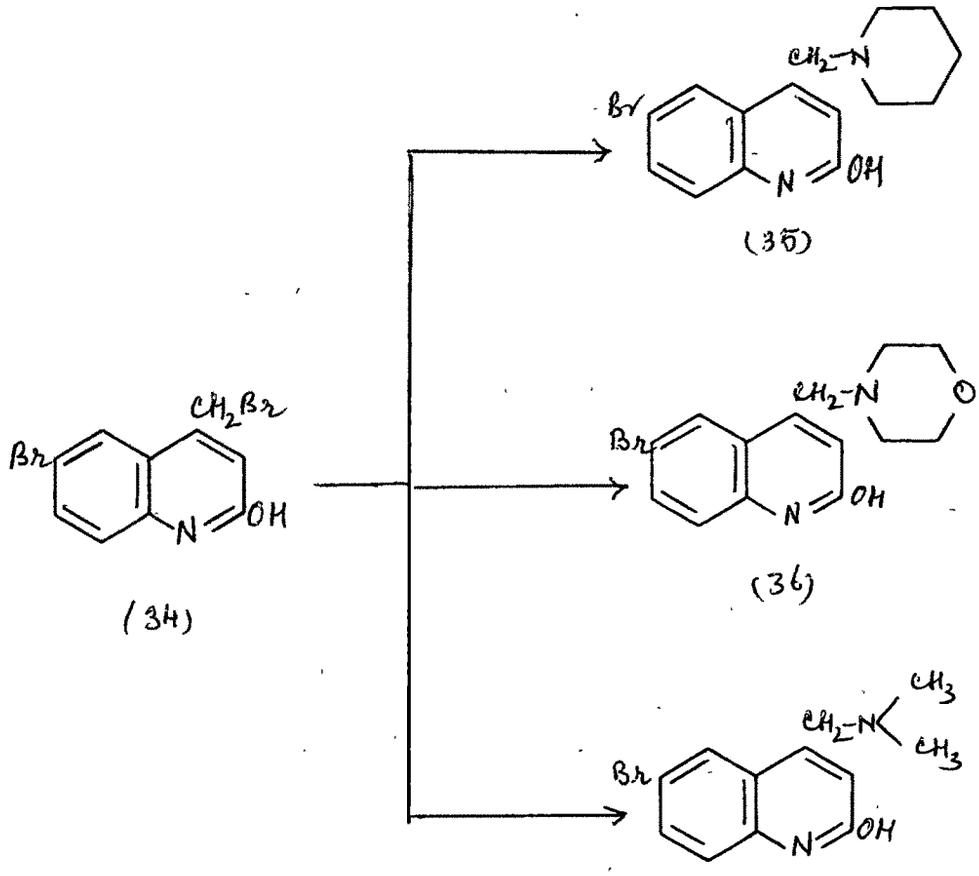


<u>Mannich bases from 6-bromo-4-bromomethylcarbostyril</u> (34):

(a) <u>with piperidine</u> : The 6-bromo-4-bromomethyl carbostyril (34) on refluxing with piperidine in alcohol gave the 4-piperidinomethyl derivative (35).

(b) <u>with morpholine</u> : The morpholinomethyl derivative (36) of (34) was prepared by refluxing it with morpholine in alcohol.

(c) <u>with dimethylamine</u> : The 4-bromomethyl derivative (34) reacted with dimethylamine to give the 6-bromo-4-dimethylaminomethyl carbostyril (37).



(34)

(35)

(36)

(37)

EXPERIMENTAL

Mannich bases from 4-bromomethyl carbostyril :

4-Piperidinomethyl carbostyril :

4-Bromomethyl carbostyril (0.5 g.) was refluxed with alcohol (20 ml.) and piperidine (0.3 g.) for 2 hr. On cooling the separated product was filtered and crystallised from alcohol, m.p. 209°. Yield 0.4 g.

Analysis : Found : C,74.16 ; H,7.00; N,11.99 %.

$C_{15}H_{18}ON_2$ requires : C,74.39 ; H,7.43 ; N,11.57 %.

4-Morpholinomethyl carbostyril :

4-Bromomethyl carbostyril (0.5 g.) was refluxed on a water bath with alcohol (20 ml.) and morpholine(0.3 g.) for 2 hr. On cooling the separated product was filtered and crystallised from alcohol,m.p.235°. Yield 0.3 g.

Analysis : Found : C,68.71 ; H,6.44 ; N,11.43 %.

$C_{14}H_{16}O_2N_2$ requires : C,68.85 ; H,6.55 ; N,11.48 %.

4-Dimethylaminomethyl carbostyril :

4-Bromomethyl carbostyril (0.5 g.) was refluxed on a water bath with dimethylamine (10 ml. ; 25 %) till the solution became clear (3 hr.). On cooling the product which separated crystallised from benzene,m.p.197°. Yield 0.3 g.

Analysis : Found : C,71.10 ; H,6.66 ; N,14.20%.

$C_{12}H_{14}ON_2$ requires : C,71.24 ; H,6.97 ; N,13.88 %.

4-(4'-sulphanilamido)methyl carbostyril :

4-Bromomethyl carbostyril (1 g.) was treated with sulphanilamide (1 g.) in alcohol (60 ml.). It was refluxed on a steam bath for 5 hr. It was filtered hot and the clear filtrate on cooling gave the crystalline product which was filtered and crystallised from glacial acetic acid, m.p.262°. Yield 0.5 g.

Analysis : Found : C,58.23 ; H,4.43 ; N,12.45 %.

$C_{16}H_{15}O_3N_3S$ requires : C,58.35 ; H,4.55 ; N,12.76 %.

Mannich bases from 8-methyl-4-bromomethyl-carbostyril

8-Methyl-4-piperidinomethylcarbostyril :

8-Methyl-4-bromomethylcarbostyril (0.5 g.) was refluxed with alcohol (20 ml.) and piperidine (0.3 g.) for 2 hr. The separated product was filtered and crystallised from alcohol, m.p.233°. Yield 0.4 g.

Analysis : Found : C,75.50 ; H,7.86 ; N,11.05 %.

$C_{16}H_{20}ON_2$ requires : C,75.01 ; H,7.81 ; N,10.94 %.

8-Methyl-4-morpholinomethylcarbostyril :

8-Methyl-4-bromomethylcarbostyril (0.5 g.) was refluxed with alcohol (20 ml.) and morpholine (0.3 g.) for 2 hr. On cooling the separated product was filtered and crystallised from alcohol, m.p.241°. Yield 0.3 g.

Analysis : Found : C,69.52 ; H,6.90 ; N,11.13 %.

$C_{15}H_{18}O_2N_2$ requires : C,69.77 ; H,6.95 ; N,10.85 %.

8-Methyl-4-dimethylaminomethylcarbostyril :

8-Methyl-4-bromomethylcarbostyril (0.5 g.) was treated with dimethylamine (10 ml. ; 25 %) and refluxed on a water bath for 3 hr. The clear solution on cooling gave the dimethylaminomethyl derivative, which was filtered and crystallised from benzene, m.p.199°. Yield 0.3 g.

Analysis : Found : C,72.04 ; H,7.54 ; N,12.63 %.

$C_{13}H_{16}ON_2$ requires : C,72.21 ; H,7.40 ; N,12.96 %.

8-Methyl-4-anilinomethylcarbostyril :

8-Methyl-4-bromomethylcarbostyril (0.5 g.) was heated on a sand bath with aniline (1 ml.) for 2 hr. On dilution with petroleum ether the product which separated crystallised from alcohol, m.p.235°. Yield 0.2 g.

Analysis : Found : C,77.10 ; H,6.43 ; N,10.44 %.

$C_{17}H_{16}ON_2$ requires : C,77.20 ; H,6.06 ; N,10.60 %.

8-Methyl-4-(p-sulphanilamido)methylcarbostyril :

8-Methyl-4-bromomethylcarbostyril (1 g.) in alcohol (60 ml.) was refluxed with sulphanilamide on a steam bath for 5 hr. It was filtered hot and the product obtained on cooling crystallised from acetic acid, m.p. 264°. Yield 0.5 g.

Analysis : Found : C,59.37 ; H,4.81 ; N,12.03 %.

$C_{17}H_{17}O_3N_3S$ requires : C,59.47 ; H,4.95 ; N,12.25 %.

Mannich bases from 6-methoxy-4-bromomethylcarbostyril :

6-Methoxy-4-piperidinomethylcarbostyril :

6-Methoxy-4-bromomethylcarbostyril (0.5 g.) was treated with piperidine (0.3 g.) in alcohol (20 ml.). It was refluxed on a water bath for 2 hr. On cooling the separated product was filtered and crystallisdd from alcohol, m.p. 223°. Yield 0.3 g.

Analysis : Found : C,56.44 ; H,7.48 ; N,10.17 %.

$C_{16}H_{20}O_2N_2$ requires : C,56.14 ; H,7.36 ; N,10.30 %.

6-Methoxy-4-morpholinomethylcarbostyril :

6-Methoxy-4-bromomethylcarbostyril (0.5 g.) was refluxed with morpholine (0.3 g.) in alcohol (20 ml.) on a water bath for 2 hr. The separated product was filtered and crystallised from alcohol, m.p.208°. Yield 0.3 g.

Analysis : Found : C,65.55 ; H,6.86 ; N,10.21 %.

$C_{15}H_{18}O_3N_2$ requires : C,65.69 ; H,6.56 ; N,10.22 %.

6-Methoxy-4-dimethylaminomethylcarbostyril :

6-Methoxy-4-bromomethylcarbostyril (0.5 g.) in alcohol (20 ml.) was refluxed with dimethylamine (10 ml. ; 25 %) for 3 hr. The clear solution on cooling gave the product which was filtered and crystallised from benzene, m.p.183°. Yield 0.3 g.

Analysis : Found : C,66.96 ; H,6.88 ; N,12.33 %.

$C_{13}H_{16}O_2N_2$ requires : C,67.23 ; H,6.89 ; N,12.07 %.

Mannich bases from 6-chloro-4-bromomethylcarbostyril :

6-Chloro-4-piperidinomethylcarbostyril :

6-Chloro-4-bromomethylcarbostyril (0.5 g.) in alcohol (20 ml.) was refluxed with piperidine (0.3 g.) on a water bath for 3 hr. On cooling the product which separated crystallised from alcohol, m.p. 245°. Yield 0.3 g.

Analysis : Found : C,65.37 ; H,6.54 ; N,10.23 %.

$C_{15}H_{17}ON_2Br$ requires : C,65.10 ; H,6.14 ; N,10.13 %.

6-Chloro-4-morpholinomethylcarbostyril :

6-Chloro-4-bromomethylcarbostyril (0.5 g.) in alcohol (20 ml.) was refluxed with morpholine (0.3 ml.) on a water bath for 3 hr. On cooling the separated product was filtered and crystallised from alcohol, m.p. 242°. Yield 0.3 g.

Analysis : Found : C,60.18 ; H,5.26 ; N,9.96 %.

$C_{14}H_{15}O_2N_2Cl$ requires : C,60.33 ; H,5.37 ; N,10.06 %.

6-Chloro-4-dimethylaminomethylcarbostyril :

6-Chloro-4-bromomethylcarbostyril (0.5 g.) was refluxed with dimethylamine (10 ml. ; 25 %) and alcohol (10 ml.) on a water bath for 3 hr. On cooling the separated product was filtered and crystallised from benzene, m.p. 232°. Yield 0.3 g.

Analysis : Found : C,60.78 ; H,5.21 ; N,11.89 %.

$C_{12}H_{13}ON_2Cl$ requires : C,60.92 ; H,5.49 ; N,11.85 %.

6-Chloro-4-(4'-sulphanilamido)methylcarbostyril :

6-Chloro-4-bromomethylcarbostyril (1 g.), sulphanilamide (1 g.) and alcohol (60 ml.) were refluxed on a steam bath for 5 hr. On cooling the product which separated crystallised from acetic acid, m.p. 249°. Yield 0.5 g.

Analysis : Found : C,52.47 ; H,3.55 ; N,11.21 %.

$C_{16}H_{14}O_3N_3ClS$ requires : C,52.82 ; H,3.85 ; N,11.55 %.

Mannich bases from 7-chloro-4-bromomethylcarbostyril :

7-Chloro-4-piperidinomethylcarbostyril :

7-Chloro-4-bromomethylcarbostyril (0.5 g.), piperidine (0.3 g.) and alcohol (20 ml.) were refluxed on a water bath for 3 hr. On working up as usual the product crystallised from benzene, m.p. 239°. Yield 0.3 g.

Analysis : Found : C,64.99 ; H,5.83 ; N,10.33 %.

$C_{15}H_{17}ON_2Cl$ requires : C,65.10 ; H,6.14 ; N,10.13 %.

7-Chloro-4-morpholinomethylcarbostyril :

7-Chloro-4-bromomethylcarbostyril (0.5 g.), morpholine (0.3 g.) and alcohol (20 ml.) were refluxed on a water bath for 3 hr. On cooling the product which separated crystallised from alcohol, m.p. 234°. Yield 0.3 g.

Analysis : Found : C,60.35 ; H,5.09 ; N,10.48 %.

$C_{14}H_{15}O_2N_2Cl$ requires : C,60.33 ; H,5.37 ; N,10.06 %.

7-Chloro-4-dimethylaminomethylcarbostyril :

7-Chloro-4-bromomethylcarbostyril (0.5 g.) and dimethylamine (10 ml. ; 25 %) was refluxed on a water bath

for 3 hr. On working up as usual the product crystallised from benzene, m.p.183°. Yield 0.3 g.

Analysis : Found : C,60.89 ; H,5.36 ; N,11.73 %.
$C_{12}H_{13}ON_2Cl$ requires : C,60.92 ; H,5.49 ; N,11.85 %.

7-Chloro-4-(p-sulphanilamido)methylcarbostyril :

7-Chloro-4-bromomethylcarbostyril (1 g.), sulphanilamide (1 g.) and alcohol (60 ml.) were refluxed on a steam bath for 6 hr. On cooling the product which separated crystallised from acetic acid, m.p. 278°. Yield 0.5 g.

Analysis : Found : C,52.76 ; H,3.55 ; N,11.09 %.
$C_{16}H_{14}O_3N_3ClS$ requires : C,52.82 ; H,3.85 ; N,11.55 %.

Mannich bases from 6-bromo-4-bromomethylcarbostyril :

6-Bromo-4-piperidinomethylcarbostyril :

6-Bromo-4-bromomethylcarbostyril (0.5 g.) in alcohol (20 ml.) was refluxed with piperidine (0.3 g.) for 3 hr. On working up as usual the product crystallised from alcohol, m.p.242°. Yield 0.4 g.

Analysis : Found : C,55.65 ; H,5.11 ; N,8.41 %.
$C_{15}H_{17}ON_2Br$ requires : C,55.39 ; H,5.23 ; N,8.61 %.

6-Bromo-4-morpholinomethylcarbostyril :

6-Bromo-4-bromomethylcarbostyril (0.5 g.), morpholine (0.3 g.) and alcohol (20 ml.) were refluxed on a water bath for 3 hr. On cooling the product which separated crystallised from alcohol, m.p.230°. Yield 0.3 g.

Analysis : Found : C,51.88 ; H,4.58 ; N,8.38 %.
$C_{14}H_{15}O_2N_2Br$ requires : C,52.01 ; H,4.64 ; N,8.67 %.

6-Bromo-4-dimethylaminomethylcarbostyril :

6-Bromo-4-bromomethylcarbostyril (0.5 g.) was refluxed with dimethylamine (10 ml. ; 25 %). On cooling the product which separated crystallised from benzene, m.p. 230°. Yield 0.3 g.

Analysis : Found : C,51.36 ; H,4.50 ; N,10.22 %.

$C_{12}H_{13}ON_2Br$ requires : C,51.25 ; H,4.62 ; N, 9.96 %.

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CHAPTER III

Studies on 4-bromomethylcarbostyril derivatives

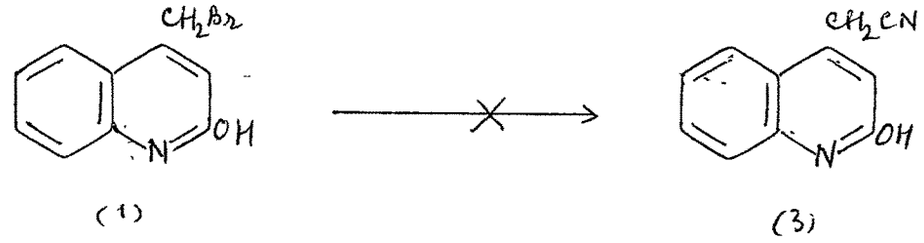
Section II

Syntheses of 1,2-bis(2-chloro-4-quinolyl)ethane derivatives :

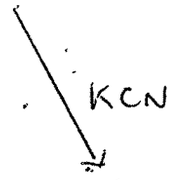
Theoretical

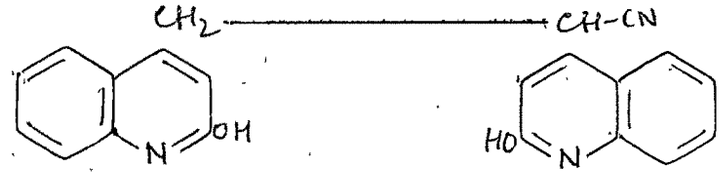
The present work was undertaken in continuation of the study of the reactivity of 4-bromomethylcarbostyril derivatives described in section I. 4-Bromomethylcarbostyril (1) when reacted with potassium cyanide, gave 1-cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane (2) instead of 4-cyanomethylcarbostyril (3) which can be converted into quinoline-4-acetic acid derivative after hydrolysis. This is a novel observation in this series. As the compounds in this series have very high melting points and are insoluble in most organic solvents, they are converted into their 2-chloro derivatives by treatment with phosphorus oxychloride. Thus 1-cyano-1,2-bis-(2-hydroxy-4-quinolyl)ethane (2) gave 1-cyano-1,2-bis-(2-chloro-4-quinolyl)ethane (4). The structure (4), was assigned on the basis of analytical data and was further confirmed by its IR and NMR spectra. It will be of interest to review here some of the methods used for the synthesis of chloroquinolines and their reactions.

The chloroquinolines have a characteristic mouse-like odour. Phosphorus oxychloride, phosphorus pentachloride or a mixture of the two are the reagents

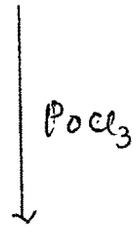

CH_2Br
OH
N
CH_2CN
OH
N

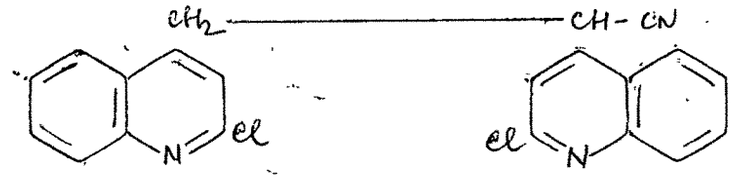
(1) (3)


KCN


CH_2
CH-CN
OH
N
HO
N

(2)

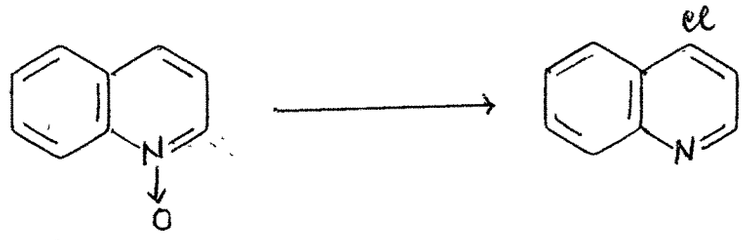

$POCl_3$


CH_2
CH - CN
Cl
N
Cl
N

(4)

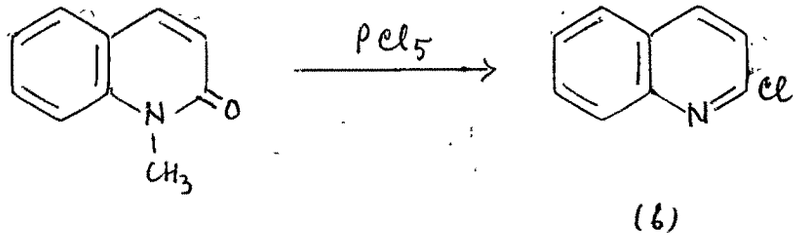
most useful for the conversion of the hydroxyquinolines to chloroquinolines.

Meisenheimer[1] prepared 4-chloroquinoline (5) from the reaction of quinoline-N-oxide with sulphuryl chloride or phosphorus oxychloride.



(5)

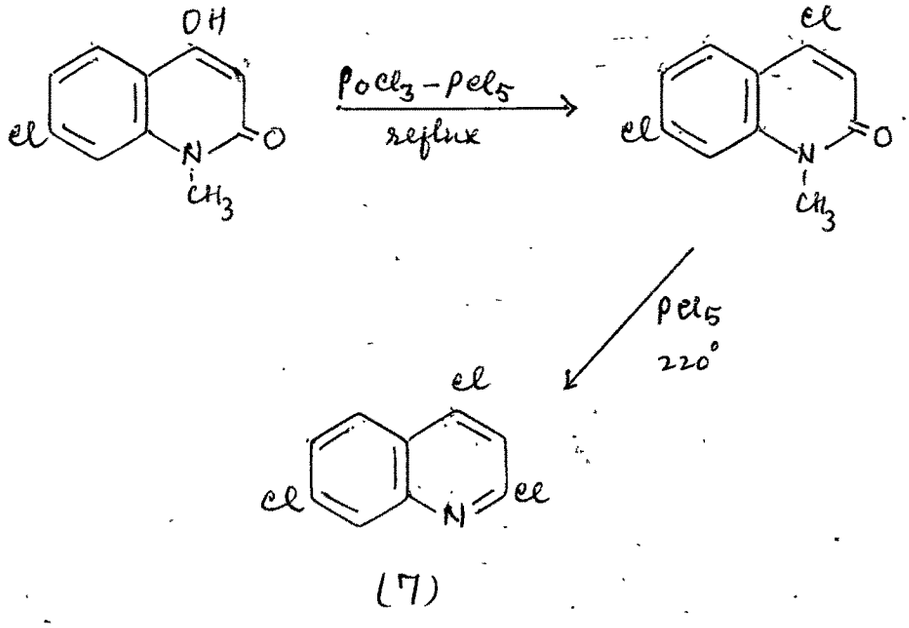
With substituted quinoline-N-oxides, phosphorus oxychloride is a more satisfactory reagent.[2,3,4] 1-Methyl-2-quinolone and its derivatives are converted into 2-chloroquinoline (6) and its derivatives when treated with phosphorus pentachloride.[5,6,7]



(6)

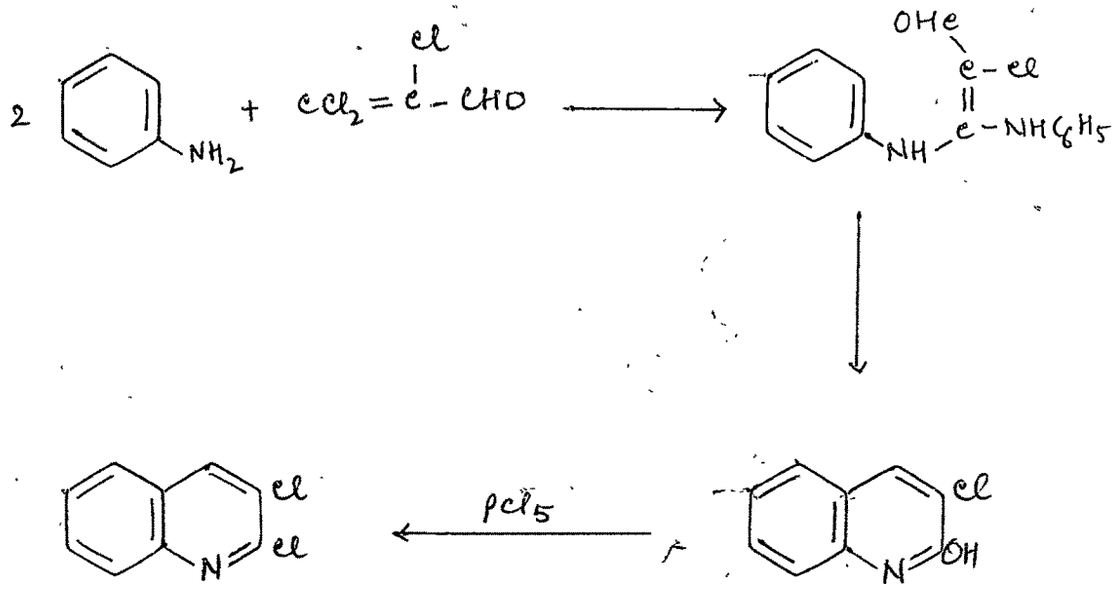
Lutz et al.[8] illustrated in the preparation of 2,4,7-trichloroquinoline(7) that the conversion of an N-methyl-2-quinolone to a 2-chloroquinoline takes place

with greater difficulty than simple replacement of a 2 or 4-hydroxyl group.



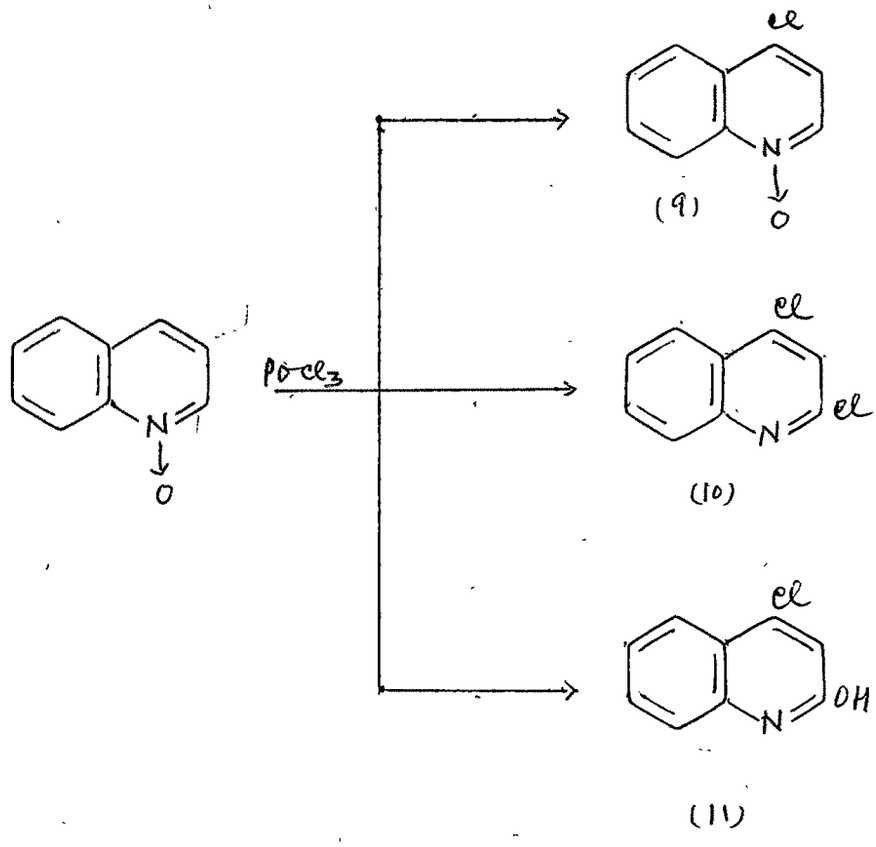
(7)

Roedig et al.[9] synthesised 2,3-dichloroquinoline (8) as follows :



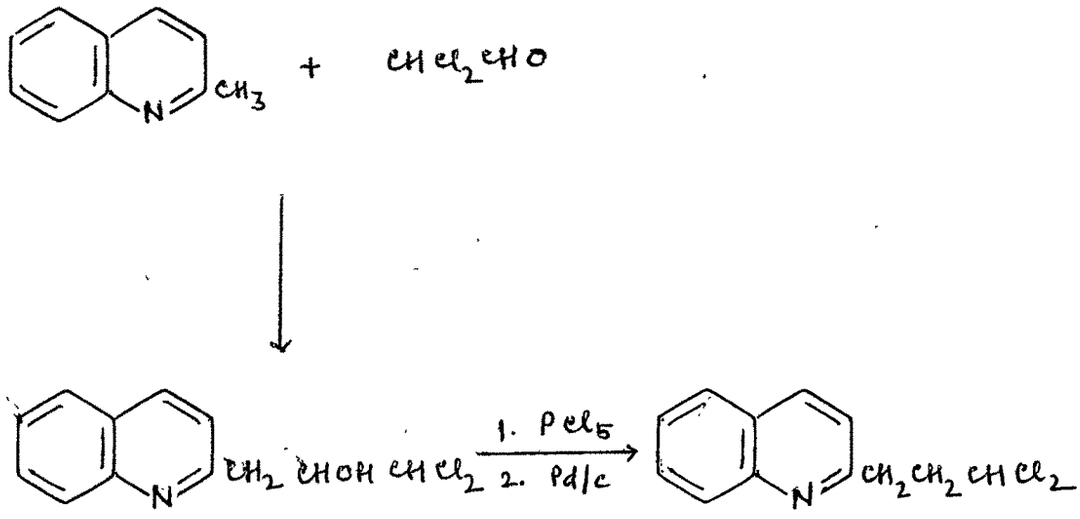
(8)

Takanobu[10] reacted 4-nitroquinoline-1-oxide with phosphorus oxychloride and obtained 4-chloroquinoline-1-oxide (9), 2,4-dichloroquinoline (10) and 4-chlorocarbostyril (11). But the reaction with sulphuryl chloride gave only the 2,4-dichloroquinoline (10). Hamana[11] studied the action of phosphorus trichloride on 4-nitroquinoline-1-oxide and obtained the mixture of products as reported by Takanobu.



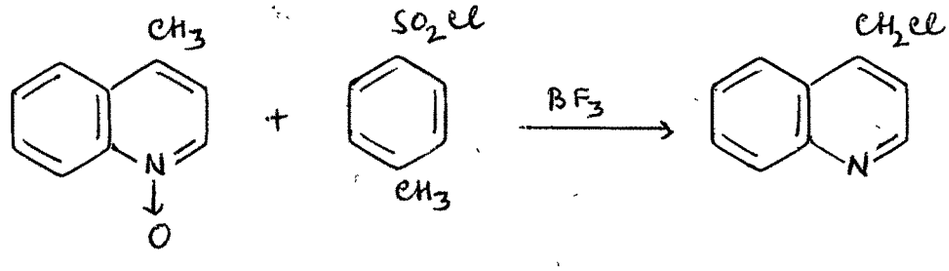
In a few instances, 4-haloquinolines have been prepared by application of the Sandmeyer reaction to 4-aminoquinolines[11]. Hammick[12] obtained a quantitative yield of α-trichloromethylquinoline from quinaldine by reacting with chlorine in the presence of sodium acetate.

Kondo and Matsuno[13] condensed dichloroacetaldehyde with quinaldine and obtained (12) from which 2-(γ,γ-dichloropropyl)quinoline (13) was prepared.



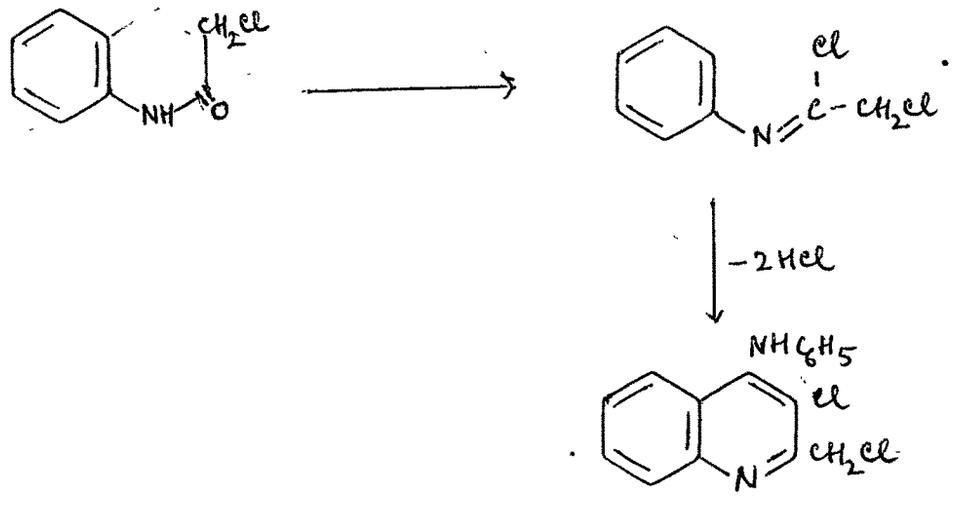
(12) (13)

Tanida[14,15] prepared 4-chloromethylquinoline(14) by refluxing lepidine-N-oxide with p-toluene sulphonyl chloride in the presence of boron trifluoride.



(14)

Braun and Heymons[16] prepared 2-chloromethyl-3-chloro-4-anilinoquinoline (15) by the reaction of phosphorus pentachloride on chloroacetanilide.



(15)

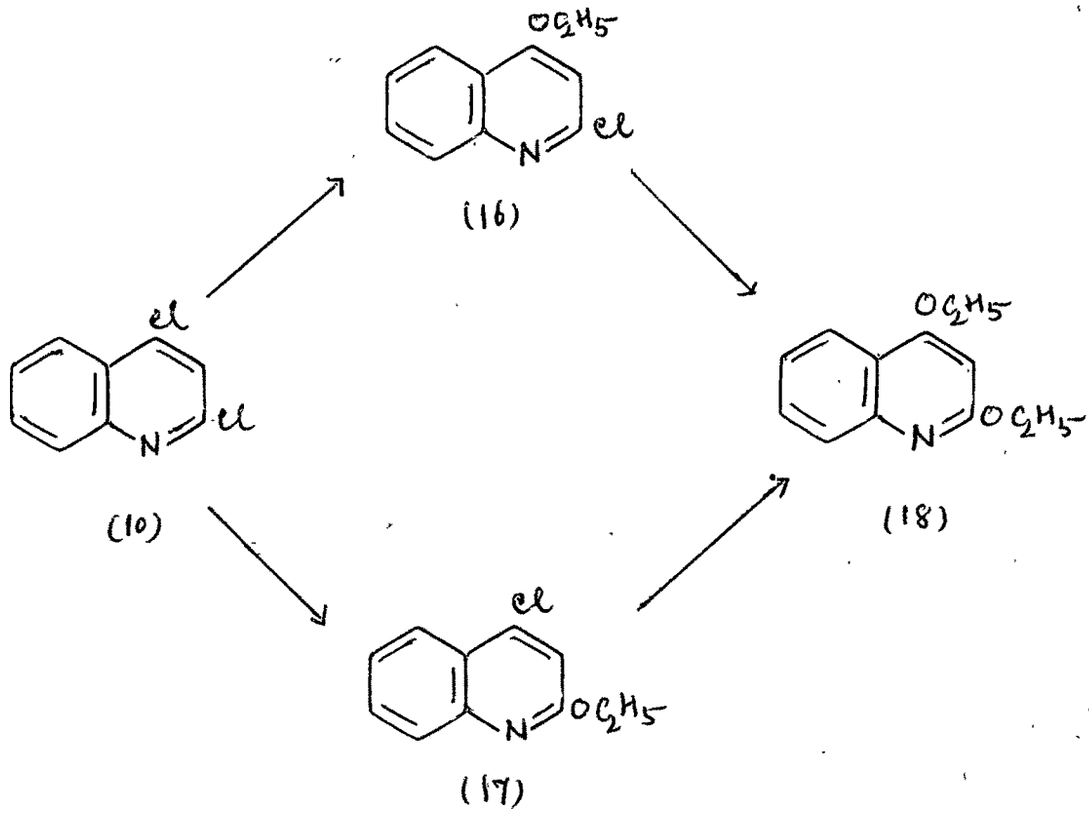
Reactions :

Halogen atoms in the 2 and 4 positions of quinoline are reactive to nucleophilic reagents because they are located on carbon atoms which have a low electron density. Many such displacements have been recorded. As illustrations, the conversion of 4-chloroquinolines to 4-alkylamino derivatives, conversion of 4-chloroquinolines to sulphonic acids by reaction with sodium bisulphite,[17] replacement of a 4-chloro group by p-sulphonamidoamino,[18] by methoxy[19] and replacement of 2-chloro substituents by a number of nucleophilic reagents[20] may be mentioned.

Jansen and Wibaut[21] obtained carbostyril by reacting 2-bromoquinoline with potassium cyanide or

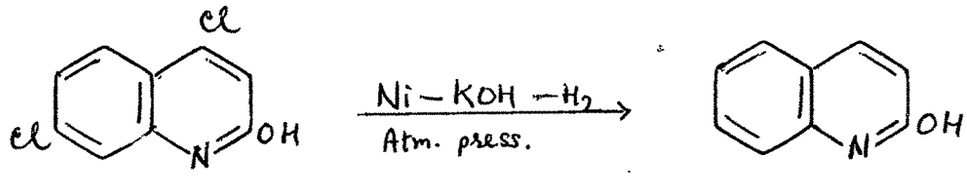
with a mixture of potassium cyanide and cuprous cyanide at 200°. Craig[22] prepared 2-cyanoquinoline by heating 2-bromoquinoline with cuprous cyanide.

Buchmann and Hamilton[23] found that when 2,4-dichloroquinoline (10) was treated with potassium ethoxide under specific conditions, 2-chloro-4-ethoxyquinoline (16) and 4-chloro-2-ethoxyquinoline (17) were obtained. The chlorine in (17) was found considerably less active than the chlorine in (16) during their conversion to 2,4-diethoxyquinoline (18).



Rowlett and Lutz[24] also found that 2-chlorine is more active than the 4-chlorine in certain quinoline derivatives. They also removed chlorine atom by ctalytic

reduction from 4,7-dichlorocarbostyril as follows.

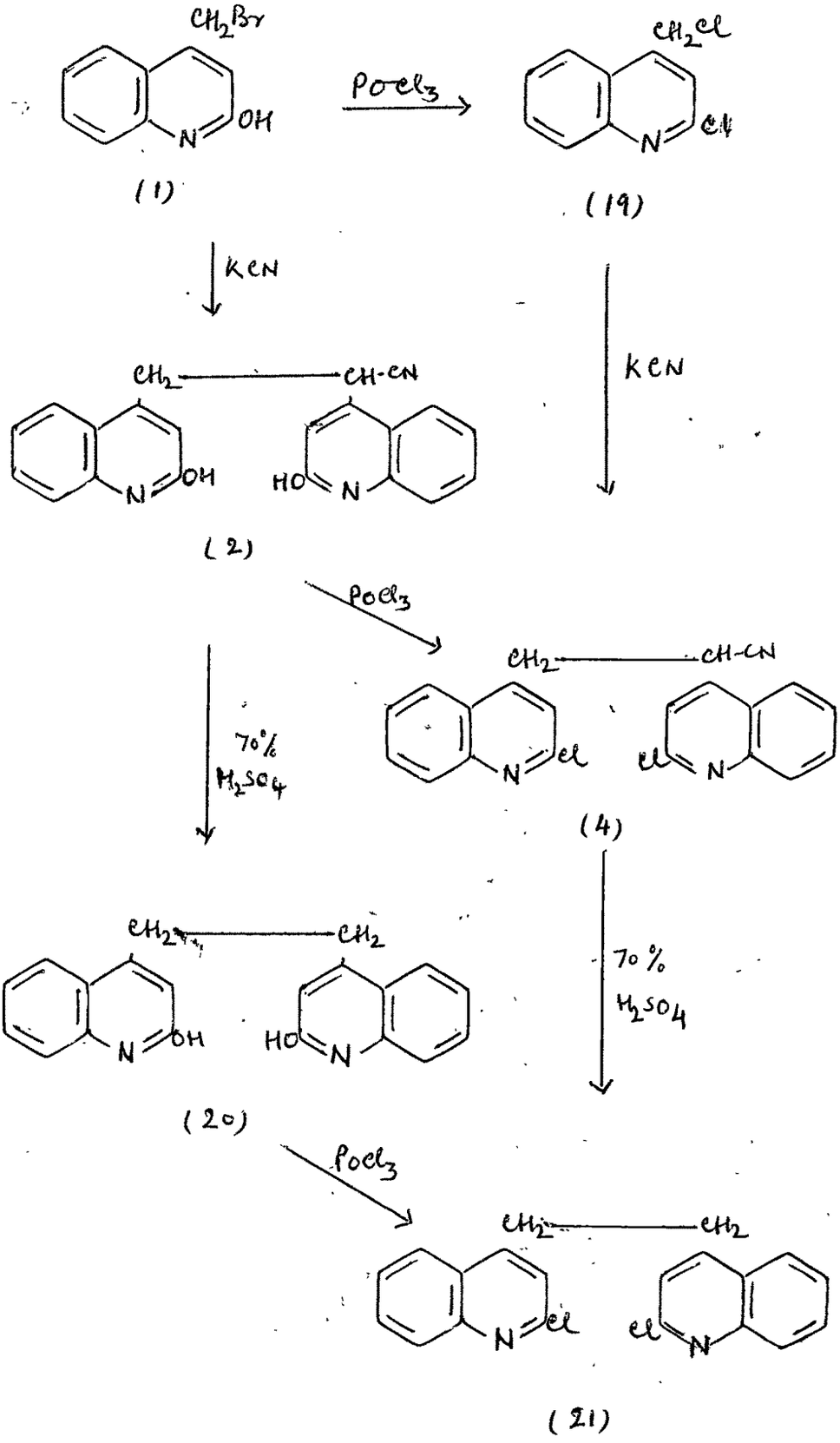


The reaction of 4-chloroquinoline with hydrazine is interesting, since in addition to normal hydrazide at elevated temperature an isomer distinct from 3,4-diaminoquinoline is obtained.[25,26]

The present work deals with the synthesis of 1,2-bis(2-chloro-4-quinolyl)ethane derivatives starting with 4-bromomethylcarbostyril derivatives.

1,2-Bis(2-chloro-4-quinolyl)ethane (21) :

4-Bromomethylcarbostyril (1) on treatment with potassium cyanide in alcoholic solution gave 1-cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane (2). This on treatment with phosphorus oxychloride gave 1-cyano-1,2-bis(2-chloro-4-quinolyl)ethane (4). This was also obtained by first treating 4-bromomethylcarbostyril with phosphorus oxychloride to give 4-chloromethyl-2-chloroquinoline (19) followed by treatment with potassium cyanide. 1-Cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane (2) on hydrolysis with 70 % sulphuric acid gave 1,2-bis(2-hydroxy-4-quinolyl) ethane (20) which was converted into corresponding


CH2Br
OH
N
POCl3
CH2Cl
Cl
(1)
(19)
KCN
KCN
CH2
CH-CN
OH
HO
N
(2)
POCl3
70%
H2SO4
Cl
(4)
70%
H2SO4
(20)
POCl3
(21)

2-chloro derivative (21) by treatment with phosphorus oxychloride. This was also obtained when 1-cyano-1,2-bis(2-chloro-4-quinolyl)ethane (4) was subjected to action of 70 % sulphuric acid.

IR Spectra of 1-cyano-1,2-bis(2-chloro-4-quinolyl)ethane (4) showed a characteristic nitrile band at 2240 cm^{-1}. The structure (4) was further confirmed by NMR Spectra.

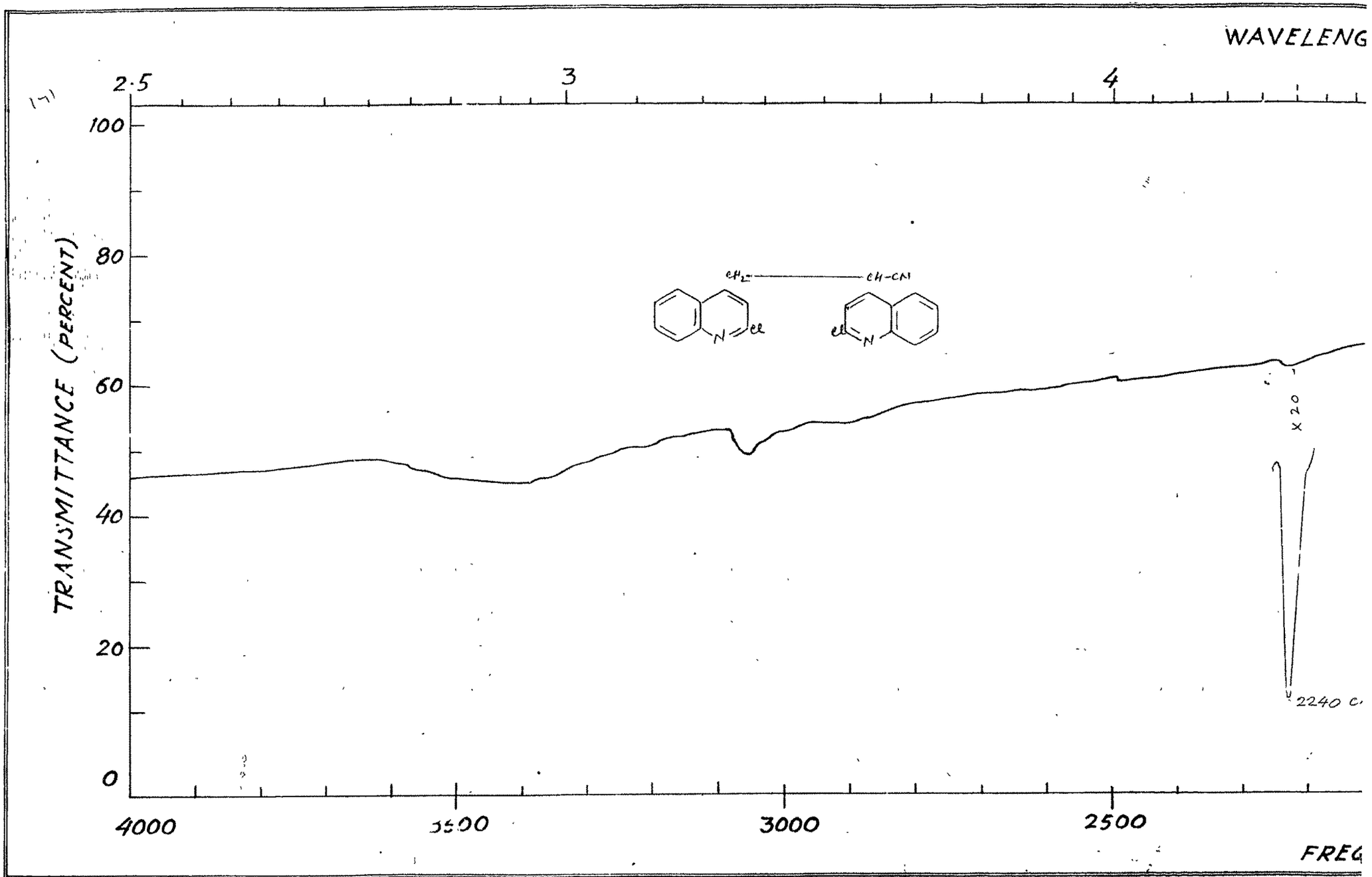
NMR Spectrum of 1-cyano-1,2-bis(2-chloro-4-quinolyl) ethane (4) :

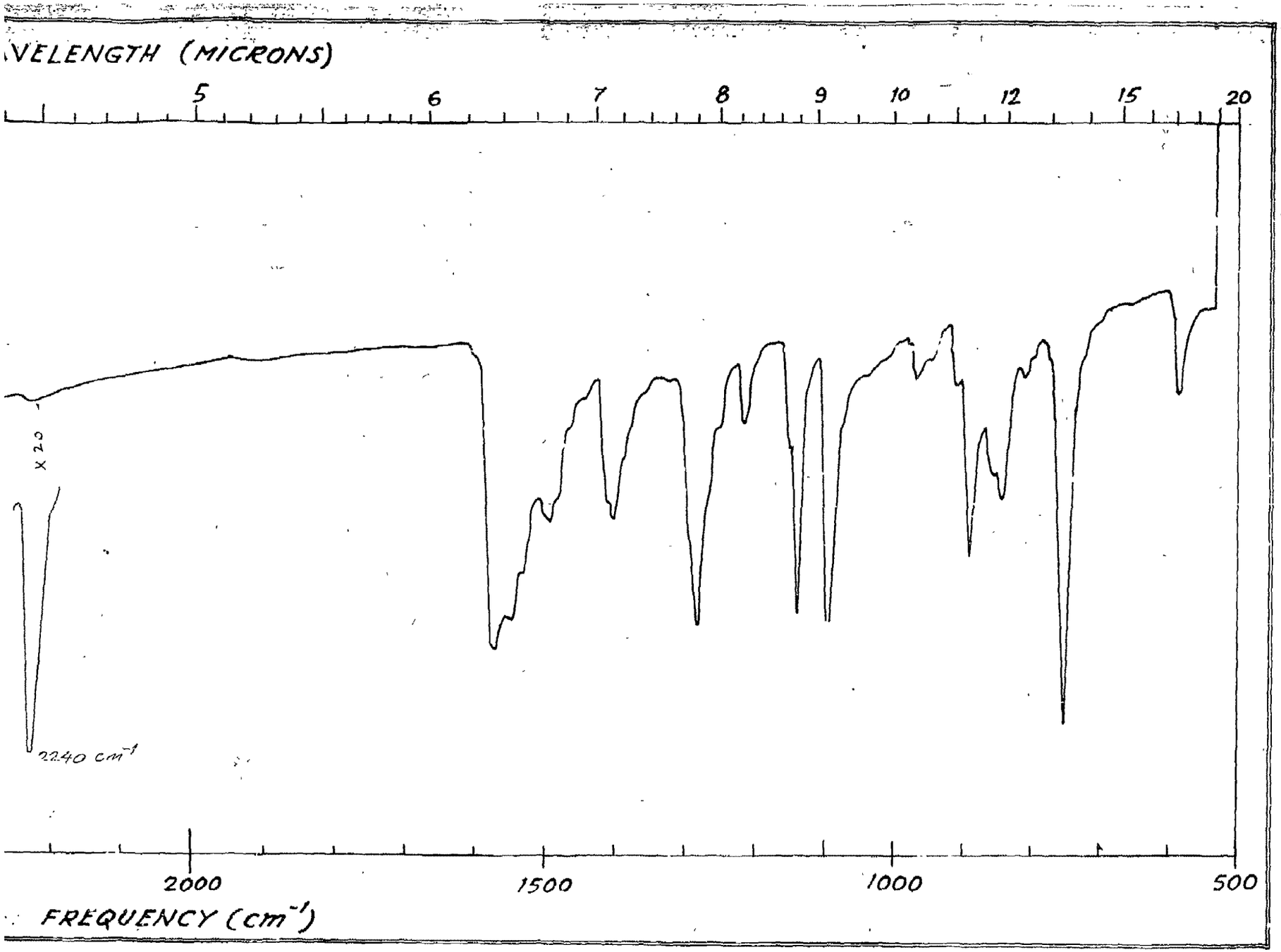
The spectrum was recorded in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The assignments of the various signals and the chemical shifts are as follows.

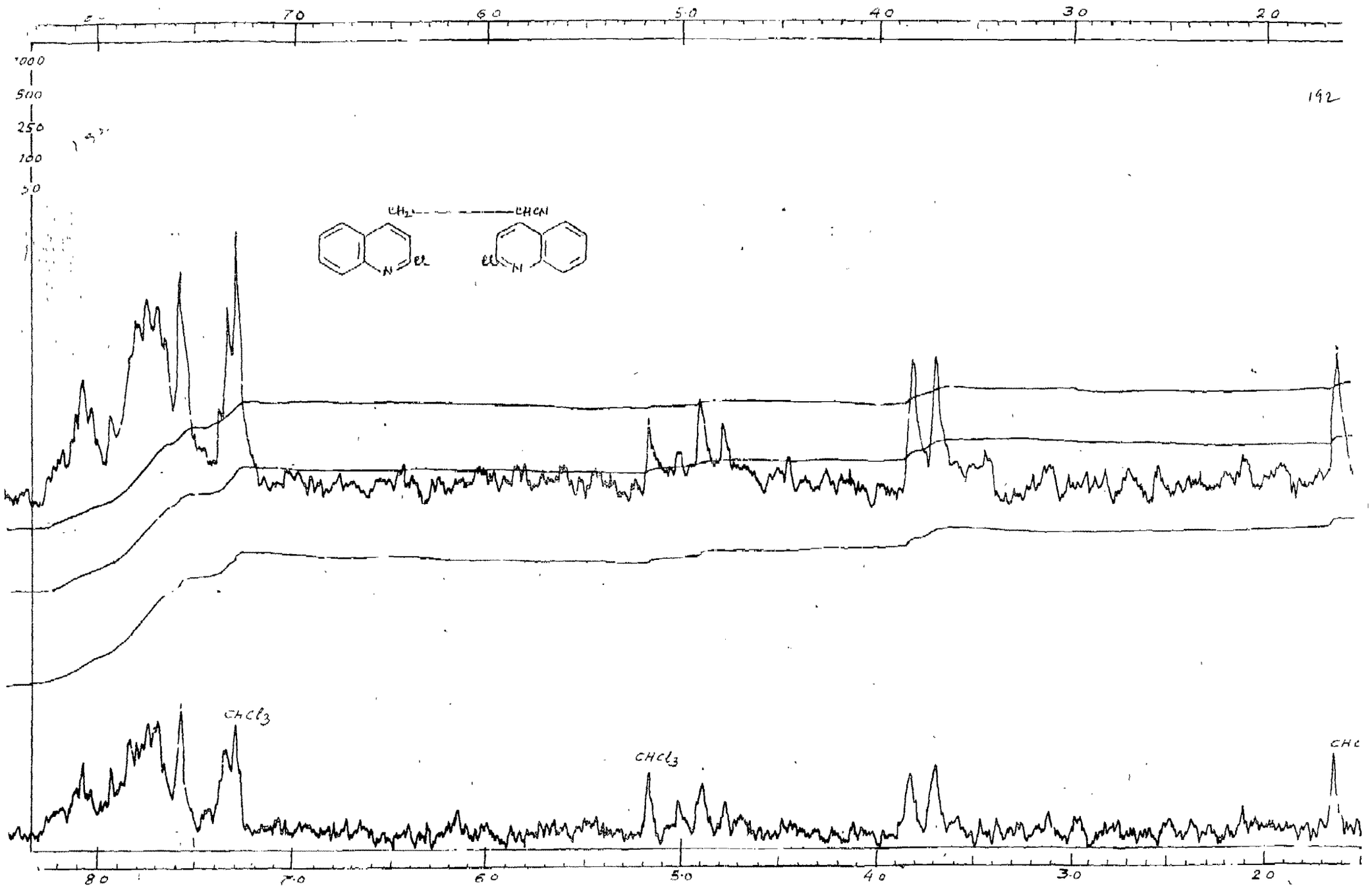
Shift (δ)	Coupling constant J (C/Sec)	Signals	Assignment
7.5 to 8.5	-	Multiplet	10 H (aromatic)
5.1	8	Triplet	1 H
4.2	8	Doublet	2 H

The formation of 1-cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane can be explained as follows.

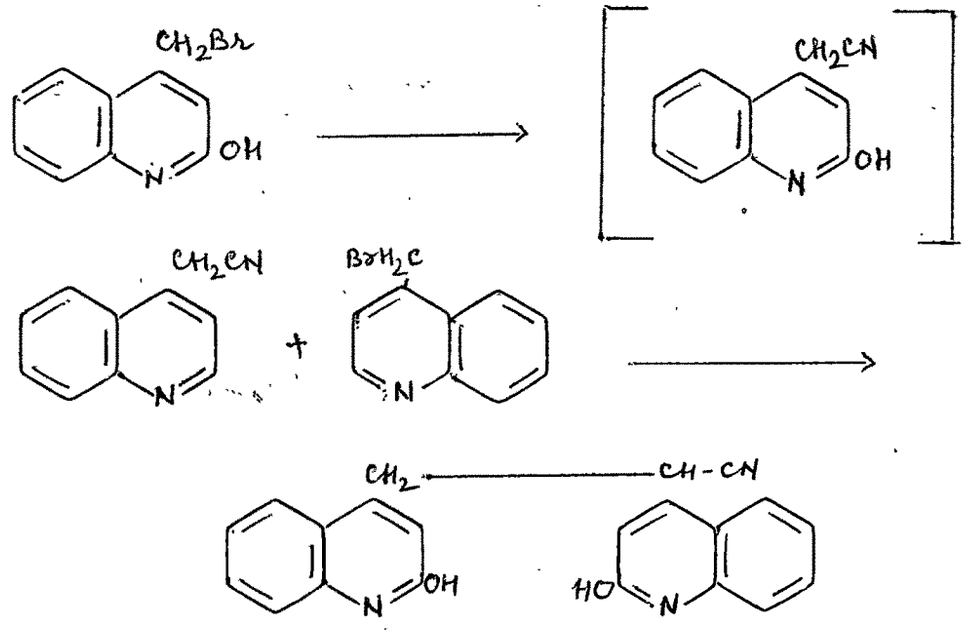
The first step in the reaction between


WAVELENG
2·5
3
4
100
80
60
40
20
0
TRANSMITTANCE (PERCENT)
CH2
CH-CN
N
N
X 20
2240 c
4000
3500
3000
2500
FREQ


VELENGTH (MICRONS)
5
6
7
8
9
10
12
15
20
X 20
2240 cm⁻¹
2000
1500
1000
500
FREQUENCY (cm⁻¹)


192
CH₂
CHCN
CHCl₃
CHCl₃
CHC
8.0
7.0
6.0
5.0
4.0
3.0
2.0

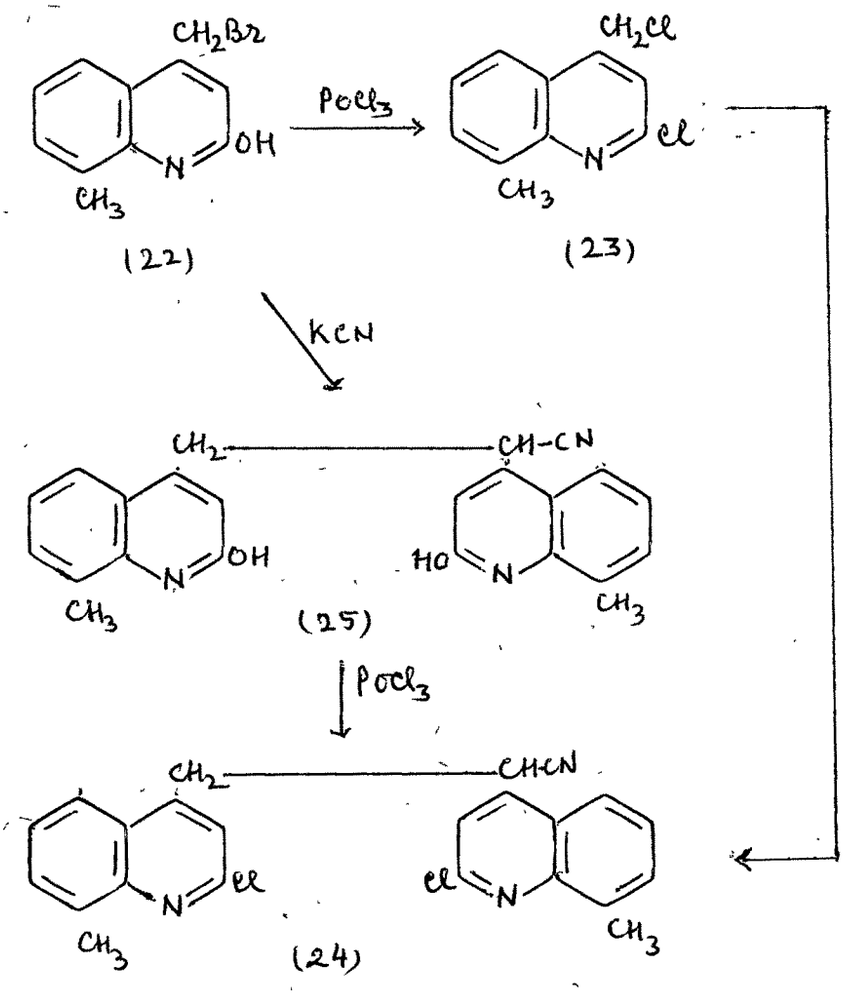
4-bromomethylcarbostyril and potassium cyanide may be the formation of 4-cyanomethylcarbostyril. As this compound possesses the reactive methylene group, it reacts further with second mole of 4-bromomethylcarbostyril to form 1-cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane.

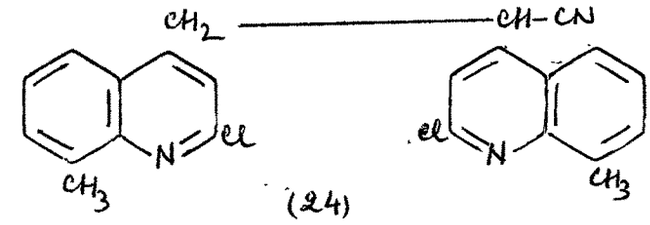


Using these procedures, the following 2-chloro-4-chloromethylquinoline derivatives, 1-cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane derivatives, 1-cyano-1,2-bis(2-chloro-4-quinolyl)ethane derivatives, 1,2-bis(2-chloro-4-quinolyl)ethane derivatives have been prepared from (1)8-methyl-4-bromomethylcarbostyril, (2)6-chloro-4-bromomethylcarbostyril and (3)6-bromo-4-bromomethylcarbostyril.

1,2-Bis(8-methyl-2-chloro-4-quinolyl)ethane (26):

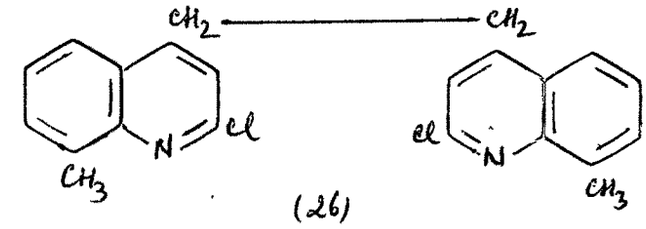
8-Methyl-4-bromomethylcarbostyril (22) on treatment with phosphorus oxychloride gave 8-methyl-2-chloro-4-chloromethylquinoline (23) which with potassium cyanide in alcohol afforded 1-cyano-1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane (24). This was also prepared from 8-methyl-4-bromomethylcarbostyril by first reacting it with potassium cyanide to give 1-cyano-1,2-bis(8-methyl-2-hydroxy-4-quinolyl)ethane (25) followed by treatment with phosphorus oxychloride. 1-Cyano-1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane (24) on hydrolysis with





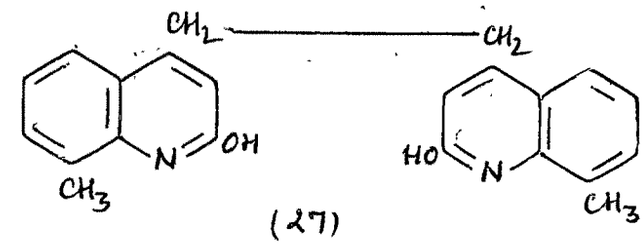
(24)

70 %
H_2SO_4



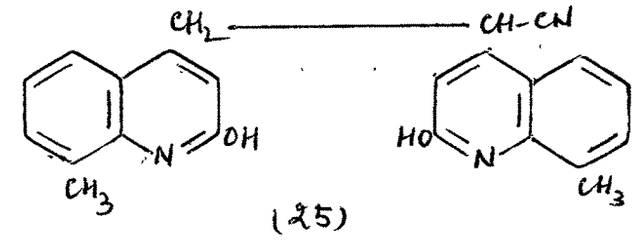
(26)

$POCl_3$



(27)

70 %
H_2SO_4

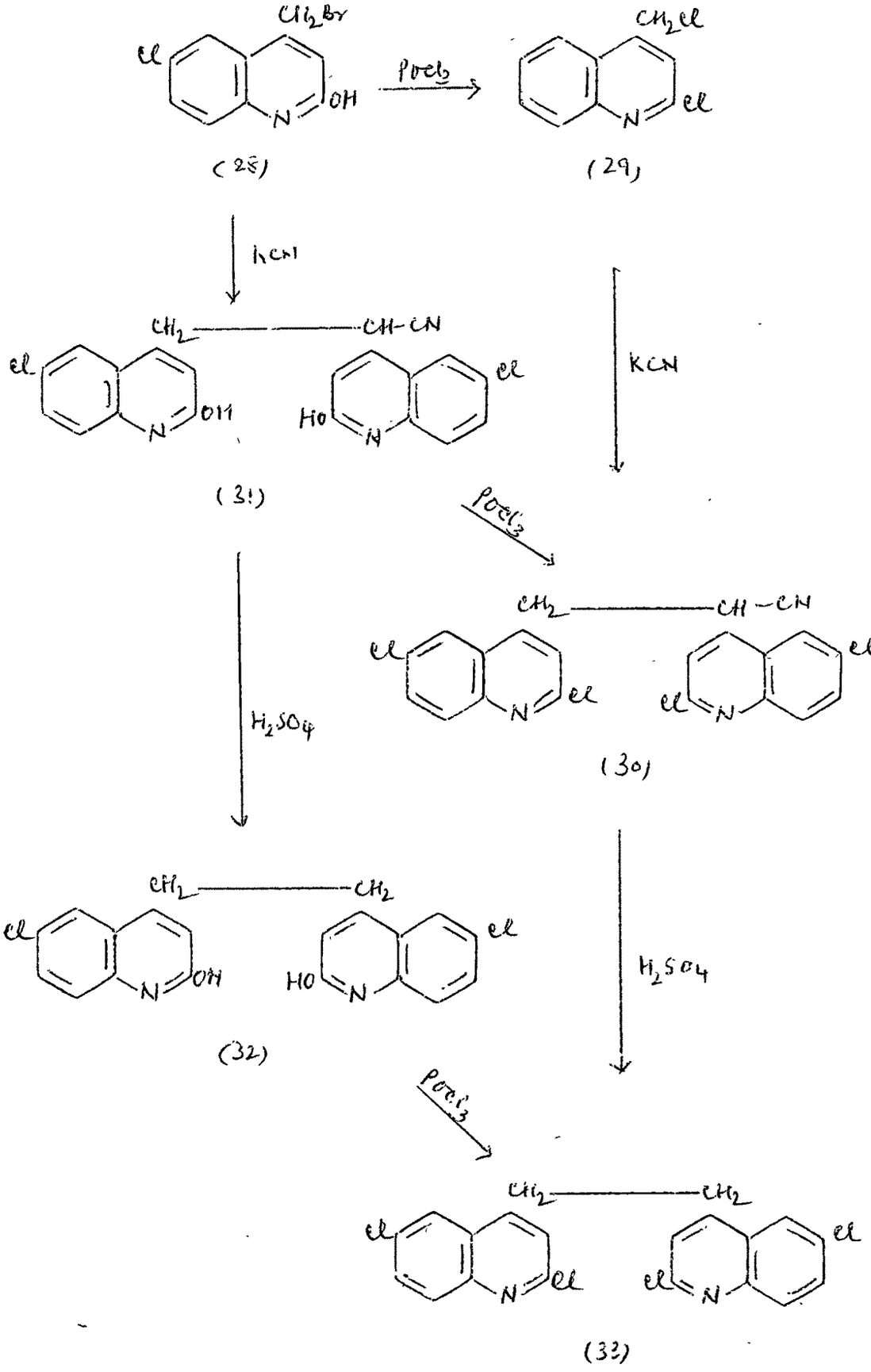


(25)

70 % sulphuric acid gave 1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane (26). Again this compound (26) was also obtained from 1-cyano-1,2-bis(8-methyl-2-hydroxy-4-quinolyl)ethane (25) by first hydrolysing it with 70 % sulphuric acid to give 1,2-bis(8-methyl-2-hydroxy-4-quinolyl)ethane (27) followed by treatment with phosphorus oxychloride.

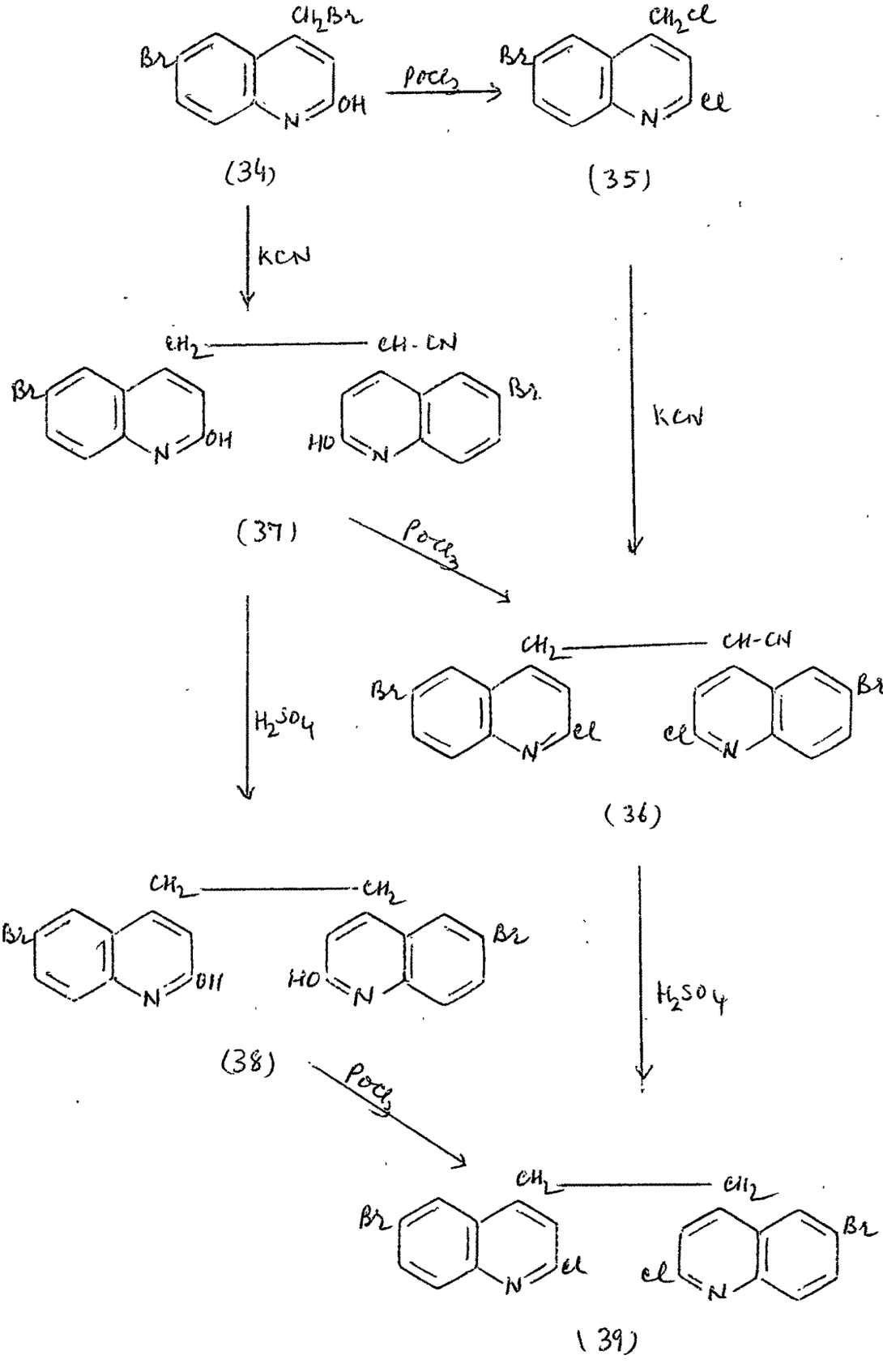
1,2-Bis(2,6-dichloro-4-quinolyl)ethane (33) :

6-Chloro-4-bromomethylcarbostyril (28) with phosphorus oxychloride gave 2,6-dichloro-4-chloromethyl-quinoline (29). This chloromethyl derivative with alcoholic potassium cyanide afforded 1-cyano-1,2-bis-(2,6-dichloro-4-quinolyl)ethane (30). This was also obtained by reacting 6-chloro-4-bromomethylcarbostyril (28) first with alcoholic potassium cyanide solution to give 1-cyano-1,2-bis(6-chloro-2-hydroxy-4-quinolyl) ethane (31) followed by treatment with phosphorus oxychloride. 1-Cyano-1,2-bis(6-chloro-2-hydroxy-4-quinolyl) ethane (31) on hydrolysis with 70 % sulphuric acid gave 1,2-bis(6-chloro-2-hydroxy-4-quinolyl)ethane (32) which with phosphorus oxychloride yielded 1,2-bis(2,6-dichloro-4-quinolyl)ethane (33). This was also obtained when 1-cyano-1,2-bis(2,6-dichloro-4-quinolyl)ethane (30) was subjected to the action of 70 % sulphuric acid.


CH2Br
Cl
OH
N
POCl3
CH2Cl
Cl
N
Cl
(28)
(29)
KCN
CH2
CH-CN
Cl
OH
N
HO
N
Cl
(31)
KCN
POCl3
CH2
CH-CN
Cl
Cl
N
Cl
Cl
N
Cl
(30)
H2SO4
CH2
CH2
Cl
OH
N
HO
N
Cl
(32)
H2SO4
POCl3
CH2
CH2
Cl
Cl
N
Cl
Cl
N
Cl
(33)

1,2-Bis(6-bromo-2-chloro-4-quinolyl)ethane (39) :

6-Bromo-4-bromomethylcarbostyril (34) on treatment with phosphorus oxychloride gave 6-bromo-2-chloro-4-chloromethylquinoline (35). This on treatment with alcoholic potassium cyanide solution gave 1-cyano-1,2-bis(6-bromo-2-chloro-4-quinolyl)ethane (36). This was also obtained by first treating 4-bromomethyl derivative (34) with potassium cyanide to give 1-cyano-1,2-bis(6-bromo-2-hydroxy-4-quinolyl)ethane (37) followed by treatment with phosphorus oxychloride. Again 1-cyano-1,2-bis(6-bromo-2-hydroxy-4-quinolyl)ethane (37) on hydrolysis with 70 % sulphuric acid gave 1,2-bis(6-bromo-2-hydroxy-4-quinolyl) ethane (38) which was converted into 1,2-bis(6-bromo-2-chloro-4-quinolyl)ethane (39) by treatment with phosphorus oxychloride. This was also obtained directly when 1-cyano-1,2-bis(6-bromo-2-chloro-4-quinolyl)ethane (36) was subjected to the action of 70 % sulphuric acid.


CH_2Br
Br
OH
N
$POCl_3$
CH_2Cl
Cl
(34)
(35)
KCN
CH_2
CH-CN
HO
(37)
H_2SO_4
(36)
(38)
(39)

EXPERIMENTAL

1,2-Bis(2-chloro-4-quinolyl)ethane

2-Chloro-4-chloromethylquinoline :

4-Bromomethylcarbostyril (5 g.) was treated with phosphorus oxychloride (15 ml.) and heated in an oil bath at 110-20° for 2 hr. It was poured over ice water with stirring and the solution was neutralised with sodium hydroxide solution. The separated product was filtered and crystallised from benzene-petroleum ether mixture (1:1) (charcoal), m.p. 99°. Yield 3 g.

Analysis	:Found	: N,6.53 ; Cl,33.10 %.
$C_{10}H_7NCl_2$	requires	: N,6.60 ; Cl,33.49 %.

1-Cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane :

4-Bromomethyl carbostyril (3 g.) in alcohol (100 ml.) was treated with potassium cyanide (1.5 g. in 5 ml. water) on a steam bath for 3 hr. On cooling the separated product was filtered and crystallised from glacial acetic acid, m.p.> 350°. Yield 1.5 g.

Analysis	: Found	: C,73.67 ; H,4.22 ; N,12.31 %.
$C_{21}H_{15}N_3O_2$	requires	: C,73.83 ; H,4.39 ; N,12.33 %.

(Analysised after heating in vacuumm at 110° for 4 hr.)

1-Cyano-1,2-bis(2-chloro-4-quinolyl)ethane :

The above hydroxy derivative (2 g.) was treated with phosphorus oxychloride (8 ml.) and heated in an oil bath at 110-20° for 4 hr. It was poured over ice water

and the solution made alkaline with sodium hydroxide. The separated product was filtered and crystallised from benzene-petroleum ether mixture (1:1), m.p.211°. Yield 1 g.

Analysis : Found : C,67.00 ; H,3.23 ; N,11.08 ; Cl,18.42%.
$C_{21}H_{13}N_3Cl_2$ requires : C,66.66 ; H,3.44 ; N,11.11 ; Cl,18.78%.

The same product was obtained when 2-chloro-4-chloromethylquinoline was treated with potassium cyanide as follows :

2-Chloro-4-chloromethylquinoline (3 g.) in alcohol (30 ml.) was treated with potassium cyanide (1.5 g. in 5 ml. water) and refluxed on a steam bath for 3 hr. On cooling the product which separated crystallised from benzene-petroleum ether mixture (1:1), m.p.211°. Yield 1.5 g. Mixed m.p. with the product described above was not depressed.

1,2-Bis(2-chloro-4-quinolyl)ethane :

1-Cyano-1,2-bis(2-chloro-4-quinolyl)ethane (1 g.) was treated with sulphuric acid (10 ml. ; 70 %) and heated on a sand bath for 6 hr. On pouring the reaction mixture over ice water the product which separated crystallised from xylene (charcoal), m.p.219°. Yield 0.4 g.

Analysis : Found : C,67.63 ; H,3.62 ; N,8.05 %.
$C_{20}H_{14}N_2Cl_2$ requires : C,67.98 ; H,3.96 ; N,7.93 %.

The above compound was also prepared as follows:

1-Cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane (1 g.) was treated with sulphuric acid (10 ml. ; 70 %) for 5 hr.

on a sand bath. The product obtained on dilution of the reaction mixture could not be crystallised in a pure form. This product was reacted further.

The above hydroxy derivative (0.5 g.) was treated with phosphorus oxychloride (3 ml.) and heated in an oil bath at 120° for 4 hr. On pouring over ice water the separated product was filtered and crystallised from alcohol, m.p. 219°. Yield 0.2 g. Mixed m.p. with 1,2-bis (2-chloro-4-quinolyl)ethane described above was not depressed.

1,2-Bis(8-methyl-2-chloro-4-quinolyl)ethane

8-Methyl-2-chloro-4-chloromethylquinoline :

8-Methyl-4-bromomethylcarbostyril (5 g.) was treated with phosphorus oxychloride (15 ml.) in an oil bath at 120° for 2 hr. On working up as before the product crystallised from petroleum ether, m.p. 80°. Yield 3 g.

Analysis : Found : N, 5.95 ; Cl, 31.78 %.

$C_{11}H_9NCl_2$ requires : N, 6.19 ; Cl, 31.42 %.

1-Cyano-1,2-bis(8-methyl-2-hydroxy-4-quinolyl)ethane :

8-Methyl-4-bromomethylcarbostyril (3 g.) in alcohol (100 ml.) was refluxed with potassium cyanide (1.5 g. ; 5 ml. water) for 4 hr. On cooling the product which separated crystallised from glacial acetic acid, m.p. 305°. Yield 1.5 g.

Analysis : Found : C, 74.68 ; H, 4.91 ; N, 11.28 %.

$C_{23}H_{19}O_2N_3$ requires : C, 74.79 ; H, 5.15 ; N, 11.38 %.

1-Cyano-1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane :

1-Cyano-1,2-bis(8-methyl-2-hydroxy-4-quinolyl) ethane (3 g.) described above was treated with phosphorus oxychloride (12 ml.) and heated in an oil bath at 110-20° for 3 hr. On working up as before the separated product was filtered and crystallised from benzene, m.p. 178°. Yield 1 g.

Analysis : Found : C,68.42; H,4.17; N,10.29; Cl,17.27 %.
$C_{23}H_{17}N_3Cl_2$ requires : C,67.98; H,4.18; N,10.34; Cl,17.48%.

The same product was obtained when 8-methyl-2-chloro-4-chloromethylquinoline (2 g.) was refluxed with potassium cyanide (1 g. in 5 ml. water) in alcohol (20 ml.) on a steam bath for 3 hr. M.P. and mixed m.p. with 1-cyano-1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane (described above) was not depressed.

1,2-Bis(8-methyl-2-hydroxy-4-quinolyl)ethane :

1-Cyano-1,2-bis(8-methyl-2-hydroxy-4-quinolyl) ethane (1 g.) was refluxed with sulphuric acid (10 ml. ; 70 %) on a sand bath for 5 hr. On dilution of the reaction mixture the product which separated crystallised from glacial acetic acid, m.p. > 350°.

Analysis : Found : C,76.56 ; H,5.78 ; N,8.24 %.
$C_{22}H_{20}O_2N_2$ requires : C,76.73 ; H,5.81 ; N,8.14 %.

1,2-Bis(8-methyl-2-chloro-4-quinolyl)ethane :

The above hydroxy derivative (0.5 g.) was heated in an oil bath at 120° (with PCl5) for 3 hr. On working up as usual the

product crystallised from benzene, m.p.225°. Yield 0.2 g.

Analysis : Found : C,69.23 ; H,4.33 ; N,7.49 %.

$C_{22}H_{18}N_2Cl_2$ requires : C,69.30 ; H,4.72 ; N,7.35 %.

The above compound was also prepared as follows :

1-Cyano-1,2-bis(8-methyl-2-chloro-4-quinolyl) ethane (1 g.) was heated on a sand bath with sulphuric acid (10 ml. ; 70 %) for 5 hr. The reaction mixture was poured in water. The product which separated crystallised from benzene, m.p.225°. Yield 0.4 g. Mixed m.p. with 1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane described above was not depressed.

1,2-Bis(2,6-dichloro-4-quinolyl)ethane :

2,6-Dichloro-4-chloromethylquinoline :

6-Chloro-4-bromomethylcarbostyril (5 g.) was heated in an oil bath at 110-20° for 3 hr. with phosphorus oxychloride (15 ml.). On working up as usual the product crystallised from benzene-petroleum ether mixture (1:1) in needles, m.p.116°. Yield 3 g.

Analysis : Found : N,5.45 ; Cl,42.74 %.

$C_{10}H_6NCl_3$ requires : N,5.68 ; Cl,43.20 %.

1-Cyano-1,2-bis(6-chloro-2-hydroxy-4-quinolyl)ethane :

6-Chloro-4-bromomethylcarbostyril (3 g.) in alcohol (80 ml.) was treated with potassium cyanide (1.5 g. in 5 ml. water). The reaction mixture was refluxed on a steam bath for 3 hr. The product which separated on cooling crystallised from glacial acetic acid, m.p.> 350°. Yield 1.5 g.

The analysis was carried out after heating in vacuum at 110° for 4 hr.

Analysis : Found : C,61.29 ; H,2.82 ; N,10.57 %.

$C_{21}H_{13}O_2N_3Cl_2$ requires : C,61.45 ; H,3.17 ; N,10.24 %.

1-Cyano-1,2-bis(2,6-dichloro-4-quinolyl)ethane :

The above hydroxy derivative (2 g.) was treated with phosphorus oxychloride (8 ml.) and heated in an oil bath at 110-20° for 3 hr. On working up as usual the product crystallised from benzene, m.p.274°. Yield 1 g.

Analysis : Found : C,56.08 ; H,2.63 ; N,9.47 %.

$C_{21}H_{11}N_3Cl_4$ requires : C,56.38 ; H,2.46 ; N,9.39 %.

The same compound was also prepared when 2,6-dichloro-4-chloromethylquinoline (2 g.) was refluxed with potassium cyanide (1 g. in 5 ml. water) in alcohol (20 ml.) on a steam bath for 3 hr. M.P. and mixed m.p. with 1-cyano-1,2-bis(2,6-dichloro-4-quinolyl)ethane described above was 274°.

1,2-Bis(2,6-dichloro-4-quinolyl)ethane :

The above cyano derivative (1 g.) was treated with sulphuric acid (20 ml.;70 %) and refluxed on a sand bath for 6 hr. On working up as before the product crystallised from xylene, m.p.302°. Yield 0.5 g.

Analysis : Found : C,56.47 ; H,2.76 ; N,6.42 %.

$C_{20}H_{12}N_2Cl_4$ requires : C,56.87 ; H,2.84 ; N,6.63 %.

The above compound was also prepared as follows :

1-Cyano-1,2-bis(2-hydroxy-6-chloro-4-quinolyl) ethane (1 g.) was refluxed with sulphuric acid (20 ml. ; 70 %) on a sand bath for 5 hr. On working up as usual the product could not be crystallised in a pure form. The crude product (0.5 g.) was treated with phosphorus oxychloride (3 ml.) and heated in an oil bath at 120° for 4 hr. On working up as usual the product crystallised from xylene, m.p.302°. Yield 0.2 g. Mixed m.p. with the compound prepared above was not depressed.

1,2-Bis(6-bromo-2-chloro-4-quinolyl)ethane :

6-Bromo-2-chloro-4-chloromethylquinoline :

6-Bromo-4-bromomethylcarbostyril (5 g.) was heated in an oil bath at 110-20° with phosphorus oxychloride (15 ml.) for 3 hr. On working up as before the product crystallised from benzene-petroleum ether mixture (1:1) m.p.124-5°. Yield 3 g.

Analysis : Found : C,40.91 ; H,2.06 ; N,4.71 %.
$C_{10}H_6NCl_2Br$ required : C,41.24 ; H,2.06 ; N,4.82 %.

1-Cyano-1,2-bis(6-bromo-2-hydroxy-4-quinolyl)ethane :

6-Bromo-4-bromomethylcarbostyril (3 g.) in alcohol (100 ml.) was treated with potassium cyanide (1.5 g. in 5 ml. water) and refluxed for 3 hr. On cooling the product which separated crystallised from dimethylformamide,

m.p. > 350°. Yield 1.5 g.

Analysis : Found : C,50.23 ; H,2.45 ; N,8.71 %.

$C_{21}H_{13}O_2N_3Br_2$ requires : C,50.50 ; H,2.60 ; N,8.41 %.

1-Cyano-1,2-bis(6-bromo-2-chloro-4-quinolyl)ethane :

1-Cyano-1,2-bis(6-bromo-2-hydroxy-4-quinolyl) ethane (1 g.) was treated with phosphorus oxychloride (4 ml.) and heated in an oil bath at 110-20° for 4 hr. On working up as usual the product crystallised from benzene, m.p. 271-2°. Yield 0.4 g.

Analysis : Found : C,47.21 ; H,2.10 ; N,8.14 %.

$C_{21}H_{11}N_3Cl_2Br_2$ requires : C,47.01 ; H,2.05 ; N,7.83 %.

This was also obtained when 6-bromo-2-chloro-4-chloromethylquiroline (1 g.) was refluxed with potassium cyanide (0.5 g.) in alcohol (20 ml.) for 3 hr. M.P. and mixed m.p. with the compound described above was 271°.

1,2-Bis(6-bromo-2-chloro-4-quinolyl)ethane :

1-Cyano-1,2-bis(6-bromo-2-chloro-4-quinolyl) ethane (1 g.) was refluxed with sulphuric acid (20 ml. ; 70 %) on a sand bath for 6 hr. On working up as usual the product crystallised from xylene (charcoal), m.p. 298°. Yield 0.5 g.

Analysis : Found : C,46.87 ; H,2.68 ; N,5.49 %.

$C_{20}H_{12}N_2Cl_2Br_2$ requires : C,46.96 ; H,2.34 ; N,5.48 %.

The same compound was also prepared for comparison as follows :

1-Cyano-1,2-bis(6-bromo-2-hydroxy-4-quinolyl) ethane (1 g.) was refluxed with sulphuric acid (20 ml. ; 70 %) on a sand bath for 6 hr. The crude product obtained on dilution with water was reacted further. This product (0.5 g.) was heated in an oil bath at 110-20° with phosphorus oxychloride (4 ml.) for 4 hr. On working up as usual the product crystallised from xylene, m.p. 298°. Mixed m.p. with 1,2-bis(6-bromo-2-chloro-4-quinolyl) ethane prepared above was not depressed.

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CHAPTER III

Studies on 4-bromomethylcarbostyril derivatives

Section III

Synthesis of 2,2-dicarboethoxy-1,3-bis(2-chloro-4-quinolyl)propane derivatives :

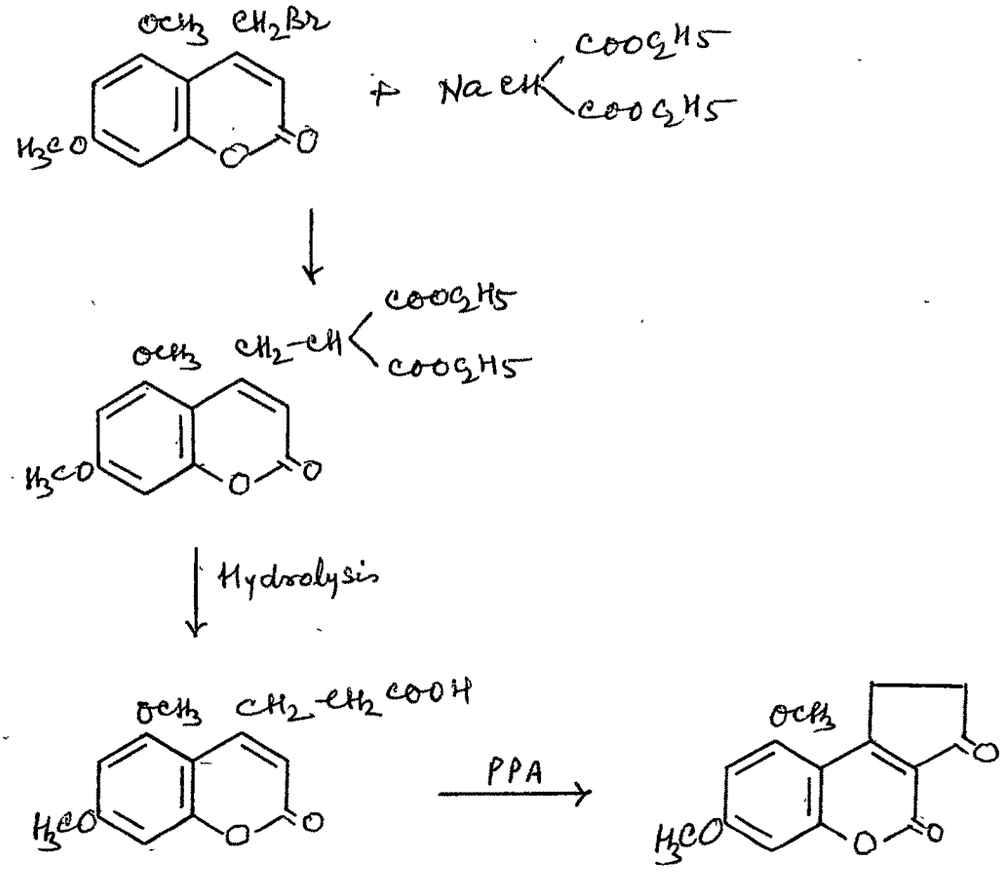
Theoretical

Having studied the reactivity of 4-bromomethyl-carbostyril derivatives with (a) primary and secondary amines as described in sec.I and (b) potassium cyanide as described in sec.II, it was thought of interest to study the reactivity with diethyl sodio malonate. As the bromomethyl derivatives were insoluble in inert solvents like benzene, toluene, the 2-chloro-4-chloromethyl quinoline derivatives described in section II were used in this reaction.

One of the most valuable methods for preparing substituted carboxylic acids makes the use of malonic ester synthesis. This synthesis depends upon the high acidity of α-hydrogen atoms of malonic ester and also upon the extreme ease with which substituted malonic acids undergo decarboxylation. With the help of this synthesis, it is possible to synthesis different compounds such as fatty acids, α-β-unsaturated acids, cyclic and heterocyclic compounds.

The condensation of sodio malonic ester with heterocyclic alkylhalide derivatives has not been studied in detail especially in the quinoline derivatives.

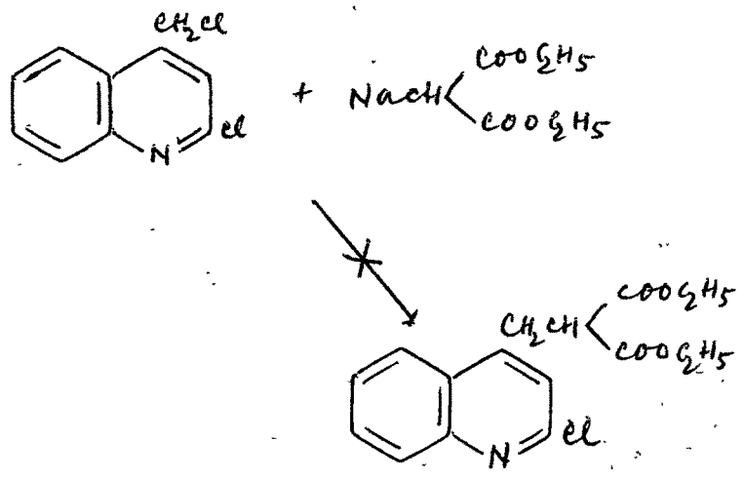
3-Bromoquinoline did not condense with sodio malonic ester[1]. The condensation of 4-bromomethylcoumarin derivative with sodio malonic ester is a good illustration for building up of cyclo pentane ring on the coumarin moiety. Sidhu[2] synthesised 5,7-dimethoxycyclopentanone(2,3-c) coumarin which is of potential interest in biological testing by condensing 5,7-dimethoxy-4-bromomethylcoumarin with sodio malonic ester, followed by hydrolysis and subsequent cyclisation with polyphosphoric acid.



The present work was undertaken with a view to build up cyclopentane ring system on quinoline moiety but different product was obtained.

Condensation of 2-chloro-4-chloromethylquinoline with sodio malonic ester :

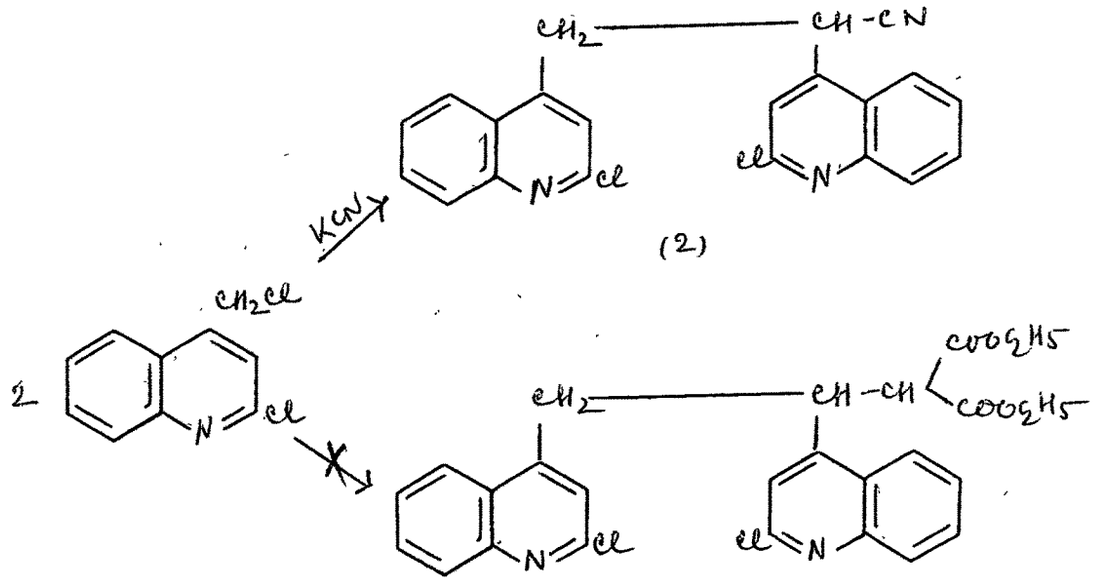
Sodio malonic ester was prepared by reacting pulverised sodium with malonic ester. This was condensed with 2-chloro-4-chloromethylquinoline by refluxing in dry benzene. The analytical results of the product obtained after the condensation did not agree with the expected product diethyl (2-chloro-4-quinolylmethyl) malonate (1).



(1)

On the basis of the previous observation in the condensation of 2-chloro-4-chloromethylquinoline with potassium cyanide, in which two quinoline moieties are taking part in the condensation to give 1-cyano-1,2-bis(2-chloro-4-quinolyl)ethane (2), the 3,3-dicarboethoxy-1,2-bis (2-chloro-4-quinolyl)propane structure (3) is tentatively

proposed for the condensation product.



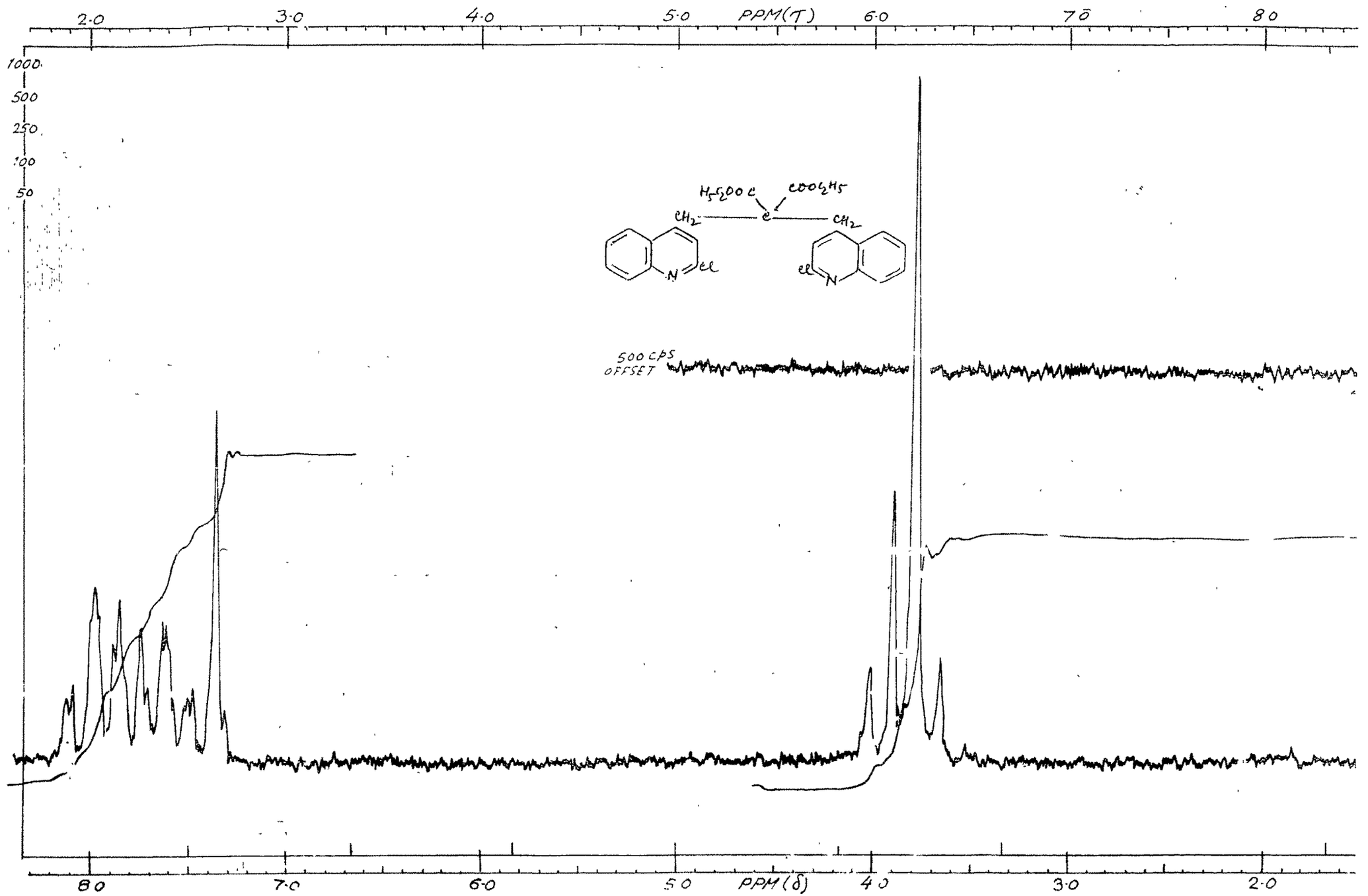
(2)

(3)

The NMR spectrum of this compound (3) was recorded in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The assignments of the various signals and the chemical shifts are as follows :

Shifts (δ)	Signals	Assignment
7.7-8.1	Multiplet	10 H aromatic protons
3.82	Quadruplet	8 H- CH_2- protons
0.9	Triplet	6 H -CH_3- protons

The NMR spectrum clearly reveals the presence of ester groups but it does not show the coupling of -CH_2- group with -CH- group as it is shown in the case of 1-cyano-1,2-bis(2-chloro-4-quinolyl)ethane and hence 2,2-dicarboethoxy-1,3-bis(2-chloro-4-quinolyl)propane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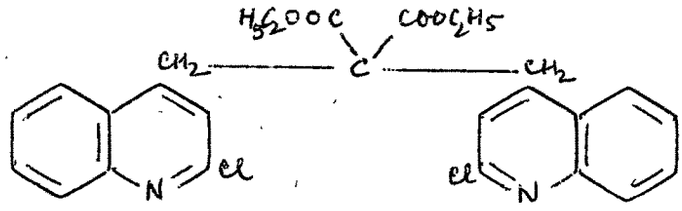
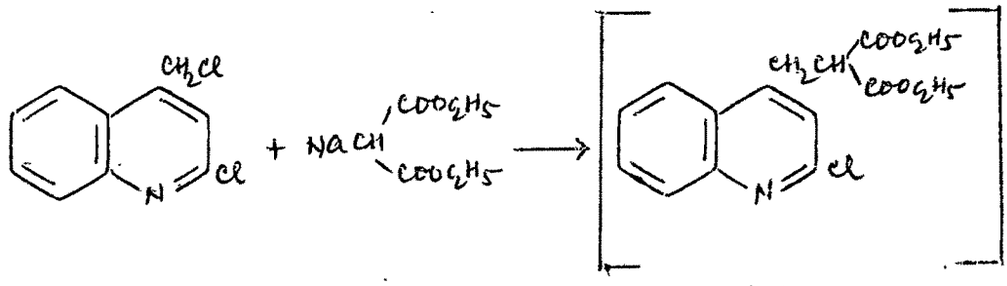
COOC2H5
CH2
C
CH2
Cl
N
Cl
N
500 CPS
OFFSET
8·0
7·0
6·0
5·0
PPM(δ)
4·0
3·0
2·0

structure (4) is assigned which can be supported by NMR spectrum. The signals of the two methylene groups attached to quinoline nucleus overlap with methylene group of the ester.

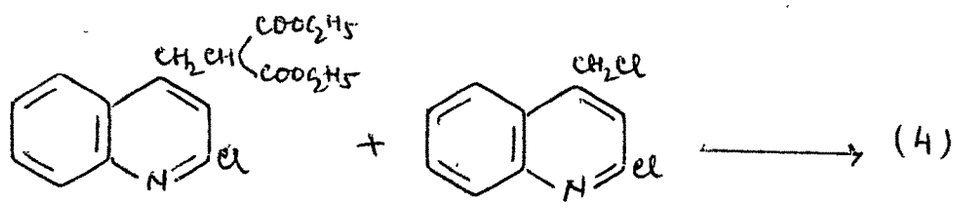


(4)

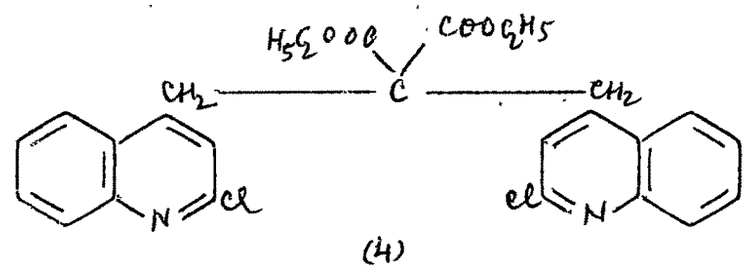
The formation of (4) can be explained by assuming that one mole of 2-chloro-4-chloromethylquinoline reacts with one mole of sodio malonic ester to give (1). This then further reacts with the second mole of 2-chloro-4-chloromethylquinoline to give (4).



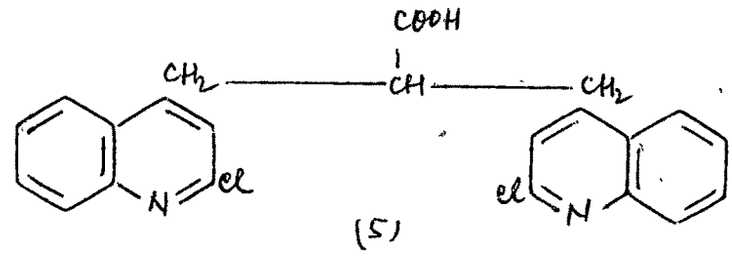
(1)



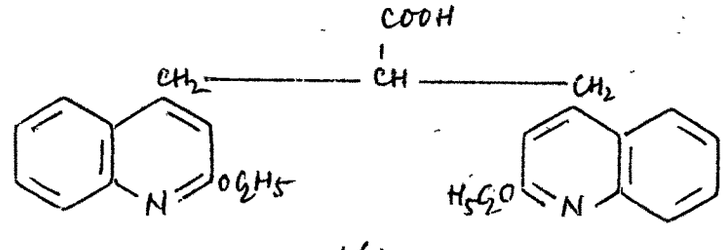
The product (4) on hydrolysis with alcoholic potassium hydroxide solution gave an acid to which 2-carboxy-1,3-bis(2-chloro-4-quinolyl)propane (5) structure is assigned on the basis of analytical results. This was further refluxed with alcoholic potassium hydroxide to give 2-carboxy-1,3-bis(2-ethoxy-4-quinolyl) propane (6), wherein 2-chloro group has been replaced by an ethoxy group.



(4)



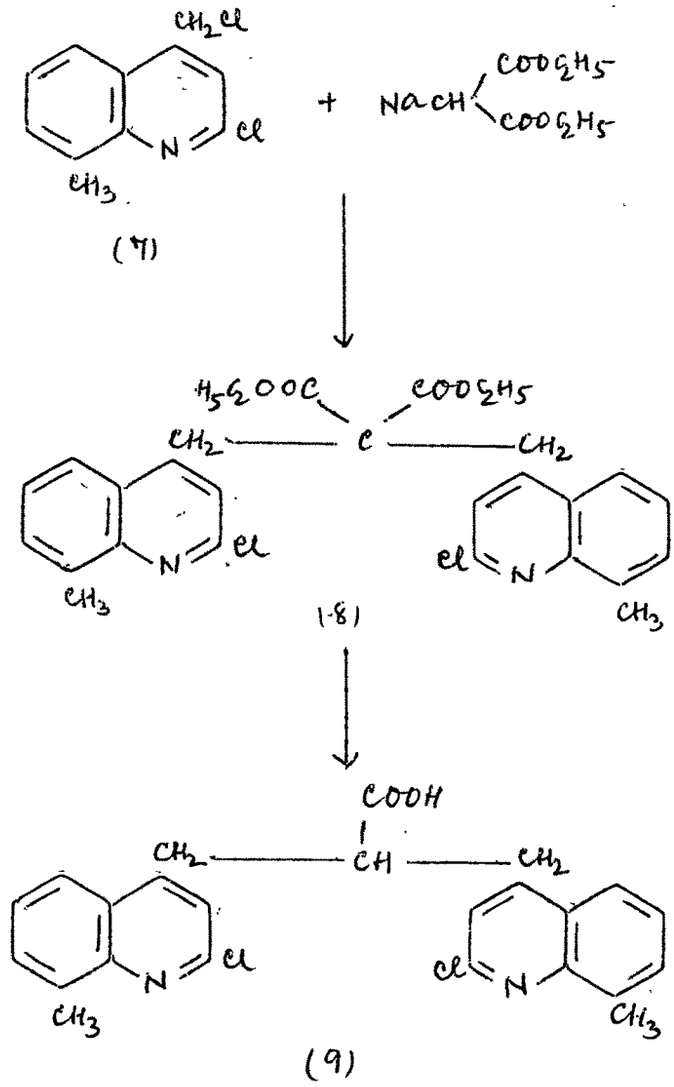
(5)



(6)

Condensation of 8-methyl-2-chloro-4-chloromethyl-quinoline with sodio malonic ester :

Sodio malonic ester was condensed with 8-methyl-2-chloro-4-chloromethylquinoline (7) by refluxing in dry benzene. The product obtained has been assigned 2,2-dicarboethoxy-1,3-bis(8-methyl-2-chloro-4-quinolyl)propane (8) structure. On hydrolysis with alcoholic potassium hydroxide it gave 2-carboxy-1,3-bis(8-methyl-2-chloro-4-quinolyl)propane (9).



EXPERIMENTAL

Condensation of 2-chloro-4-chloromethylquinoline with sodio malonic ester : 2,2-Dicarboethoxy-1,3-bis(2-chloro-4-quinolyl)propane :

A mixture of pulverised sodium (0.23 g.),diethyl malonate (1.6 g.) and dry benzene (30 ml.) was left overnight with calcium chloride guard tube. Next day 2-chloro-4-chloromethylquinoline (2.1 g.) was added and the reaction mixture refluxed on a steam bath for 12 hr. The product obtained on removal of benzene was washed with dilute alcohol. It crystallised from alcohol,m.p. 172°. Yield 1.2 g.

Analysis : Found : C,63.25 ; H,4.59 ; N,5.78 %.

$C_{27}H_{24}O_4N_2Cl_2$ requires : C,63.40 ; H,4.69 ; N,5.47 %.

2-Carboxy-1,3-bis(2-chloro-4-quinolyl)propane :

The above ester derivative (1 g.) was treated with alcoholic potassium hydroxide solution (20 ml. ;10 %) and heated on a water bath for 5 hr. The reaction mixture after dilution with water and neutralisation with dilute hydrochloric acid gave the product which was purified by treatment with sodium bicarbonate solution. It crystallised from alcohol,m.p.214. Yield 0.5 g.

Analysis : Found : C,64.43 ; H,3.93 ; N,6.59 %.

$C_{22}H_{16}O_2N_2Cl_2$ requires : C,64.25 ; H,3.89 ; N,6.81 %.

2-Carboxy-1,3-bis(2-ethoxy-4-quinolyl)propane :

2-Carboxy-1,3-bis(2-chloro-4-quinolyl)propane (0.5 g.) in alcohol (20 ml.) was treated with potassium hydroxide (4 g.) and refluxed on a sand bath for 8 hr. The product obtained on dilution with water and neutralisation with dilute hydrochloric acid was filtered and crystallised from benzene-petroleum ether mixture (1:1), m.p.184°.

Yield 0.2 g.

Analysis : Found : C,72.36 ; H,6.10 ; N,6.15 %.

$C_{26}H_{26}O_4N_2$ requires : C,72.55 ; H,6.04 ; N,6.51 %.

Condensation of 8-methyl-2-chloro-4-chloromethyl-quinoline with sodio malonic ester : 2,2-Dicarbo-ethoxy-1,3-bis(8-methyl-2-chloro-4-quinolyl)propane

A mixture of pulverised sodium (0.23 g.), diethylmalonate (1.6 g.) and dry benzene (30 ml.) was left overnight with calcium chloride guard tube. Next day 8-methyl-2-chloro-4-chloromethylquinoline (2.2 g.) was added to it and the reaction mixture refluxed on a steam bath for 12 hr. On working up as before the product crystallised from alcohol, m.p.168°. Yield 1 g.

Analysis : Found : C,64.28 ; H,5.36 ; N,5.31 %.

$C_{29}H_{28}O_4N_2Cl_2$ requires : C,64.56 ; H,5.19 ; N,5.19 %.

2-Carboxy-1,3-bis(8-methyl-2-chloro-4-quinolyl) propane :

The above ester derivative (1 g.) was treated

with alcoholic potassium hydroxide solution (20 ml. ; 10 %) and heated on a water bath for 5 hr. The reaction mixture after dilution with water and neutralisation with dilute hydrochloric acid gave the product which was purified by treatment with sodium bicarbonate solution . It crystallised from alcohol, m.p. 204°. Yield 0.5 g.

Analysis : Found : C,65.16 ; H,4.43 ; N,6.16 %.

$C_{24}H_{20}O_2N_2Cl_2$ requires : C,65.60 ; H,4.55 ; N,6.37 %.

REFERENCES

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