CHAPTER II

Studies in the synthesis of 2-hydroxycinchoninic acids

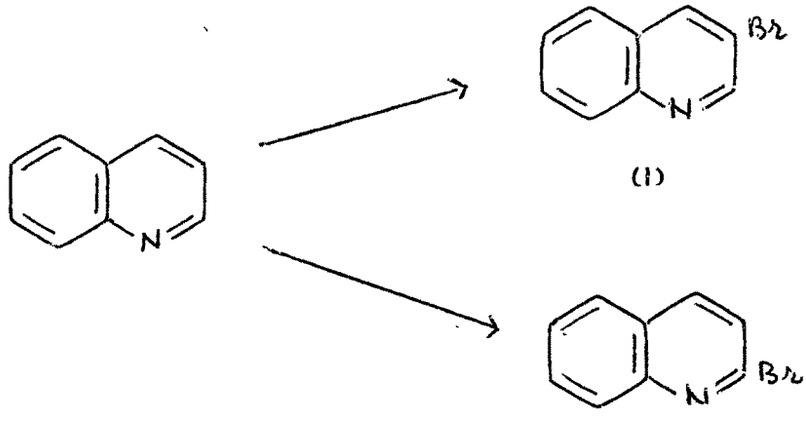
CHAPTER II

Section I

Bromoquinolines

Theoretical

The present work deals with the synthesis of bromoquinoline derivatives, it will be, therefore, of interest to review the preparation and properties of halogenated quinoline derivatives. Jansen and Wibaut[1] were the first to carry out the bromination of quinoline in gaseous phase between 300-500° and found that the first bromine atom only entered in the pyridine nucleus. 3-Bromoquinoline (1) was prepared by passing preheated vapours of quinoline and bromine through a tube, filled with pumice at 300° while at 450-500° the product was 2-bromoquinoline (2) in 50-60 % yield.

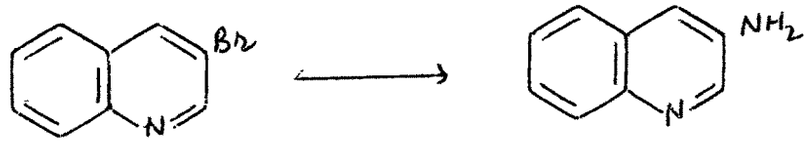


(1)

(2)

Edinger[2] however, prepared 3-bromoquinoline most conveniantly by direct bromination of quinoline in the presence of a relatively large amount of sulphur. Presumably sulphurylbromide is the actual brominating agent. Similarly Edinger and Lubberger[3], Baker et al.[4] carried out the chlorination of quinoline at 3-position by refluxing it with sulphur dichloride.

Renshaw and Friedman[5] observed that bromination of quinoline with sulphur and bromine gave 3-bromoquinoline. Heating 3-bromoquinoline with conc. ammonium hydroxide and copper sulphate as catalyst in a rocking autoclave at 160° for 2 hours and after extraction with ether gave 3-amino-quinoline. Mills and Watson[6] prepared 3-quinolinol (3) by diazotisation of 3-aminoquinoline, which is in turn prepared by treatment of 3-bromoquinoline with ammonia in the presence of copper.[7]



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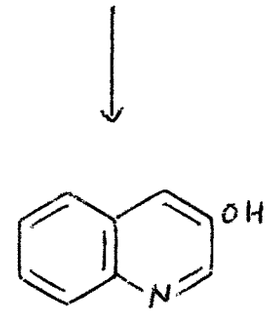
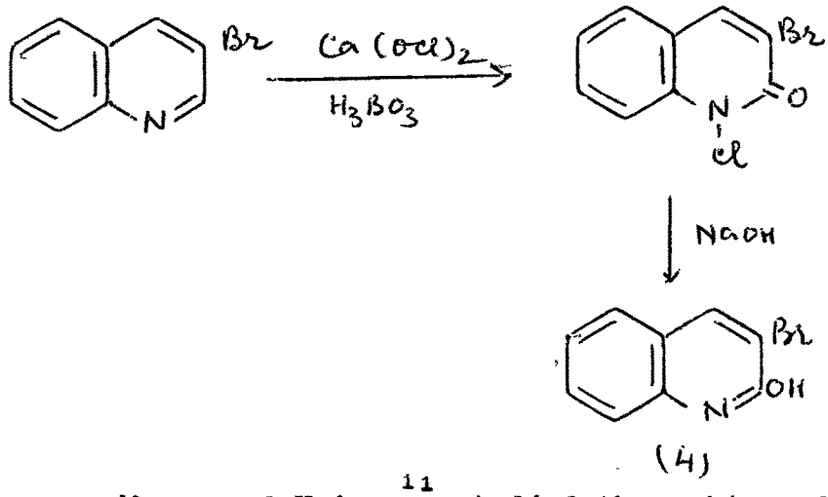


(3)

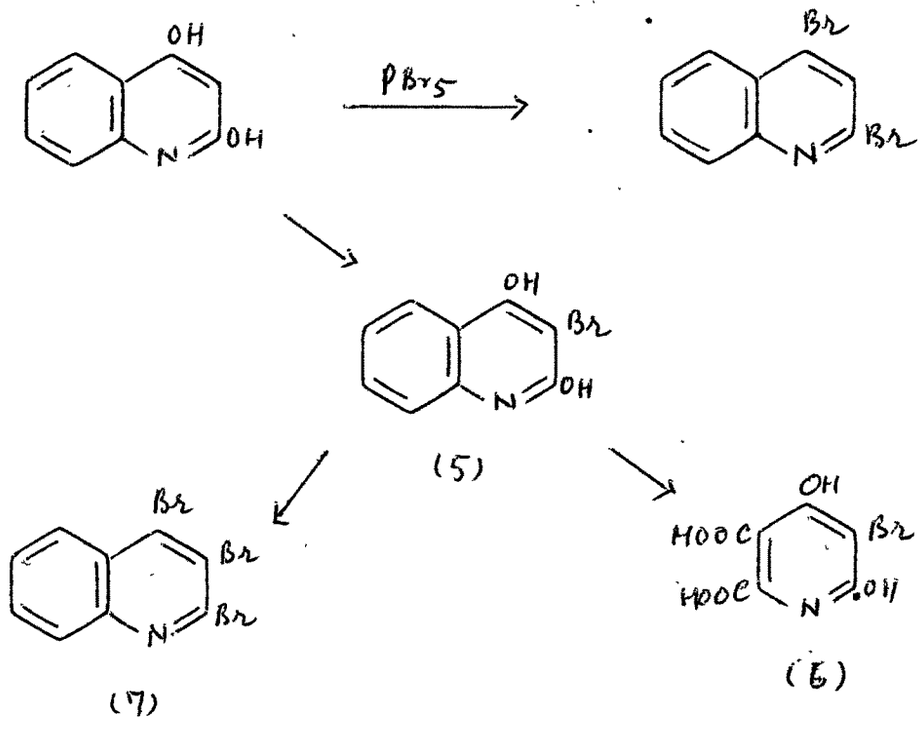
LaCoste[8] obtained a bromoquinoline when a solution of quinoline in hydrochloric acid was warmed with bromine. Claus and Collischonn[9] obtained the same compound by heating the quinoline dibromide hydrobromide $C_9H_7N.HBr.Br_2$ and assigned it the structure of 4-bromo-quinoline. But Decker[10] found that the above compound was 3-bromoquinoline by converting it into 3-bromocarbostyril(4) as under.



(4)

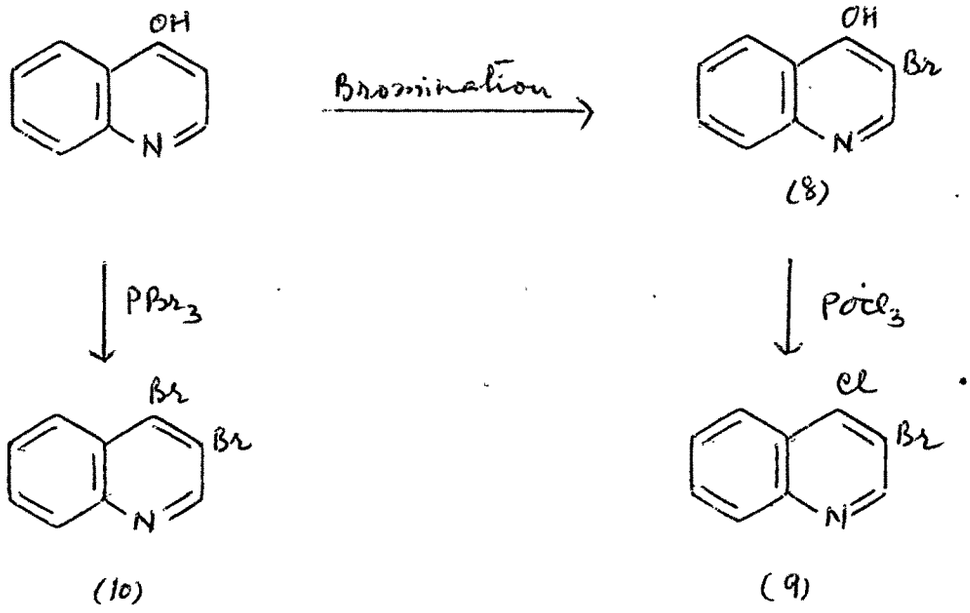
Meyer and Heiman[11] studied the action of bromine on 2,4-dihydroxyquinoline and obtained (?)-bromo-2,4-dihydroxyquinoline in cold acetic acid in a quantitative yield and with excess of bromine in hot got 3-bromo-2,4-dihydroxyquinoline (5). Now 2,4-dihydroxyquinoline and (?)-bromo-2,4-dihydroxyquinoline on oxidation with hot potassium permanganate gave the same 2,4-dihydroxyquinolinic acid while 3-bromo-2,4-dihydroxyquinoline on similar oxidation gave 3-bromo-2,4-dihydroxyquinolinic acid(6). Hence the bromine atom in (?)-bromo-2,4-dihydroxyquinoline

is in undectected position in the benzene ring. Again 2,4-dihydroxyquinoline,(?)-bromo-2,4-dihydroxyquinoline and 3-bromo-2,4-dihydroxyquinoline on treatment with phosphorus pentabromide gave 2,4-dibromo,(?),2,4,-tribromo and 2,3,4-tribromoquinoline (7) respectively. Therefore the (?)-bromo derivative must not be the same 3-bromo-2,4-dihydroxyquinoline (5).



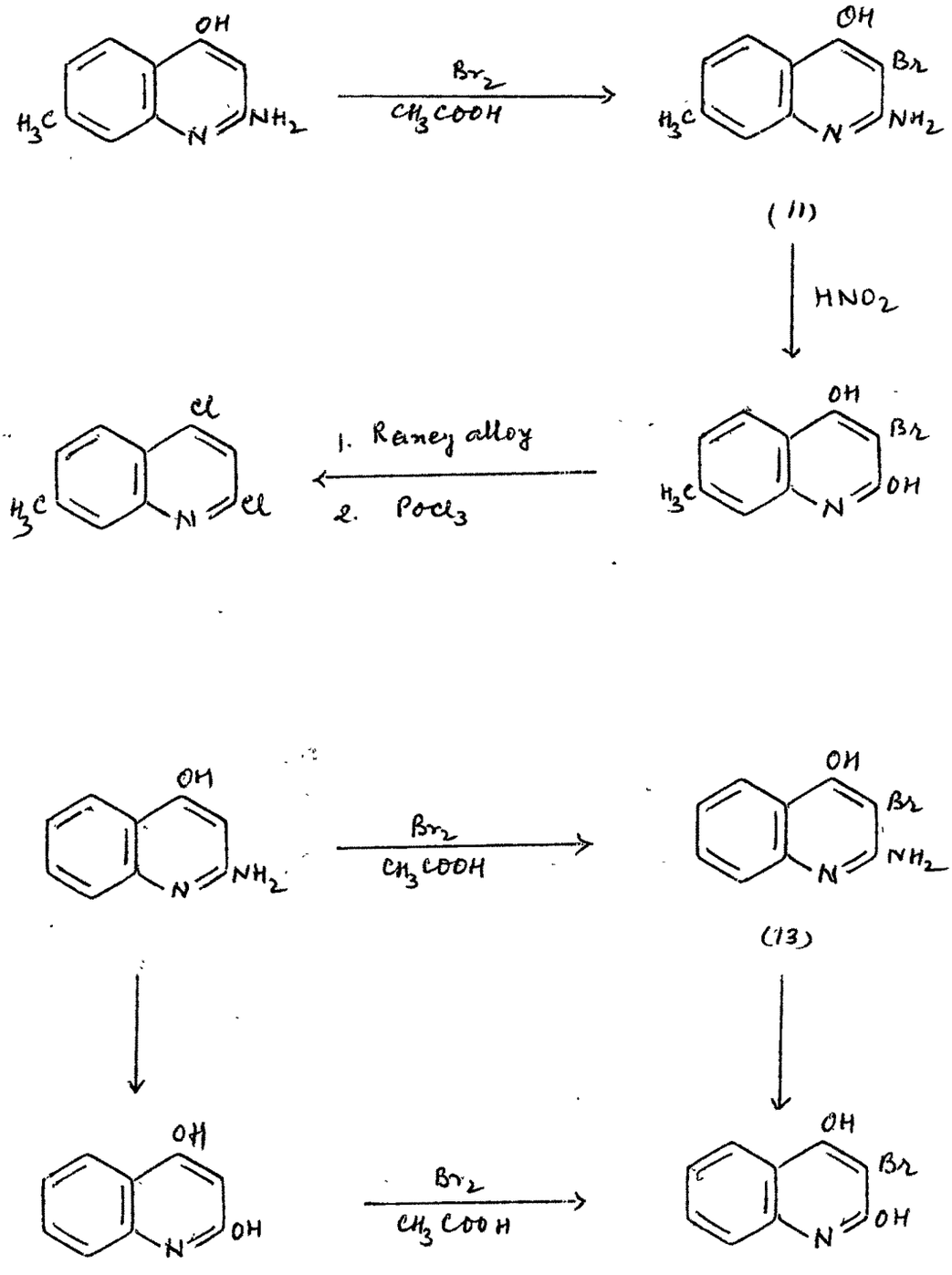
Riegel et al.[12] have prepared 3-bromo-4-quinolinol (8) from 4-quinolinol by reacting it with bromine. Further 3-bromo-4-quinolinoll with phosphorus oxychloride gave 3-bromo-4-chloroquinoline (9) but this compound was unreactive towards amines in the coupling reaction,so a search for more reactive compound was made. 4-Quinolinol on treatment with phosphorus tribromide gave 3,4-dibromo-quinoline (10) which was the starting material for the

synthesis of the antimalarial drugs.

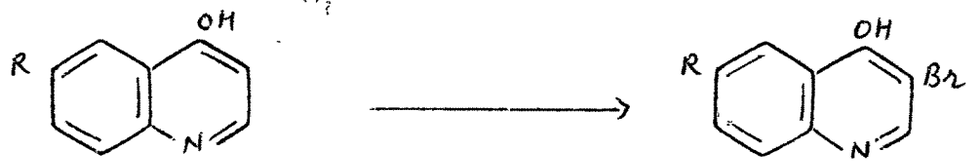


Hardman and Partridge[13] studied the bromination of 2-amino-4-hydroxy-7-methylquinoline and observed that the bromine entered into the 3-position. The 3-bromo derivative (11) on treatment with nitrous acid, furnished the bromohydroxyquinoline and the removal of bromine by reduction with raney alloy gave the dihydroxyquinoline from which the dichloroquinoline (12) was obtained on treatment with phosphorus oxychloride. 2,4-Dihydroxyquinoline was also obtained when 2-amino-4-quinolinol was fused at 250-290^{0} with potassium hydroxide and then acidified with hydrochloric acid. Further bromination of 2-amino-4-quinolinol in glacial acetic acid gave a monobromo derivative which on treatment with nitrous acid furnished the same bromo-2,4-dihydroxyquinoline (5) as was obtained by a similar bromination of 2,4-dihydroxy-

quinoline. Hence it is concluded that the bromine atom has occupied the 3-position both in bromo-2,4-dihydroxyquinoline and in 2-amino-bromo-4-quinolinol (13).



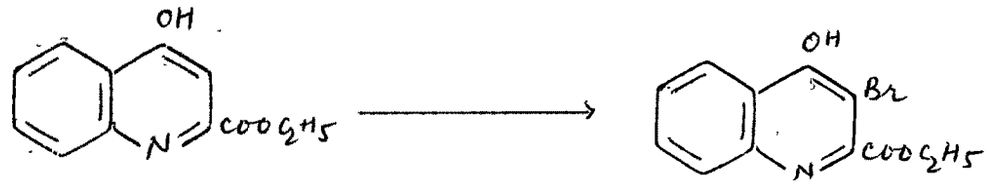
Schofield and Swain[14] carried out the bromination of 6-chloro- and 6-bromo-4-hydroxyquinoline with bromine in acetic acid and obtained 6-chloro-3-bromo- (14) and 3,6-dibromo-4-hydroxyquinoline (15) respectively.



(14), R = Cl

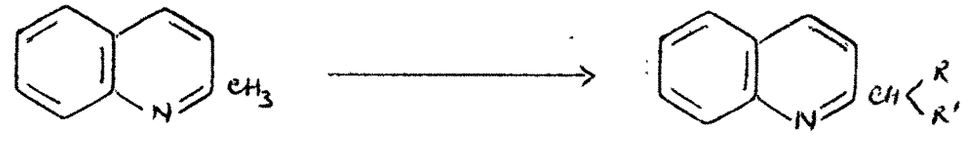
(15), R = Br

Surrey and Cutler[15] obtained ethyl 4-hydroxy-3-bromo-quinaldate[16] (17) from ethyl 4-hydroxyquinaldate (16) on bromination with bromine in acetic acid in the presence of iodine as a catalyst.



(17)

Fujino et al.[18] carried out the bromination of quinaldine (20) in the presence of borontrifluoride acetic acid and obtained monobromoquinaldine (21) with a small quantity of ω-dibromoquinaldine (22).

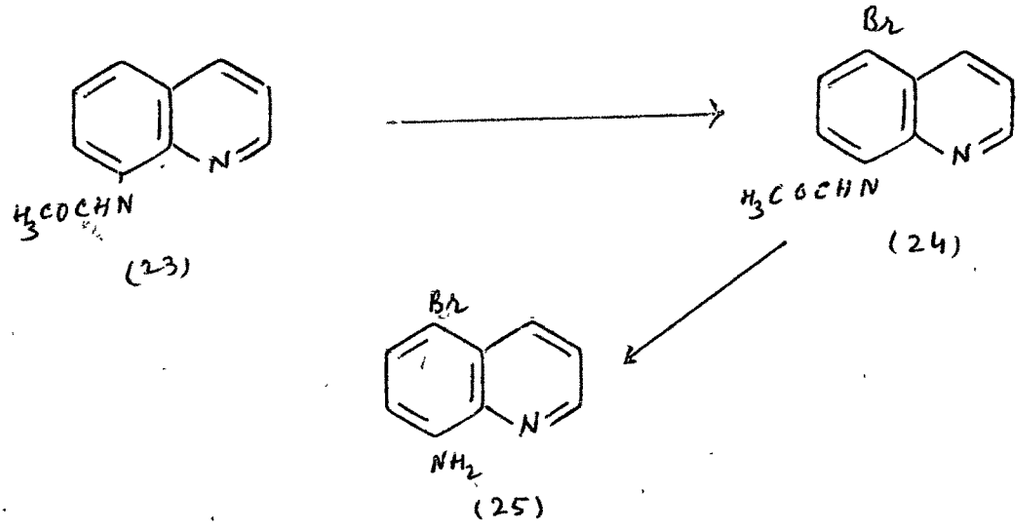


(20)

(21), R = H; R' = Br

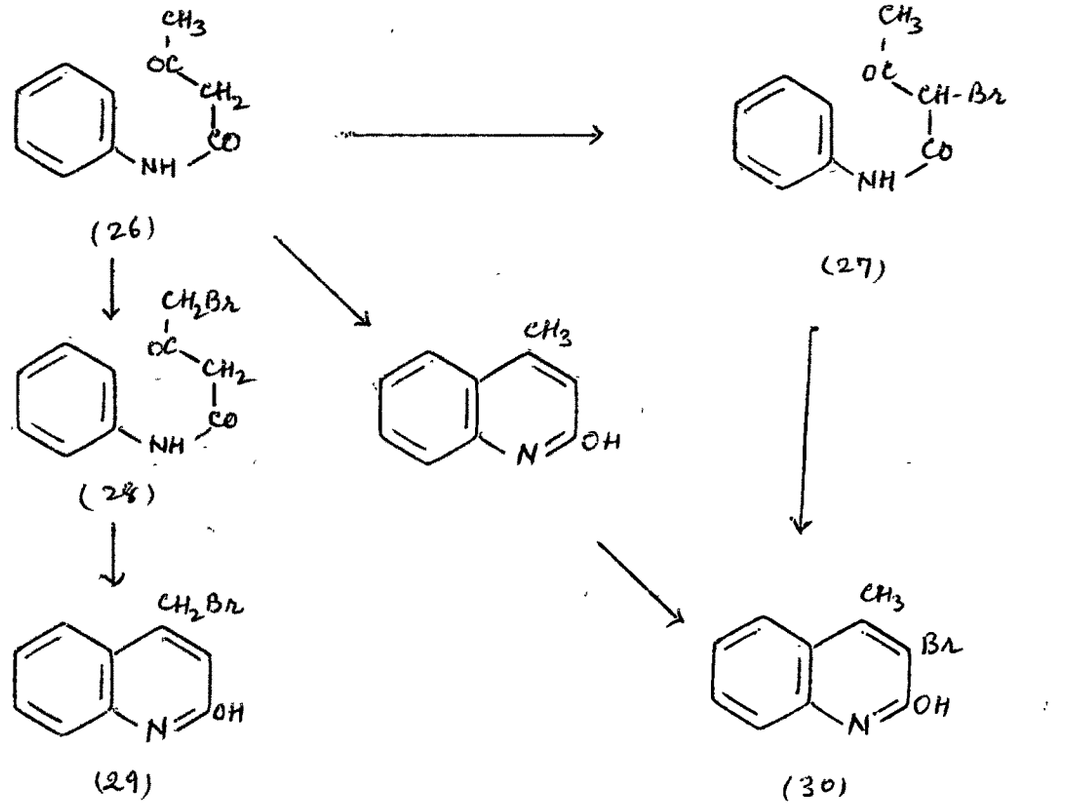
(22), R = R' = Br

Zaruma et al.[19] carried out the synthesis of 5-bromoquinoline viz. bromination of 8-acetamidoquinoline (23) at 0° in acetic acid and adjustment to pH 9 with sodium hydroxide gave 92 % yield of 5-bromo-8-acetamidoquinoline (24) from which 5-bromo-8-aminoquinoline (25) was prepared by hydrochloric acid.



In the present work, bromination of 2-hydroxy-4-methylquinoline derivatives and also the bromination of acetoacetarylamides and their subsequent ring closure were studied with the object of determining the reactivity in the quinoline nucleus ; whether the reaction was taking place on the pyridine part or the benzenoid part of the quinoline ring system. The problems of proving structures of the bromoquinolines and bromoacetoacetarylamides is of considerable importance because it has created a large amount of confusion in this field. Many controversial reports are found in the literature about this. Direct bromination of different 2-hydroxy-4-methylquinoline derivatives in acetic acid has been carried out and the corresponding 3-bromo derivatives have been prepared.

Knorr[20] brominated acetoacetanilide (26) in chloroform solution and cyclised it to 3-bromo-4-methylcarbostyril (30). He reported that the latter compound was identical with the compound obtained by the action of bromine water on 4-methylcarbostyril. As under these conditions the bromine would almost certainly occupy the 3-position so he claimed that he had prepared α-bromoacetoacetanilide (27).



Later on Hasegawa[21] and Cook[22] repeated the above experiment in chloroform and regarded the product as ω-bromoacetoacetanilide (28)

Mehta et al.[30] brominated acetoacetanilide in acetic acid with iodine as catalyst and claimed to have obtained α-bromoacetoacetanilide (27). They further claimed that this product on cyclisation gave

3-bromo-4-methylcarbostyril (30) which was identical with the product obtained on bromination of 4-methylcarbostyril.

In view of these contradictory reports, it was thought of interest to repeat the work by both the procedures. In both the cases, however, the same product was obtained which is assigned ω-bromoacetoacetanilide structure (28) as it gave on cyclisation 4-bromomethyl-carbostyril (29). The latter was different from the 3-bromo-4-methylcarbostyril (30) obtained by bromination of 4-methylcarbostyril. 4-Bromomethylcarbostyril (29) on reduction with zinc dust and acetic acid gave the known 4-methylcarbostyril while the 3-bromo derivative (30) under similar condition remain unaffected. The structure of ω-bromoaceto acetanilide (28) was further confirmed by its NMR Spectra and also by its conversion to known 2-hydroxycinchoninic acid.

NMR Spectra of ω-bromoacetoacetanlide (28) Fig.I

(56.445 MC/S $CDCl_3$)

Shift (δ)	Signals	Assignment
7.27	Multiplet	5H (Aromatic)
4.06	Singlet	2H ($Br-CH_2-CO$)
3.79	Singlet	2H ($CO-CH_2-CO$)

In view of the above results of bromination of acetoacetarylamide, it was thought of interest to study chlorination of this compound. Bulow and King[31] reported that acetoacetanilide on chlorination with

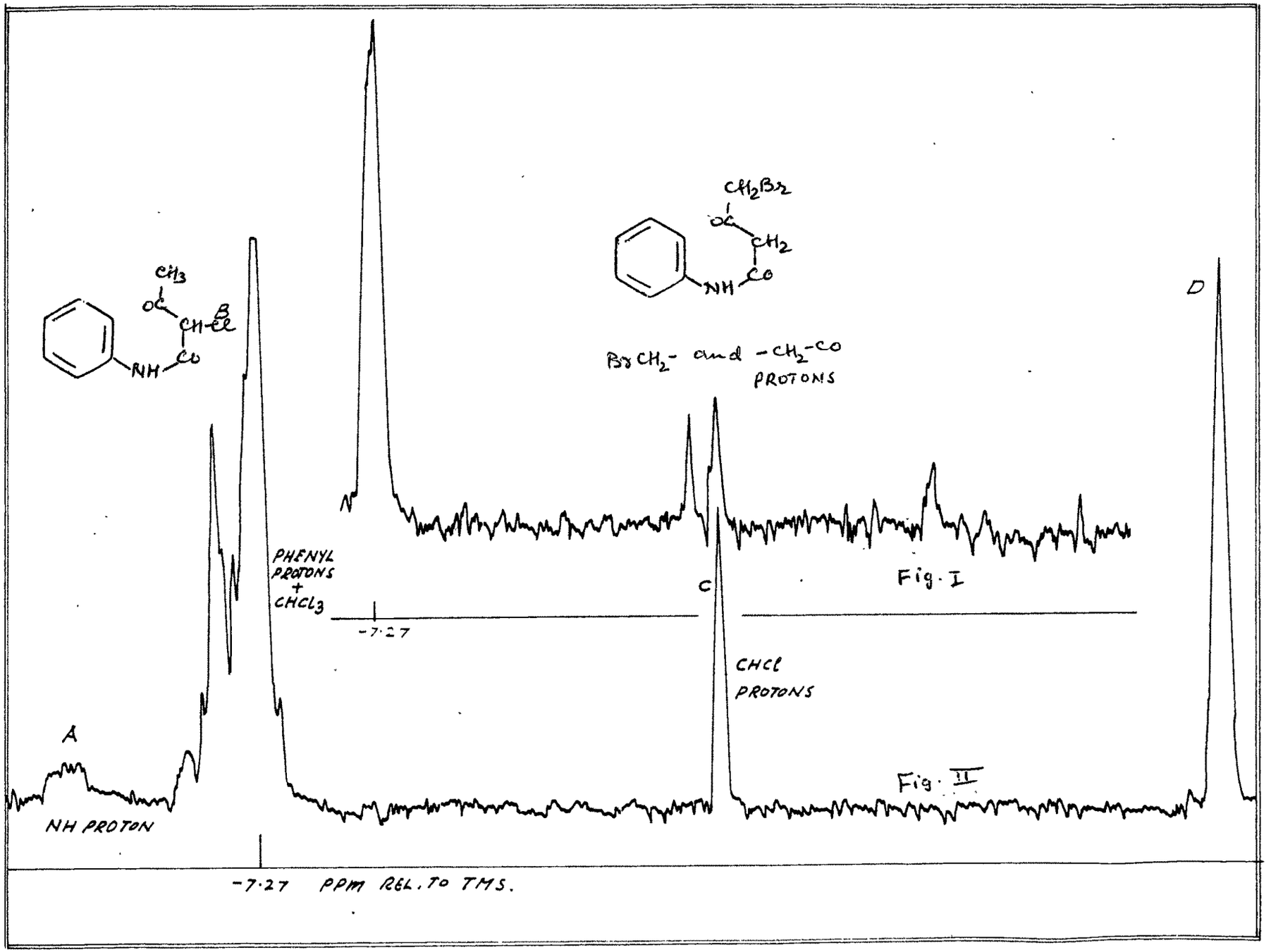

CH3
CH-Br
NH
CO
CH2Br2
CH2
NH
CO
BrCH2- and -CH2-CO
PROTONS
D
PHENYL
PROTONS
+
CHCl3
-7·27
C
CHCl
PROTONS
A
NH PROTON
-7·27 PPM REL. TO TMS.

Fig. I

Fig. II

sulphuryl chloride gave α-chloroacetoacetanilide. The same was prepared and its structure was confirmed on the basis of NMR spectrum.

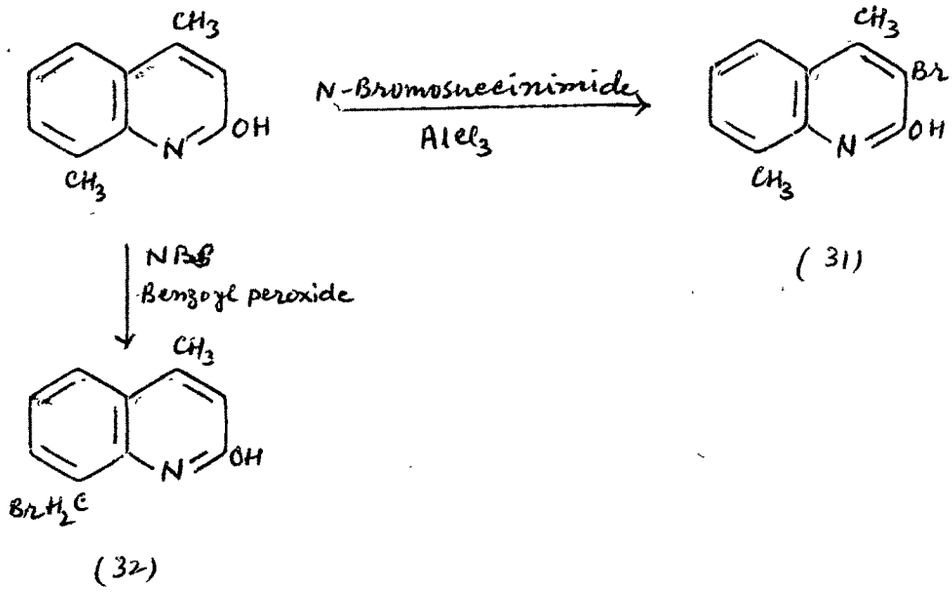
NMR Spectra of α-chloroacetoacetanilide Fig. II

(56.445 MC/S $CDCl_3$)

Shift (δ)	Signals	Assignment
7.27	Multiplet	5H (Aromatic)
4.96	Singlet	1H -CO-CHCl-CO-
2.46	Singlet	3H $-CO-CH_3$

It is interesting to note that bromination of acetoacetanilide gives ω-bromo derivative while chlorination gives α-chloro derivative.

Cook et al.[22] studied the bromination with N-bromosuccinimide. They prepared 3-bromo-4,8-dimethylcarbostyril (31) from 4,8-dimethylcarbostyril with N-bromosuccinimide in the presence of aluminium chloride as catalyst. 8-Bromomethyl-4-methylcarbostyril (32) was the product when benzoylperoxide was used as catalyst.



(31)

(32)

Campbell et al.[234] prepared 4-bromomethylquinoline, an extremely unstable substance by the action of N-bromo-succinimide on lepidine. It is well known that N-bromo-succinimide is a useful reagent for the side chain bromination in aromatic methyl groups. However the bromine will enter in side chain or nucleus depends upon the reactivity of the compound concerned. It was, therefore, thought of interest to carry out the bromination of 4-methylcarbostyril and its derivatives with N-bromo-succinimide to establish the pattern of substitution with this reagent. When bromination of 4-methylcarbostyril was carried out with one mole of N-bromosuccinimide, no definite pure product could be isolated from the reaction mixture and so it was brominated with two moles of N-bromosuccinimide. In this reaction 4-bromomethyl-3-bromo-carbostyril was isolated in pure state and was identical with the product obtained by bromination of 4-bromomethyl-carbostyril with bromine in acetic acid. It is interesting to note that both side chain bromination as well as ring bromination occurred in this case.

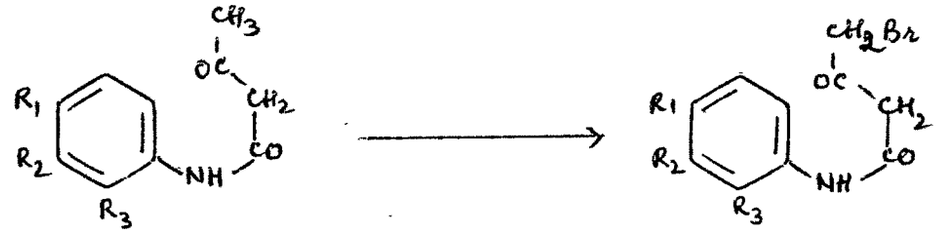
Bromination method of acetoacetarylamides with

(a) Bromine in acetic acid :

Acetoacetarylamide was dissolved in minimum amount of hot glacial acetic acid and bromine in acetic acid was added and left overnight. Some bromo compounds separated on standing while others were obtained on dilution with water. They were crystallised either from alcohol or dilute acetic acid.

(b) Bromine in chloroform :

Acetoacetarylamide was dissolved in minimum amount of chloroform and bromine in chloroform was added. The product either separated or obtained on evaporation of the solvent crystallised from dilute acetic acid or alcohol or benzene.



(28)

The melting point and the mixed m.p. of the ω-bromo derivative obtained in both the cases was the same. The following acetoacetarylamides are brominated in the present work.

(1) Acetoacetanilide (28, $R_1=R_2=R_3=H$)

(2) Acetoacet-o-toluidide (28, $R_1=R_2=H, R_3=CH_3$)

(3) Acetoacet-p-anisidide (28, $R_1=OCH_3, R_2=R_3=H$)

(4) Acetoacet-p-chloroanilide (28, $R_1=Cl, R_2=R_3=H$)

(5) Acetoacet-m-chloroanilide (28, $R_1=R_3=H, R_2=Cl$)

(6) Acetoacet-m-xylidide (28, $R_1=R_3=CH_3, R_2=H$)

(7) Acetoacet-p-bromoanilide (28, $R_1=Br, R_2=R_3=H$)

(8) Acetoacet-o-chloroanilide (28, $R_1=R_2=H, R_3=Cl$)

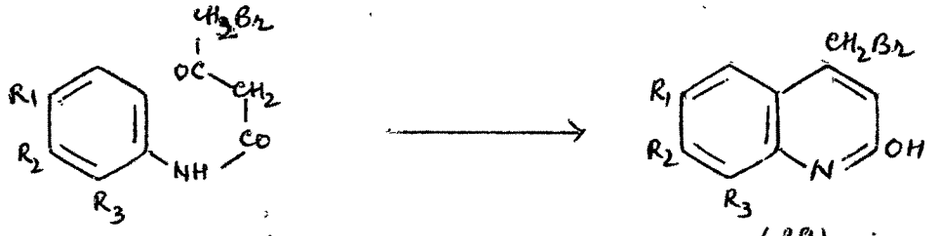
(9) Acetoacet-α-naphthylamide (28, R_2-R_3=benzo, $R_1=H$)

(10) Acetoacet-p-phenetidide (28, $R_1=OC_2H_5, R_2=R_3=H$)

(11) Acetoacet-p-toluidide (28, $R_1=CH_3, R_2=R_3=H$)

Cyclisation of the ω-bromoacetoacetarylamides to 4-bromomethylcarbostyril derivatives with conc. sulphuric acid :

ω-Bromoacetoacetarylamide was heated on a water bath with conc.sulphuric acid for 2-3 hr. The reaction mixture gave the product on dilution with ice cold water. It crystallised from glacial acetic acid or alcohol.



(29)

All the ω-bromo derivatives described above were cyclised with conc.sulphuric acid to the following corresponding 4-bromo-methyl carbostyril derivatives.

(1) 4-Bromomethylcarbostyril (29, $R_1=R_2=R_3=H$)

(2) 8-Methyl-4-bromomethylcarbostyril (29, $R_1=R_2=H, R_3=CH_3$)

(3) 6-Methoxy-4-bromomethylcarbostyril (29, $R_1=OCH_3, R_2=R_3=H$)

(4) 6-Chloro-4-bromomethylcarbostyril (29, $R_1=Cl, R_2=R_3=H$)

(5) 7-Chloro-4-bromomethylcarbostyril (29, $R_1=R_3=H, R_2=Cl$)

(6) 6,8-Dimethyl-4-bromomethylcarbostyril (29, $R_1=R_3=CH_3, R_2=H$)

(7) 6-Bromo-4-bromomethylcarbostyril (29, $R_1=Br, R_2=R_3=H$)

(8) 8-Chloro-4-bromomethylcarbostyril (29, $R_1=R_2=H, R_3=Cl$)

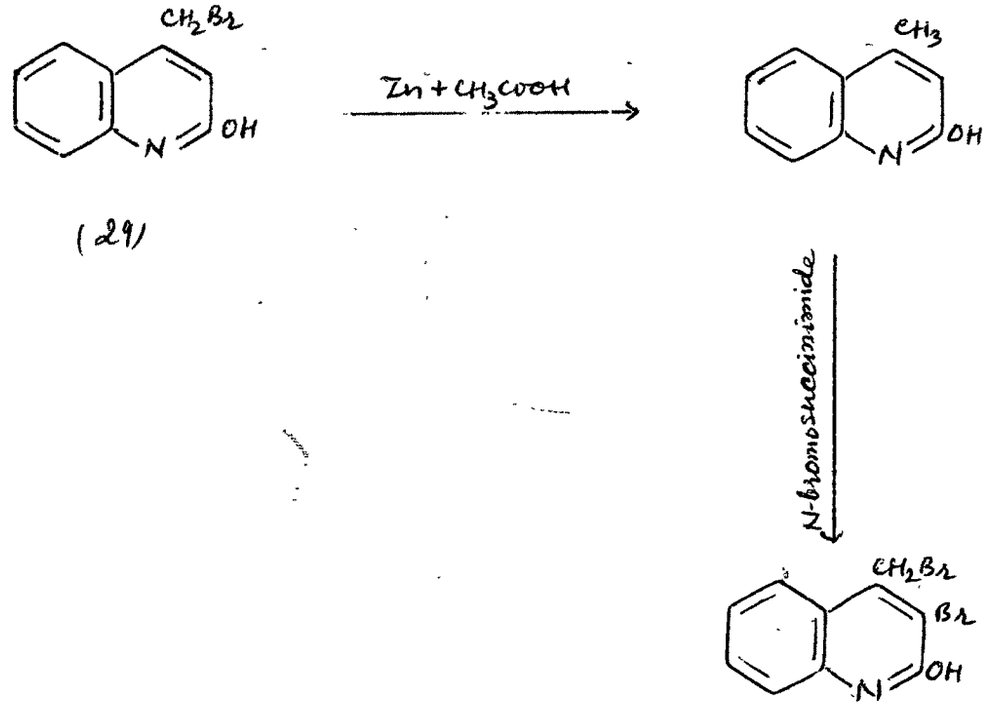
(9) 7,8-Benzo-4-bromomethylcarbostyril (29, R_2-R_3=benzo, $R_1=H$)

(10) 6-Ethoxy-4-bromomethylcarbostyril (29, $R_1=OC_2H_5, R_2=R_3=H$)

(11) 6-Methyl-4-bromomethylcarbostyril (29, $R_1=CH_3, R_2=R_3=H$)

Reduction of 4-bromomethylcarbostyril to 4-methyl-carbostyril

The above bromomethyl derivative (29) on treatment with zinc dust and glacial acetic acid was reduced to 4-methylcarbostyril. The mixed m.p. with the 4-methylcarbostyril derivative prepared from cyclisation of acetoacetarylamide with conc. sulphuric acid was not depressed. No reduction would have taken place if bromine were in the three position of the quinoline ring system.



Bromination of 4-methylcarbostyril derivatives :

(a) **With bromine in acetic acid** (b) **With N-bromo-succinimide in chloroform**

(a) The 4-methylcarbostyril was dissolved in warm glacial acetic acid to which bromine in acetic acid

was slowly added with stirring and left overnight. The separated product was purified by crystallisation.

(b) 4-Methylcarbostyril suspended in chloroform was refluxed with N-bromosuccinimide for 7-8 hr. The separated product on repeated crystallisation gave the dibromo derivative which was also prepared from 4-methyl-3-bromo-carbostyril as well as 4-bromomethylcarbostyril. In all the cases the 4-bromomethyl-3-bromocarbostyril was obtained.

In a very similar manner the different 4-methylcarbostyril derivatives are brominated. The following is the list of the compounds prepared in this series.

1. 3-Bromo-4-methylcarbostyril
2. 3-Bromo-4-bromomethylcarbostyril
3. 4,8-Dimethyl-3-bromocarbostyril
4. 8-Methyl-3-bromo-4-bromomethylcarbostyril
5. 6-Methoxy-3-bromo-4-methylcarbostyril
6. 4-Methyl-7,8-benzo-3-bromocarbostyril
7. 4,6-Dimethyl-3-bromocarbostyril
8. 6-Chloro-3-bromo-4-methylcarbostyril
9. 7-Chloro-4-methyl-3-bromocarbostyril
10. 3,6-Dibromo-4-methylcarbostyril
11. 4,6,8-Trimethyl-3-bromocarbostyril

EXPERIMENTAL

Bromination of acetoacetarylamides :

ω-Bromoacetoacetanilide :

Acetoacetanilide (1.7 g.) was dissolved in warm glacial acetic acid (5 ml.) to which bromine in acetic acid (16 ml. ; 10 %) was slowly added with continous stirring. The reaction mixture was kept overnight at room temperature. The separated product was filtered and crystallised from dilute acetic acid in white plates, m.p.135-36°. Yield 1.2 g.

Analysis : Found : N,5.85 ; Br,31.69 %.

$C_{10}H_{10}O_2NBr$ requires : N,5.46 ; Br,31.25 %.

The same ω-bromo derivatives was obtained by brominating acetoacetanilide (1.7 g.) in chloroform(2 ml.) with bromine in chloroform (8 ml. ; 20 %). The separated product was filtered and crystallised from dilute acetic acid, m.p. and mixed m.p. was 135°.

ω-Bromoacetoacet-o-toluidide :

Acetoacet-o-toluidide (1.91 g.) was dissolved in warm glacial acetic acid (5 ml.) to which bromine in acetic acid (16 ml. ; 10 %) was added with stirring and left overnight. The reaction mixture was poured into ice cold water and the precipitate obtained was filtered and crystallised from methyl alcohol,m.p.85°. Yield 0.9 g.

Analysis : Found : N,4.98 ; Br,29.45 %.

$C_{11}H_{12}O_2NBr$ requires : N,5.18 ; Br,29.63 %.

The same ω-bromo derivative was obtained with bromine in chloroform in the usual manner as described above.

ω-Bromoacetoacet-p-anisidide :

Acetoacet-p-anisidide (2.0 g.) and bromine in acetic acid (1.6 g.) were treated as above and the ω-bromoacetoacet-p-anisidide thus obtained was crystallised from benzene in shining white leaflets, m.p.137-38°. Yield 1.3 g.

Analysis : Found : Br, 28.11 %.

$C_{11}H_{12}O_3NBr$ requires : Br, 27.97 %.

The same ω-bromo derivative was obtained by brominating acetoacet-p-anisidide in chloroform with bromine in chloroform.

ω-Bromoacetoacet-p-chloroanilide :

Acetoacet-p-chloroanilide (2.11 g.) and bromine in acetic acid (1.6 g.) were treated as above and the separated product was filtered and crystallised from dilute acetic acid, m.p.130-32°. Yield 1.2 g.

Analysis : Found : C,41.71 ; H,3.40 ; N,4.64 %.

$C_{10}H_9O_2NBrCl$: requires : C,41.31 ; H,3.09 ; N,4.82 %.

Bromination in chloroform also gave the same ω-bromo derivative.

ω-Bromoacetoacet-m-chloroanilide :

Acetoacet-m-chloroanilide (2.11 g.) and bromine in acetic acid (1.6 g.) were treated as above and the

ω-bromo derivative separated on dilution with cold water was filtered and crystallised from methyl alcohol in white buds, m.p.97°. Yield 1.0 g.

Analysis	: Found	: C,41.63 ; H,3.32 ; N,4.52 %.
$C_{10}H_9O_2NBrCl$	requires	: C,41.31 ; H,3.09 ; N,4.82 %.

Bromination in chloroform gave the same ω-bromo derivative.

ω-Bromoacetoacet-m-xylidide :

Acetoacet-m-xylidide (2.0 g.) and bromine in acetic acid (1.6 g.) were treated as above and the product obtained on dilution with ice cold water was filtered and crystallised from benzene-petroleum ether mixture(1:1) in white buds, m.p.98°. Yield 1.2 g.

Analysis	: Found	: Br, 28.28 %.
$C_{12}H_{14}O_2NBr$	requires	: Br, 28.17 %.

It gave the same ω-bromo derivative when bromination was carried out in chloroform.

ω-Bromoacetoacet-p-bromoanilide :

Acetoacet-p-bromoanilide (2,5 g.) and bromine in acetic acid (1.6 g.) were treated as above and the ω-bromoacetoacet-p-bromoanilide, thus obtained was crystallised from benzene-petroleum ether mixture(1:1), m.p.126°. Yield 1.5 g.

Analysis	: Found	: Br, 47.49 %.
$C_{10}H_9O_2NBr_2$	requires	: Br, 47.76 %.

The same ω-bromo derivative was obtained when bromination was carried out in chloroform.

ω-Bromoacetoacet-o-chloroanilide :

Acetoacet-o-chloroanilide (2.1 g.) was dissolved in minimum quantity of acetic acid and bromine (1.6 g.) in acetic acid (16 ml.) was added. The reaction mixture was left overnight. On dilution the product which separated crystallised from benzene-petroleum ether mixture, m.p. 71-2°. Yield 0.8 g.

Analysis : Found : C,41.54 ; H,3.22 ; N,4.77 %.

$C_{10}H_9O_2NBrCl$ requires : C,41.31 ; H,3.09 ; N,4.82 %.

The same ω-bromo derivative was obtained when bromination was carried out in chloroform. Mallams and Israelstam[24] report the same m.p.

ω-Bromoacetoacet-α-naphthylamide :

Acetoacet-α-naphthylamide (2.2 g.) was dissolved in minimum quantity of acetic acid and bromine (1.6 g.) in acetic acid (16 ml.) was added and left overnight. The product which separated crystallised from acetic acid in light yellow needles, m.p.237° (decomp.). Yield 1 g.

Analysis : Found : Br, 26.0 %.

$C_{14}H_{12}O_2NBr$ requires : Br, 26.19 %.

Bromination in chloroform gave the same ω-bromo derivative.

ω-Bromoacetoacet-p-phenetidide :

Acetoacet-p-phenetidide (2.2 g.) in acetic acid (5 ml.) was treated with bromine (1.6 g.) in acetic acid (16 ml.). The reaction mixture was left overnight. The product which separated crystallised from benzene, m.p.147°. Yield 1.1 g.

Analysis : Found : Br, 26.40 %.

$C_{12}H_{14}O_3NBr$ requires : Br, 26.66 %.

The same ω-bromo derivative was obtained when bromination was carried out in chloroform.

ω-Bromoacetoacet-p-toluidide :

Acetoacet-p-toluidide (1.9 g.) in acetic acid (5 ml.) was treated with bromine (1.6 g.) in acetic acid (16 ml.). The reaction mixture was left overnight. The product which separated crystallised from dilute acetic acid in needles, m.p.148°. Yield 1.2 g.

Analysis : Found : Br, 29.61 %.

$C_{11}H_{12}O_2NBr$ requires : Br, 29.63 %.

The same ω-bromo derivative was obtained when bromination was carried out in chloroform.

Cyclisation of ω-bromoacetoacetarylamides to 4-bromomethyl carbostyril derivatives with concentrated sulphuric acid: 4-Bromomethyl carbostyril :

ω-Bromoacetoacetanilide (3 g.) as described earlier was treated with conc.sulphuric acid (6 ml.) and heated

on a water bath for 1 1/2 hours. The reaction mixture was poured in water and the product which separated crystallised from alcohol in needles, m.p. 254-56° (decomp.). Yield 1.8 g.

Analysis : Found : N, 5.68 ; Br, 33.79 %.

$C_{10}H_8ONBr$ requires : N, 5.88 ; Br, 33.61 %.

Reduction of 4-bromomethylcarbostyril:

4-Methylcarbostyril :

The above 4-bromomethylcarbostyril (0.5 g.) was dissolved in glacial acetic acid (10 ml.) and zinc dust (1 g.) was added to it. The reaction mixture was heated on a sand bath for 45 minutes. It was then filtered hot and diluted with ice cold water. The separated product was filtered and crystallised from water in needles, m.p. 222°.

Again 4-methylcarbostyril was prepared according to Knorr[20] by cyclising acetoacetanilide with conc. sulphuric acid. The mixed m.p. of the above compound was not depressed with authentic specimen.

8-Methyl-4-bromomethylcarbostyril :

ω-Bromoacetoacet-o-toluidide (3 g.) as described before was cyclised with conc. sulphuric acid (6 ml.) by heating on a water bath for 1 1/4 hours. The crude product obtained on dilution with water was filtered and crystallised from acetic acid in needles, m.p. 241°. Yield 1 g.

Analysis : Found : N, 5.34 ; Br, 31.27 %.

$C_{11}H_{10}ONBr$ requires : N, 5.55 ; Br, 31.75 %.

4,8-Dimethylcarbostyril :

8-Methyl-4-bromomethylcarbostyril (0.5 g.) dissolved in glacial acetic acid (10 ml.) was refluxed on a sand bath with zinc dust (1 g.) for half an hour. The product obtained on dilution with ice cold water was filtered and crystallised from dilute acetic acid. The melting point and mixed m.p. with 4,8-dimethylcarbostyril prepared according to Monti and Cirelli[25] from acetoacet-o-toluidide by cyclising with conc.sulphuric acid was 218°.

6-Methoxy-4-bromomethylcarbostyril :

ω-Bromoacetoacet-p-anisidide (3 g.) as described earlier was heated on a water bath with conc.sulphuric acid (6 ml.) for 1 hr. On working up as usual the product which separated crystallised from dilute acetic acid, m.p.249-50°. Yield 1.2 g.

Analysis : Found : Br, 30.04 %.

$C_{11}H_{10}O_2NBr$ requires : Br, 29.85 %.

6-Methoxy-4-methylcarbostyril :

The above bromomethyl derivative (0.5 g.) was refluxed with zinc dust (1 g.) and acetic acid (10 ml.) for 40 minutes. On working up as usual the product which separated crystallised from dilute acetic acid, m.p.268°. Mixed m.p. with 6-methoxy-4-methylcarbostyril prepared according to Monti and Cirelli[25] was not depressed.

6-Chloro-4-bromomethylcarbostyril :

ω-Bromoacetoacet-p-chloroanilide (3 g.) described

earlier was treated conc.sulphuric acid (6 ml.) and heated on a water bath for 2 hr. On working up as usual the separated product crystallised from alcohol, m.p.247°. Yield 1.8 g.

Analysis : Found : C,44.44 ; H,2.51 ; N,4.99 %.
$C_{10}H_7ONBrCl$ requires : C,44.03 ; H,2.56 ; N,5.13 %.

6-Chloro-4-methylcarbostyril :

6-Chloro-4-bromomethylcarbostyril (0.5 g.) was refluxed with zinc dust (1 g.) and glacial acetic acid (10 ml.) for 40 minutes. The reaction mixture was then filtered hot and diluted with water. The product which separated crystallised from dilute acetic acid, m.p.292°. Mixed m.p. with 6-chloro-4-methylcarbostyril prepared according to Monti and Cirelli[25] was not depressed.

7-Chloro-4-bromomethylcarbostyril :

ω-Bromoacetoacet-m-chloroanilide (3 g.) as described before was treated with conc.sulphuric acid (6 ml.) and heated on a water bath for 2 hr. It was poured over ice water. The product which separated was filtered and crystallised from dilute acetic acid, m.p.261-62°. Yield 1.8 g.

Analysis : Found : C,44.34 ; H,2.31 ; N,4.92 %.
$C_{10}H_7ONBrCl$ requires : C,44.03 ; H,2.56 ; N,5.13 %.

7-Chloro-4-methylcarbostyril :

The above bromomethyl derivative (0.5 g.) was refluxed with zinc dust (1 g.) and glacial acetic acid (10 ml.)

for 30 minutes. The product obtained on diliting the clear filtrate was filtered and crystallised from dilute acetic acid, m.p.271-72°. Mixed m.p. with the authentic specimen[26] prepared by cyclising acetoacet-m-chloroanilide with conc. sulphuric acid was not depressed.

6,8-Dimethyl-4-bromomethylcarbostyril :

ω-Bromoacetoacet-m-xylidide (3 g.) described earlier was heated on a water bath with conc.sulphuric acid for 2 hr. On dilution with cold water it gave a white product which was filtered and crystallised from dilute acetic acid in needles, m.p.254°. Yield 1.5 g.

Analysis : Found : Br, 30.53 %.

$C_{12}H_{12}ONBr$ requires : Br, 30.08 %.

4,6,8-Trimethylcarbostyril :

The above bromomethyl derivative (0.5 g.) was refluxed with zinc dust (1 g.) and glacial acetic acid (10 ml.) for 40 minutes. It was then filtered hot and diluted with water. The product which separated crystallised from dilute acetic acid, m.p. 252°. Mixed m.p. with 4,6,8-trimethylcarbostyril prepared according to Kaslow and Sommer[27] was not depressed.

6-Bromo-4-bromoethylcarbostyril :

ω-Bromoacetoacet-p-bromoanilide (3 g.) described earlier was heated with conc.sulphuric acid (6 ml.) for 2 hr. On working up as usual the product which separated

crystallised from acetic acid, m.p. 278°. Yield 1.8 g.

Analysis : Found : Br, 50.17 %.

$C_{10}H_7ONBr_2$ requires : Br, 50.47 %.

6-Bromo-4-methylcarbostyril :

6-Bromo-4-bromomethylcarbostyril (0.5 g.) was refluxed with zinc dust (1 g.) and glacial acetic acid (10 ml.) for half an hour. The reaction mixture was filtered hot and diluted with water. The product which separated crystallised from acetic acid, m.p. 292°. Mixed m.p. with 6-bromo-4-meethylcarbostyril prepared according to Monti and Cirelli[25] was not depressed.

8-Chloro-4-bromomethylcarbostyril :

ω-Bromoacetoacet-o-chloroanilide (3 g.) as described before was cyclised using conc.sulphuric acid (6 ml.). The crude product obtained on addition of water was filtered and crystallised from dilute acetic acid, m.p.218°. Yield 0.8 g.

Analysis : Found : C,44.19 ; H,2.33 ; N,5.34 %.

$C_{10}H_7ONBrCl$ requires : C,44.03 ; H,2.56 ; N,5.13 %.

8-Chloro-4-methylcarbostyril :

The above bromomethyl derivative (0.5 g.) was refluxed with zinc dust (1 g.) and acetic acid (10 ml.). On working up as usual the product crystallised from dilute acetic acid in needles, m.p.228°. Mixed m.p. with 8-chloro-4-methylcarbostyril prepared according to Monti and Cirelli[25] was not depressed.

6-Methyl-4-bromomethylcarbostyril :

ω-Bromoacetoacet-p-toluidide (3 g.) was cyclised using conc.sulphuric acid (6 ml.) and heating it on a water bath for 2 hr. The reaction mixture was poured in ice water and the product which separated crystallised from acetic acid in needles, m.p. 265°. Yield 1.6 g.

Analysis : Found : Br, 32.0 %.

$C_{11}H_{10}ONBr$ requires : Br, 31.75 %.

4,6-Dimethylcarbostyril :

The above bromomethyl derivative (0.5 g.) was refluxed with zinc dust (1 g.) and glacial acetic acid (10 ml.) for half an hour. It was then filtered hot and dilute with water. The product which separated crystallised from dilute acetic acid in needles, m.p. 249°. Mixed m.p. with 4,6-dimethylcarbostyril prepared according to Monti and Cirelli[25] was not depressed.

7,8-Benzo-4-bromomethylcarbostyril :

ω-Bromoacetoacet-α-naphthylamide (3 g.) was heated on a water bath with conc.sulphuric acid (6 ml.) for 2 hr. The reaction mixture was poured in water and the product which separated crystallised from acetic acid in light yellow needles, m.p. 249°. Yield 0.8 g.

Analysis : Found : Br, 27.99 %.

$C_{14}H_{10}ONBr$ requires : Br, 27.79 %.

4-Methyl-7,8-benzocarbostyril :

The above bromomethyl derivative (0.5 g.) was refluxed with zinc dust (1 g.) and glacial acetic acid (10 ml.) for half an hour. The clear filtrate on dilution with water gave the product which was filtered and crystallised from acetic acid in needles, m.p. 292°. Mixed m.p. with 4-methyl-7,8-benzocarbostyril prepared according to Mallams et al.[28] was not depressed.

6-Ethoxy-4-bromomethylcarbostyril :

ω-Bromoacetoacet-p-phenetidide (3 g.) was heated with conc. sulphuric acid (6 ml.) on water bath for 2 hr. On dilution the product which separated crystallised from acetic acid, m.p. 257°. Yield 1 g.

Analysis : Found : Br, 28.03 %.

$C_{12}H_{12}O_2NBr$ requires : Br, 28.37 %.

6-Ethoxy-4-methylcarbostyril :

The above bromomethyl derivative was refluxed with zinc dust (1 g.) and glacial acetic acid (10 ml.) for 40 minutes. The clear filtrate on dilution with water gave the product which was filtered and crystallised from acetic acid, m.p. 232°. Mixed m.p. with 6-ethoxy-4-methyl-carbostyril prepared according to Backeberg[29] was not depressed.

Bromination of 4-methylcarbostyril: 3-Bromo-4-methyl-carbostyril :

4-Methylcarbostyril (1.5 g.) was dissolved in

warm glacial acetic acid (20 ml.) to which bromine in acetic acid (16 ml. ; 10 %) was slowly added with continuous stirring and left overnight. The separated product crystallised from acetic acid in needles, m.p.274°. Yield 1 g.

Analysis : Found : N,5.84 ; Br,33.97 %.
$C_{10}H_8ONBr$ requires : N,5.88 ; Br,33.61 %.

Bromination of 4-methylcarbostyril with N-bromosuccinimide : 4-Bromomethyl-3-bromocarbostyril :

4-Methylcarbostyril (1 g.) suspended in chloroform (30 ml.) was treated with N-bromosuccinimide (3 g.). The reaction mixture was refluxed for 7-8 hr. The separated product was filtered and the residue washed with acetic acid and water. The product crystallised from acetic acid, m.p.303°. Yield 0.5 g.

Analysis : Found : Br, 50.42 %.
$C_{10}H_7ONBr_2$ requires : Br, 50.47 %.

The same dibromo derivative was also obtained when 3-bromo-4-methylcarbostyril (0.5 g.) in chloroform (15 ml.) was treated with N-bromosuccinimide (0.5 g.) and the reaction mixture refluxed on a steam bath for 6 hr.

4-Bromomethylcarbostyril (1.1 g.) in acetic acid (15 ml.) on bromination with bromine (0.8 g.) in acetic acid (8 ml.) also gave the same dibromo derivative.

Bromination of 4,8-dimethylcarbostyril :

4,8-Dimethyl-3-bromocarbostyril :

4,8-Dimethylcarbostyril (1.7 g.) was dissolved in warm glacial acetic acid (20 ml.) to which bromine in acetic acid (16 ml. ; 10 %) was slowly added with continuous stirring. The bromo derivative separated within half an hour. The separated product crystallised from acetic acid, m.p. 241°. Yield 1 g.

Analysis : Found : Br, 31.60%.

$C_{11}H_{10}ONBr$ requires : Br, 31.75 %.

Bromination of 4,8-dimethylcarbostyril with N-bromosuccinimide : 8-Methyl-4-bromomethyl-3-bromocarbostyril :

4,8-Dimethylcarbostyril (1 g.) suspended in chloroform (30 ml.) was treated with N-bromosuccinimide (3 g.). The reaction mixture was refluxed for 7-8 hr. The separated product was filtered and the residue washed with acetic acid and water. The product crystallised from acetic acid, m.p. 315°. Yield 0.5 g.

Analysis : Found : Br, 48.44 %.

$C_{11}H_9ONBr_2$ requires : Br, 48.34 %.

The same dibromo derivative was also obtained when 4,8-dimethyl-3-bromocarbostyril (0.5 g.) in chloroform (15 ml.) was treated with N-bromosuccinimide (0.5 g.) and the reaction mixture refluxed on a steam bath for 6 hr.

8-Methyl-4-bromomethylcarbostyril (0.6 g.) in

acetic acid (10 ml.) on bromination with bromine (0.8 g.) in acetic acid (8 ml.) also gave the same dibromo derivative.

Bromination of 6-methoxy-4-methylcarbostyril :

6-Methoxy-3-bromo-4-methylcarbostyril :

6-Methoxy-4-methylcarbostyril (1.8 g.) was dissolved in glacial acetic acid (15 ml.) and bromine (1.6 g.) in acetic acid (16 ml.) was added. The reaction mixture was kept for 3 hr. The product which separated crystallised from dilute acetic acid, m.p. 260°. Yield 0.9 g.

Analysis : Found : Br, 29.45 %.

$C_{11}H_{10}O_2NBr$ requires : Br, 29.85 %.

Bromination of 4-methyl-7,8-benzocarbostyril :

4-Methyl-7,8-benzo-3-bromocarbostyril :

4-Methyl-7,8-benzocarbostyril (1 g.) in acetic acid (20 ml.) was treated with bromine (0.8 g.) in acetic acid (8 ml.). The reaction mixture was kept for 3 hr. The product which separated crystallised from acetic acid, m.p. 313°. Yield 0.6 g.

Analysis : Found : Br, 27.61 %.

$C_{14}H_{10}ONBr$ requires : Br, 27.79 %.

Bromination of 4,6-dimethylcarbostyril : 4,6-Dimethyl-3-bromocarbostyril :

4,6-Dimethylcarbostyril (1.7 g.) was dissolved in warm glacial acetic acid (25 ml.) to which bromine in

acetic acid (16 ml. ; 10 %) was added and the reaction mixture was kept for 3 hr. The product which separated crystallised from acetic acid, m.p. 294°. Yield 1 g.

Analysis : Found : Br, 31.48 %.

$C_{11}H_{10}ONBr$ requires : Br, 31.75 %.

Bromination of 6-chloro-4-methylcarbostyril : 6-Chloro-4-methyl-3-bromocarbostyril :

6-Chloro-4-methylcarbostyril (1.9 g.) was dissolved in warm glacial acetic acid (25 ml.) to which bromine in acetic acid (16 ml. ; 10 %) was slowly added with continuous stirring. After 12 hr. the separated product was filtered and crystallised from acetic acid, m.p.273°. Yield 1 g.

Analysis : Found : C,44.14 ; H,2.42 ; N,4.76 %.

$C_{10}H_7ONBrCl$ requires : C,44.03 ; H,2.56 ; N,5.13 %.

Bromination of 7-chloro-4-methylcarbostyril : 7-Chloro-4-methyl-3-bromocarbostyril :

7-Chloro-4-methylcarbostyril (1.9 g.) was dissolved in warm glacial acetic acid (25 ml.) and bromine in acetic acid (16 ml. ; 10 %) was added. The reaction mixture was kept for 3 hr. The separated product was filtered and crystallised from dilute acetic acid, m.p. 298°. Yield 1 g.

Analysis : Found : C,44.36 ; H,2.98 ; N,5.08 %.

$C_{10}H_7ONBrCl$ requires : C,44.03 ; H,2.56 ; N,5.13 %.

Bromination of 6-bromo-4-methylcarbostyril : 3,6-Dibromo-4-methylcarbostyril :

6-Bromo-4-methylcarbostyril (2.3 g.) was dissolved in warm acetic acid (25 ml.) and bromine in acetic acid (16 ml. ; 10 %) was slowly added with continuous stirring. The reaction mixture was kept for 3 hr. The product which separated crystallised from glacial acetic acid, m.p.303°. Yield 1 g.

Analysis : Found : Br, 50.03 %.

$C_{10}H_7ONBr_2$ requires : Br, 50.47 %.

Bromination of 4,6,8-trimethylcarbostyril : 4,6,8-Trimethyl-3-bromocarbostyril :

4,6,8-Trimethylcarbostyril (1.8 g.) was dissolved in warm glacial acetic acid (20 ml.) and bromine in acetic acid (16 ml. ; 10 %) was added. The reaction mixture was kept for 6 hr. The product which separated crystallised from alcohol, m.p.272°. Yield 0.9 g.

Analysis : Found : Br, 30.11 %.

$C_{12}H_{12}ONBr$ requires : Br, 30.08 %.

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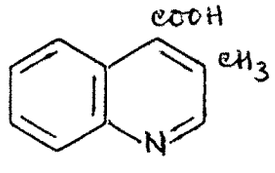
CHAPTER II

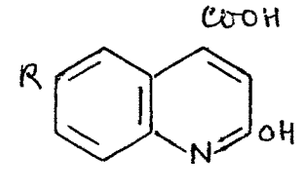
Section II

Syntheses of 2-Hydroxycinchoninic acid derivatives : Theoretical

The present work deals with the synthesis of 2-hydroxycinchoninic acids, it will be, therefore, of interest to review some of the methods for synthesis of cinchoninic acids. Quinoline-4-carboxylic acid (cinchoninic acid) and its derivatives have close relationship to the cinchona alkaloids and to the number of therapeutic agents derived from it. Two derivatives of cinchoninic acid have been isolated from natural sources. Beattie[1] obtained 3-methyl-cinchoninic acid (1) from rue anemone (Syndesmon thalictroides Hoffmg.) which showed marked fasciation. Sahashi[2] obtained 2,6-dihydroxycinchoninic acid (2) from crude oryzanin from rice polishings. Schmid and Karrer[3] isolated 2-hydroxy-cinchoninic acid (3) as natural product from Poppy Straw (Mohnstroh) after removing important alkaloids.



(1)

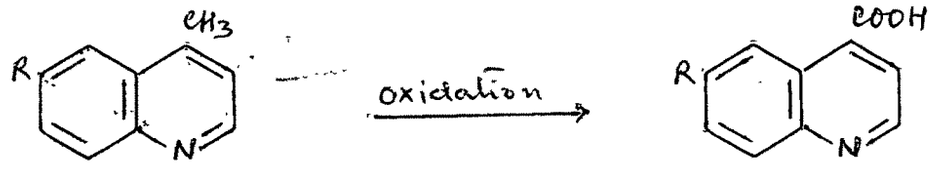


(2), R = OH

(3), R = H

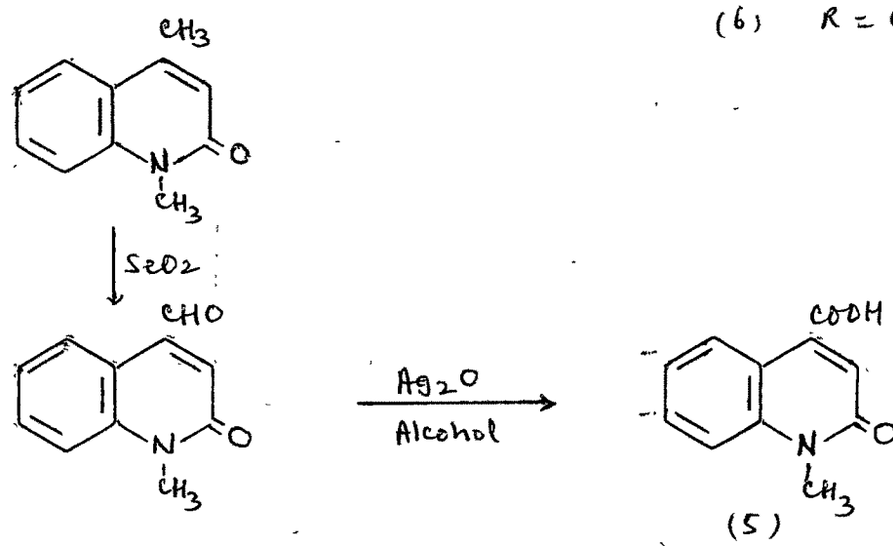
Weidel[4] oxidised lepidine with chromic oxide to cinchoninic acid (4). Ellinger and Flamand[5] obtained it in

better yield by oxidation of 4-vinylquinoline with nitric acid. 1,4-Dimethylcarbostyril with selenium dioxide gave 1-methyl-4-carbostyril carboxaldehyde which with silver oxide and alcohol yielded 1-methyl-4-carbostyril carboxylic acid[6] (5). Similarly 6-chlorolepidine in dioxane gave 6-chlorocinchoninic acid[7] (6).



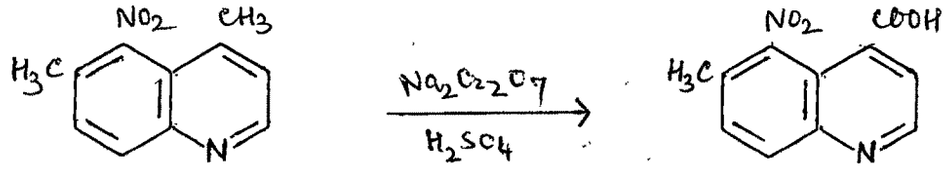
(4) R = H

(6) R = Cl



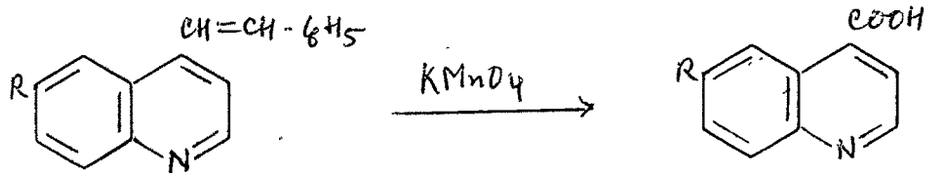
(5)

Marais and Backeberg[8] oxidised 5-nitro-4,6-dimethylquinoline with sodium dichromate and sulphuric acid to 5-nitro-6-methyl-4-quinolinecarboxylic acid (7).



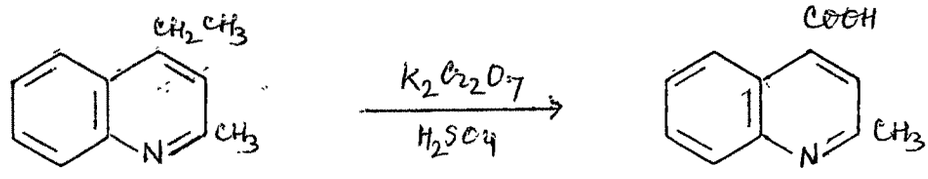
(7)

Oxidation of the 4-styryl derivative of 6-methoxy-quinoline and 6-chloroquinoline with potassium permanganate gave quininic acid[9] (8) and 6-chlorocinchoninic acid[10] (6) respectively in good yield . Renshaw and Friedman[11] decarboxylated 2,4-dicarboxylic acid to cinchoninic acid (3) in boiling nitrobenzene. 4-Ethyl-2-methylquinoline with dichromate and dilute sulphuric acid gave 2-methylcinchoninic acid[12] (9).



(8) R = OCH_3

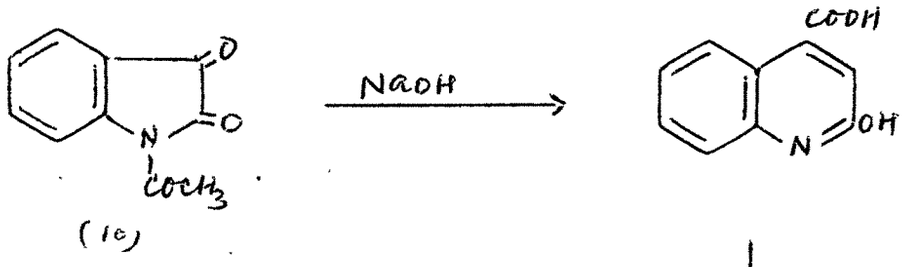
(6) R = Cl

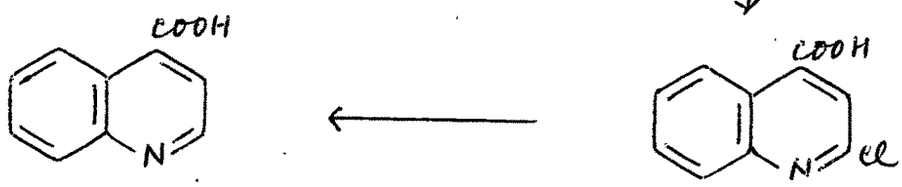


(9)

Camps[13], Ainley and King[14] gave the most convenient and economical method of preparing cinchoninic acid from N-acetylisatin (10). 2-Hydroxycinchoninic acid(3) on treatment with phosphorous oxychloride gave 2-chloro derivative(11) from which the chlorin atom could be removed

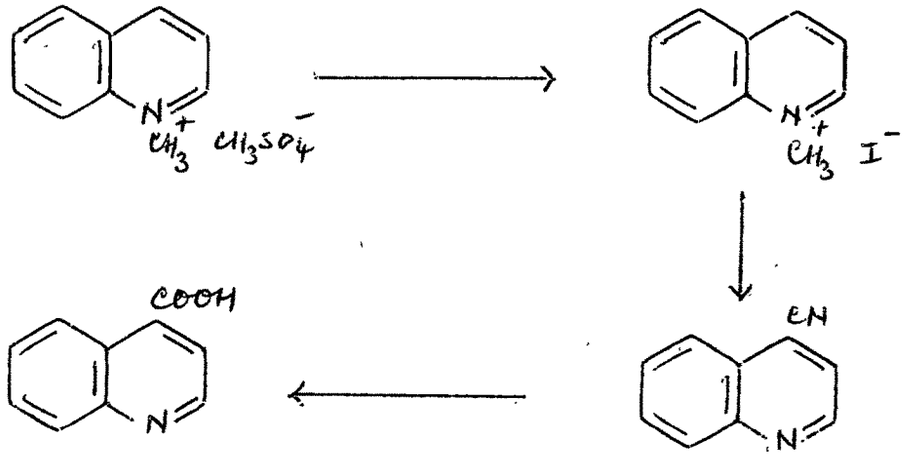
with either a palladium or nickel catalyst.





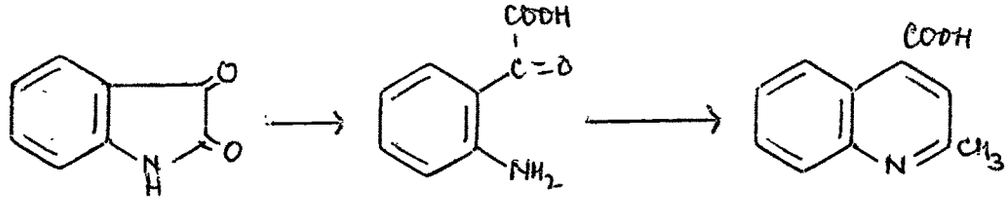
(11)

Kaufmann and coworkers[15a] synthesised cinchoninic acid in good yield by hydrolysing 4-cyanoquinoline which was obtained from methiodide of 4-cyanoquinoline. The latter was prepared by treating quinoline dimethylsulphate with potassium cyanide and subsequent treatment with iodine and pyridine in alcohol.



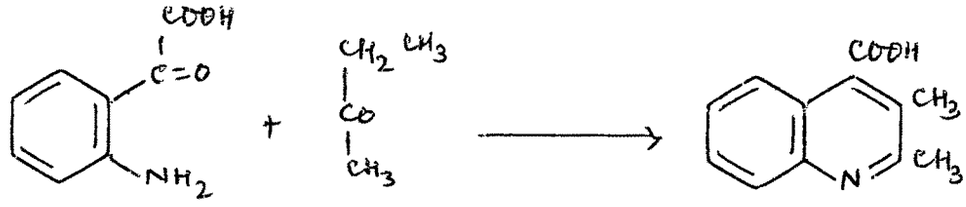
Similarly Kaufmann and Peyer[15b] prepared quininic acid but the yields were not so favourable.

Aeschlimann[16] synthesised 2-hydroxy-3-phenyl-cinchoninic acid by boiling N-phenylacetylisatin with dilute alkali. Pfitzinger[17a] first carried out the reaction in 1886 with isatic acid and ketones to synthesise cichoninic acid, which bears his name, it was not until isatin became available from the oxidation of indigo some eleven years later that the method assumed great importance. The general course of the reaction with acetone is represented as follows :



He also found that methyl ethyl ketone reacts with isatin to give 2,3-dimethylcinchoninic acid[17b] (12). This proved that the methylene group belonging to an ethyl group was far more reactive than the methyl group. Surprisingly this effect was completely reversed in the case of higher homologues of the ethyl radical the methylene group becoming less active than the methyl. Thus isatin reacted with methyl-n-propyl ketone to give

2-n-propyl cinchoninic acid[18] which was previously synthesised in a different way[19]. Symmetrical dialkyl ketones reacted normally, i.e.di-n-propyl ketone and isatic acid gave 3-ethyl-2-n-propylcinchoninic acid.

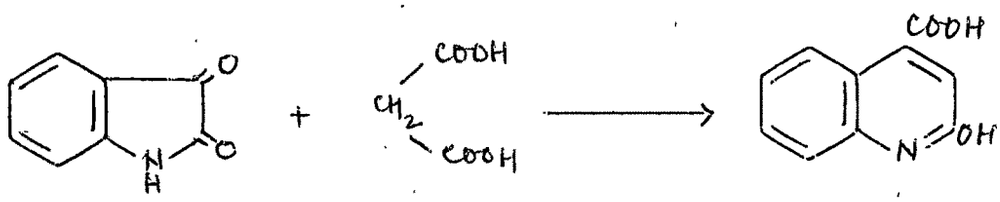


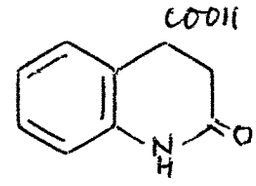
(12)

In later years the Pfitzinger method has been employed for the synthesis of a great variety of cinchoninic acids which showed promise of serving as valuable intermediates in the preparation of the therapeutic agents. Various substitutents in isatin such as alkyl,nitro,chloro,bromo,iodo,fluoro were subjected to the reaction with different types of compounds having ketonic group. A number of heterocyclic ketones were also studied. Only a few illustrative reactions are mentioned here.

Isatin condensed with phenylacetic acid[20] and with its anhydride[21] to give 3-phenylcarbostyril-4-carboxylic acid in each case.[22] This acid was also obtained by the action of hot dilute alkali on 1-phenyl acetylisatin which was prepared by the action of phenylacetyl chloride on 1-sodioisatin. From malonic acid and isatin 2-hydroxycinchoninic acid resulted when

acetic acid was the condensing agent or by the action of heat alone. The acid, on reduction gave the dihydro acid (13) which was identical with the oxindole-3-acetic acid (13) of Granacher and Mahal.[23]

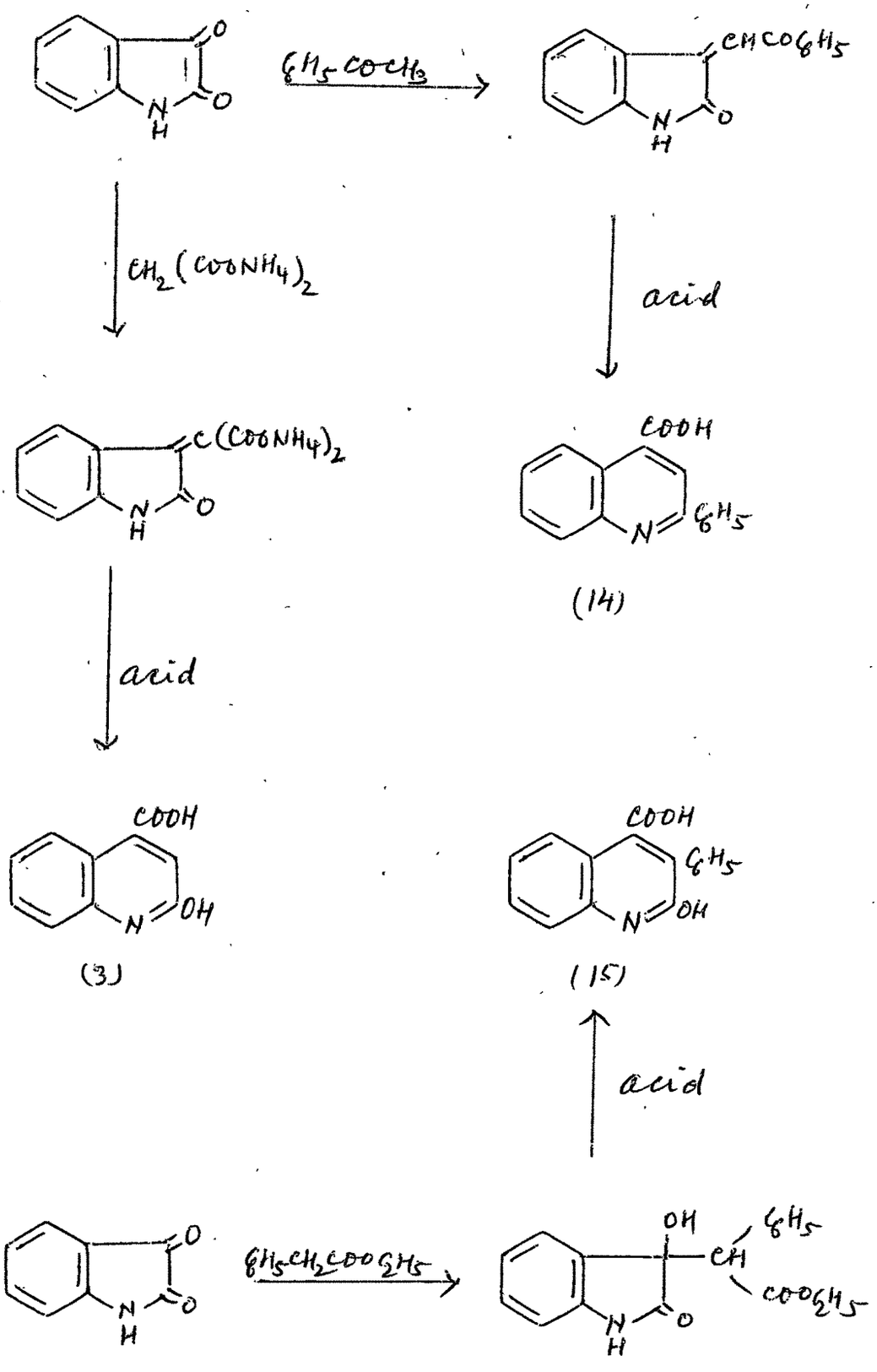




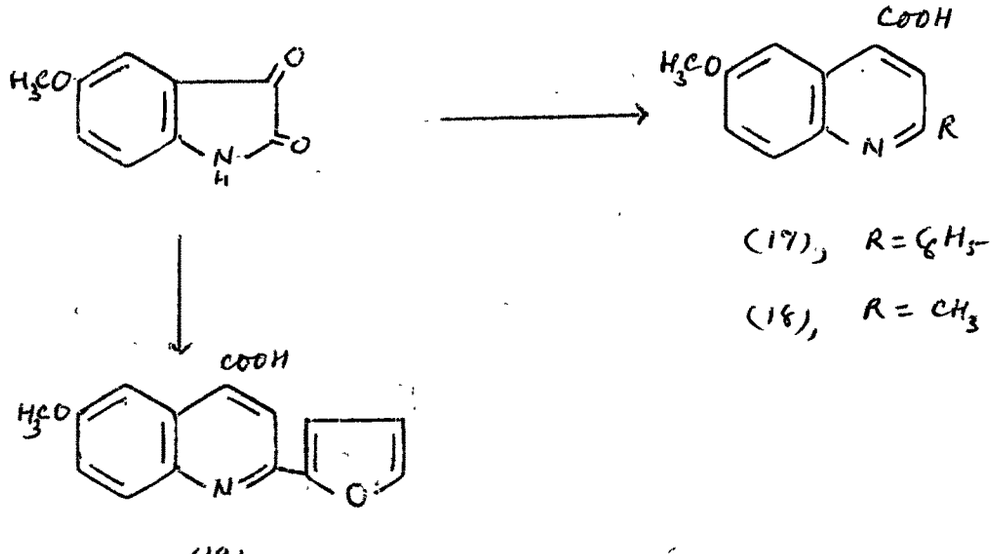
(13)

Lindwall and coworkers[24] condensed isatin with reactive methylene compounds under varying experimental condition. Thus acetophenone gave 2-phenylcinchoninic acid (14), ethylphenyl acetate gave 2-hydroxy-3-phenyl-cinchoninic acid (15) in the presence of diethyl amine while ammonium malonate yielded 2-hydroxycinchoninic acid (3).

Halberkann[25a] reacted 5-methoxyisatin with acetophenone, acetone and α-acetofuran and obtained 6-methoxy-2-phenylcinchoninic acid(17),6-methoxy-2-methyl-(18) and 6-methoxy-2-α-furylcinchoninic acid(19) respectively. He also synthesised the acid (19) from


C6H5COCH3
CH2(COONH4)2
acid
acid
acid
(14)
(3)
(15)

furfural, pyruvic acid and p-anisidine. Carboxylic acids reacted with isatic acid to yield 2-hydroxycinchoninic acid[25b] derivatives (20).

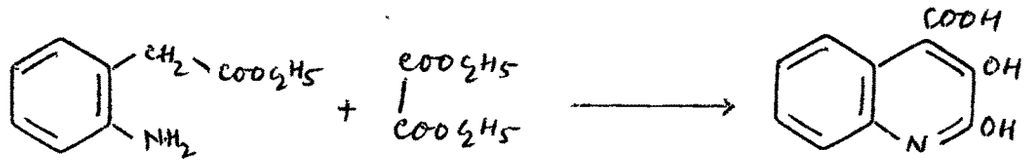


The methods of Lindwall, Bandes and Weinberg[26] for the preparation of 2-arylcinchoninic acids were extended to synthesise a variety of substituted cinchoninic acids.[27;28;29]

Thielepape[30] synthesised 2-hydroxycinchoninic acid from N-methylacetanilide and diethyloxalate.

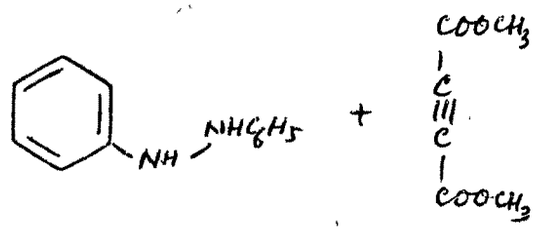
M.Colona[31] synthesised 3-nitrocinchoninic acid from isatin and nitro methane.

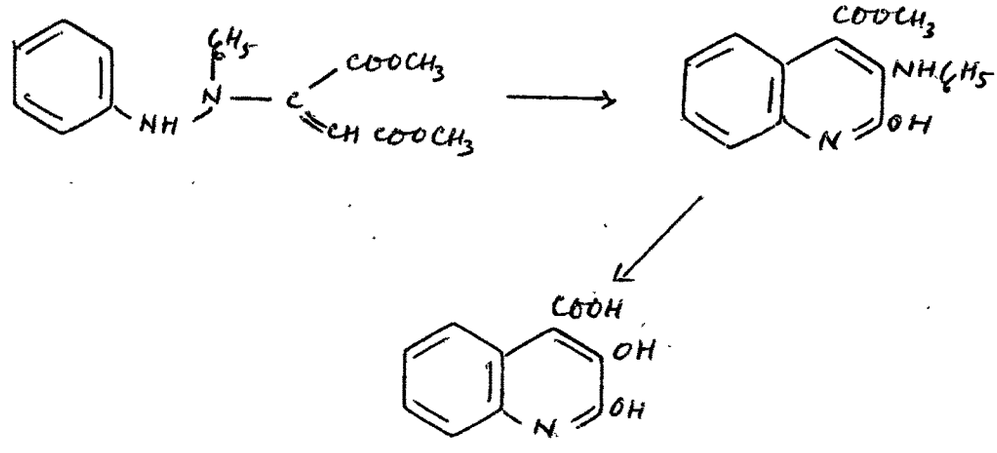
Wislicenus and Bubeck[32] synthesised 2,3-dihydroxy-cinchoninic acid (21) from ethyl o-aminophenyl acetate and diethyloxalate.



(21)

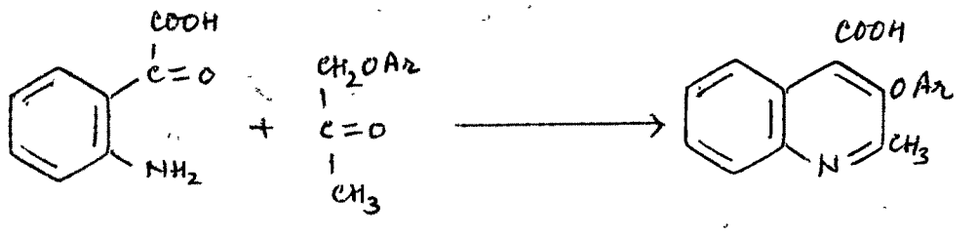
Diels and Reese[33] synthesised the same acid (21) by the following method.





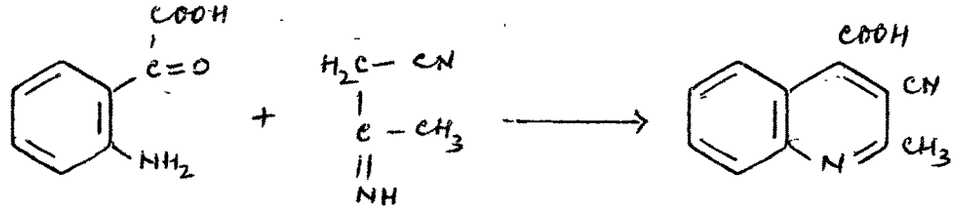
Buu-Hoi and Cagniant[34] synthesised 2-(1-naphthyl),2-(2-naphthyl),2-(2-anthryl),2-(3-pyrenyl), 2-(2-chrysenyl)cinchoninic acids from the appropriate ketones and isatin.

Lesesne and Henze[35] utilised-α-alkoxyketones with isatic acid and isolated the appropriate cinchoninic acid. Similarly Calaway and coworkers[36] condensed isatic acid with a variety of aryloxyketones and obtained 3-aryloxy-2-methylcinchoninic acid(22).



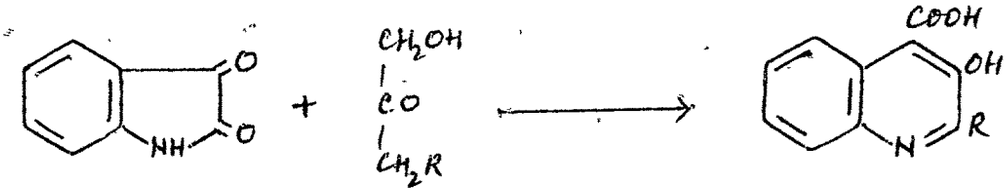
(22)

Walther[37] condensed isatic acid with aceto-dinitrile and obtained 2-methyl-3-cyanocinchoninic acid (23).



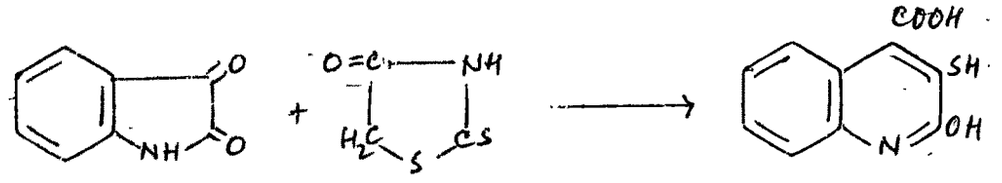
(23)

2-Phenyl-and 2-methyl-3-hydroxycinchoninic acid, which inhibit water diuresis in dogs were prepared as follows[38].



R = CH_3 or C_6H_5

Jones and Henze[39] as well as Granacher and Kouniniotis[40] condensed isatin with rhodanine (24) and obtained a 3-thiol (25) compound.



(24) (25)

Cinchophen, 2-phenylcinchoninic acid also known as atophan was formerly given as an analgesic and antipyretic. It is still used to a limited extent in the treatment of chronic gout. α-Furyl-8-methyl-, -7-methyl- and -6-methylcinchoninic acids[41] were found to be less toxic than atophan.

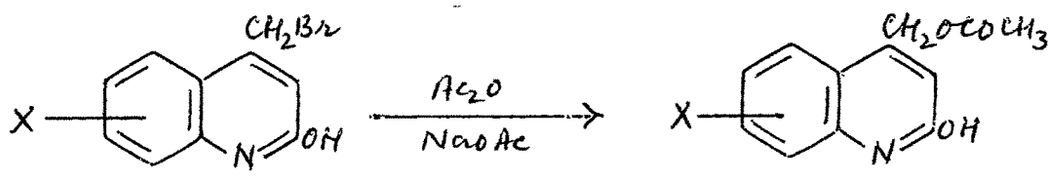
In view of the pharmacological properties of cinchoninic acid derivatives, it was thought of interest to synthesise different cinchoninic acid derivatives having substituents like bromo, chloro, methoxy and methyl groups in the benzenoid part of the quinoline ring system.

In continuation of the work described in section I, an attempt was made to convert direct 4-bromomethylcarbostyril derivative into 2-hydroxycinchoninic acid derivative by oxidation with alkaline potassium permanganate, but it met with failure. Hence these 4-bromomethylcarbostyril derivatives were first converted to 4-acetoxymethyl derivatives (33) by reacting them with acetic anhydride and fused sodium acetate. They were then hydrolysed by aqueous sodium hydroxide to 4-hydroxymethyl derivatives (34) which on oxidation with alkaline potassium permanganate gave 2-hydroxycinchoninic acid derivatives (35). These series of reactions undoubtedly confirmed that bromine is in the side chain and not in 3-position of the quinoline nucleus and at the same time gave a good method for the synthesis of cinchoninic acid derivatives.

General procedure for the preparation of 4-acetoxymethylcarbostyrils from 4-bromomethylcarbostyrils :

The 4-bromomethylcarbostyril described in section I, on treatment with acetic anhydride and freshly fused sodium acetate, gave the acetoxymethyl derivative (33)

on pouring the reaction mixture in ice water.



Using the above procedure, the following 4-acetoxymethylcarbostyril derivatives are prepared.

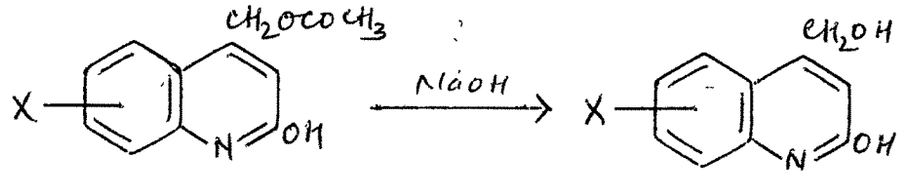
1. 4-Acetoxymethylcarbostyril (33, X = no substituent)
2. 8-Methyl-4-acetoxymethylcarbostyril (33, X=8-methyl)
3. 6-Methoxy-4-acetoxymethylcarbostyril (33, X=6-methoxy)
4. 6-Chloro-4-acetoxymethylcarbostyril (33, X=6-chloro)
5. 7-Chloro-4-acetoxymethylcarbostyril (33, X=7-chloro)
6. 6,8-Dimethyl-4-acetoxymethylcarbostyril (33, X=6,8-dimethyl)
7. 6-Bromo-4-acetoxymethylcarbostyril (33, X=6-bromo)
8. 8-Chloro-4-acetoxymethylcarbostyril (33, X=8-chloro)

Hydrolysis of 4-acetoxymethylcarbostyrils to 4-hydroxymethylcarbostyrils:

The above 4-acetoxymethylcarbostyril was heated on a water bath with aqueous sodium hydroxide. The clear solution on neutralisation with dilute hydrochloric acid gave the hydroxymethyl derivative.

Using the above procedure the following hydroxymethylcarbostyrils are prepared.

1. 4-Hydroxymethylcarbostyril (34, X= no substituent)
2. 8-Methyl-4-hydroxymethylcarbostyril (34, X=8-methyl)
3. 6-Methoxy-4-hydroxymethylcarbostyril (34, X=6-methoxy)
4. 6-Chloro-4-hydroxymethylcarbostyril (34, X=6-chloro)
5. 7-Chloro-4-hydroxymethylcarbostyril (34, X=7-chloro)
6. 6,8-Dimethyl-4-hydroxymethylcarbostyril (34, X=6,8-dimethyl)
7. 6-Bromo-4-hydroxymethylcarbostyril (34, X=6-bromo)
8. 8-Chloro-4-hydroxymethylcarbostyril (34, X=8-chloro)



(33) (34)

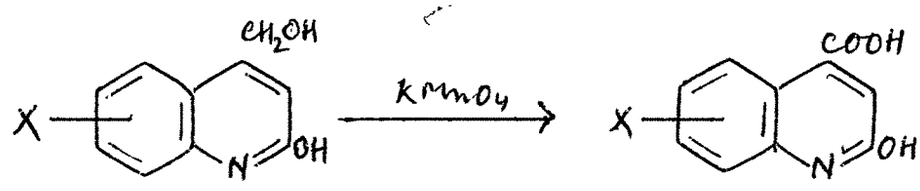
Oxidation of 4-hydroxymethylcarbostyrils to 2-hydroxycinchoninic acids :

The 4-hydroxymethylcarbostyril was treated with alkaline potassium permanganate solution with stirring. The clear filtrate on neutralisation with dilute hydrochloric acid precipitated the cinchoninic acid derivative.

Using the above procedure the following cinchoninic acid derivatives are prepared.

1. 2-Hydroxycinchoninic acid (35, X= no substituent)
2. 8-Methyl-2-hydroxycinchoninic acid (35, X=8-methyl)

3. 6-Methoxy-2-hydroxycinchoninic acid (35, X=6-methoxy)
4. 6-Chloro-2-hydroxycinchoninic acid (35, X=6-chloro)
5. 7-Chloro-2-hydroxycinchoninic acid (35, X=7-chloro)
6. 6,8-Dimethyl-2-hydroxycinchoninic acid (35, X=6,8-dimethyl)
7. 6-Bromo-2-hydroxycinchoninic acid (35, X=6-bromo)
8. 8-Chloro-2-hydroxycinchoninic acid (35, X=8-chloro)



(34) (35)

EXPERIMENTAL

4-Acetoxymethylcarbostyril :

4-Bromomethylcarbostyril (1 g.) was treated with acetic anhydride (5 ml.) and fused sodium acetate (1.5 g.) and refluxed for 2 hr. It was poured over ice water with stirring. The separated product was filtered and crystallised from alcohol in shining needles, m.p.212°. Yield 0.7 g. Cook et al.[42] reported the same m.p.

4-Hydroxymethylcarbostyril :

4-Acetoxymethylcarbostyril (1 g.) was treated with potassium hydroxide solution (50 ml. ; 10 %) and heated on a water bath for 6 hr. The clear solution on neutralisation with dilute hydrochloric acid gave 4-hydroxymethylcarbostyril which crystallised from alcohol, m.p. 271-2°. Yield 0.7 g. Cook et al.[42] obtained the same m.p.

2-Hydroxycinchoninic acid : Oxidation of 4-hydroxymethylcarbostyril with alkaline potassium permanganate :

The above hydroxy methyl derivative (1.5 g.) was dissolved in warm sodium hydroxide solution (60 ml. ; 10 %) . Potassium permanganate (5 g.) in about 50 ml. of water was added and stirred machanically for 2 hr at room temperature and left overnight. It was then filtered and the clear filtrate on neutralisation with dilute hydrochloric acid gave the product which was filtered and

purified by treatment with sodium bicarbonate solution. It crystallised from alcohol, m.p.318° which after drying at 110° for 4 hr. in vacuum gave m.p.338°. Yield 0.5 g. Jacobs et al.[43] who prepared the same acid by treating 1-acetylisatin with sodium hydroxide has reported the m.p.343°.

Analysis : Found : C,63.24 ; H,3.56 ; N,7.14 %.
Calculated for $C_{10}H_7O_3N$: C,63.49 ; H,3.70 ; N,7.04 %.

8-Methyl-2-hydroxycinchoninic acid

8-Methyl-4-acetoxymethylcarbostyril → continued on page 154

Continued from page 154 → 8-Methyl-4-~~hydr~~-acetoxymethylcarbostyril (1 g.) was treated with aqueous sodium hydroxide (50 ml. ; 10 %) and heated on a water bath for 6 hr. The clear solution on neutralisation with dilute hydrochloric acid gave the product which was filtered and crystallised from alcohol, m.p.260°. Yield 0.6 g.

Analysis : Found : C,69.17 ; H,6.22 %.
$C_{11}H_{10}O_2N$ requires : C,69.46 ; H,6.31 %.

Oxidation of 8-methyl-4-hydroxymethylcarbostyril with alkaline potassium permanganate : 8-Methyl-2-hydroxy-cinchoninic acid :

The above hydroxymethyl derivative (1.5 g.) was dissolved in warm aqueous sodium hydroxide (60 ml. ; 10 %). To this was added potassium permanganate (5 g.) in about 50 ml. of water portion wise. It was stirred mechanically for 2 hr. and left overnight. Next day it was filtered

and the clear filtrate on neutralisation with dilute hydrochloric acid gave the product which was purified by treatment with sodium bicarbonate solution. It crystallised from alcohol, m.p.323° which after drying at 110° for 4 hr. in vacuum gave m.p.335°. Yield 0.3 g.

Analysis : Found : C,64.91 ; H,4.27 ; N,6.41 %.

$C_{11}H_9O_3N$ requires : C,65.02 ; H,4.43 ; N,6.89 %.

6-Methoxy-2-hydroxycinchoninic acid

6-Methoxy-4-acetoxymethylcarbostyril :

6-Methoxy-4-bromomethylcarbostyril (1 g.) was treated with acetic anhydride (8 ml.) and freshly fused sodium acetate (1 g.) and refluxed on a wire gauze for 2 hr. It was poured over ice water with stirring. The separated acetoxymethyl derivative was filtered and crystallised from benzene in shining needles, m.p.215°. Yield 0.6 g.

Analysis : Found : C,63.09 ; H,5.18 %.

$C_{13}H_{13}O_4N$ requires : C,63.16 ; H,5.26 %.

6-Methoxy-4-hydroxymethylcarbostyril :

The above acetoxymethyl derivative (1 g.) was treated with sodium hydroxide solution (50 ml. ; 10 %) and heated on a water bath for 4 hr. The clear solution was neutralised and the product which separated crystallised from alcohol, m.p.252°. Yield 0.7 g.

Analysis : Found : C,64.22 ; H,5.05 %.

$C_{14}H_{11}O_2N$ requires : C,64.39 ; H,5.36 %.

Oxidation of 6-methoxy-4-hydroxymethylcarbostyril with alkaline potassium permanganate : 6-Methoxy-2-hydroxycinchoninic acid :

6-Methoxy-4-hydroxymethylcarbostyril (1.5 g.) was dissolved in aqueous sodium hydroxide (60 ml. ; 10 %) and potassium permanganate (5 g.) in 60 ml. of water was added portion wise during 2 hr. with mechanical stirring. Next day it was filtered and clear filtrate after concentration was neutralised with dilute hydrochloric acid. The separated product was purified by treatment with sodium bicarbonate solution and then crystallised from alcohol in light yellow needles, m.p. 323°. M.P. after drying at 110° for 4 hr. in vacuum was 334°. Yield 0.3 g.

Analysis : Found : C, 60.23 ; H, 4.55 ; N, 6.16 %.

$C_{11}H_9O_4N$ requires : C, 60.30 ; H, 4.11 ; N, 6.39 %.

6-Chloro-2-hydroxycinchoninic acid

6-Chloro-4-acetoxymethylcarbostyril :

6-Chloro-4-bromomethylcarbostyril (1 g.) was treated with acetic anhydfide (10 ml.) and freshly fused sodium acetate (1.5 g.) and refluxed for 2 hr. On working up as usual the separated product crystallised from alcohol, m.p. 224°. Yield 0.6 g.

Analysis : Found : C, 52.90 ; H, 4.48 %.

$C_{12}H_{10}O_3NCl$ requires : C, 52.74 ; H, 4.39 %.

6-Chloro-4-hydroxymethylcarbostyril :

The above acetoxymethyl derivative (1 g.) was

treated with aqueous sodium hydroxide (40 ml. ; 10 %) and heated on a water bath for 4 hr. The clear solution was neutralised with hydrochloric acid. The product which separated crystallised from acetic acid in needles, m.p. 309°. Yield 0.6 g.

Analysis : Found : C,57.56 ; H,3.81 %.
$C_{10}H_8O_2NCl$ requires : C,57.28 ; H,3.81 %.

Oxidation of 6-chloro-4-hydroxymethylcarbostyril with alkaline potassium permanganate : 6-Chloro-2-hydroxycinchoninic acid :

The above hydroxymethyl derivative (1.5 g.) was dissolved in warm aqueous sodium hydroxide (60 ml. ; 10 %). Potassium permanganate (5 g.) in about 50 ml. of water was added in portions during 1.5 hr. of mechanical stirring at room temperature and left overnight. The clear filtrate was neutralised with dilute hydrochloric acid and the separated acid was purified by treatment with sodium bicarbonate solution. It crystallised from alcohol, m.p. 344°. M.P. after heating in vacuum at 110° for 4 hr. was 370-2°. Yield 0.5 g.

Analysis : Found : C,53.48 ; H,2.21 ; Cl,15.69 %.
$C_{10}H_6O_3NCl$ requires : C,53.69 ; H,2.68 ; Cl,15.88 %.

7-Chloro2-hydroxycinchoninic acid

7-Chloro-4-acetoxymethylcarbostyril :

7-Chloro-4-bromomethylcarbostyril (1 g.) was treated with acetic anhydride (10 ml.) and freshly fused

sodium acetate (1.5 g.) and refluxed on sand bath for 2 hr. The acetoxymethyl derivative obtained on working up as usual crystallised from acetic acid, m.p.239°. Yield 0.6 g.

Analysis	: Found	: C,52.55 ; H,4.37 %.
$C_{12}H_{10}O_3NCl$	requires	: C,52.74 ; H,4.39 %.

7-Chloro-4-hydroxymethylcarbostyril :

The above acetoxymethyl derivative (1 g.) was treated with sodium hydroxide solution (50 ml. ; 10 %) and heated on a water bath for 5 hr. The clear solution was neutralised with hydrochloric acid. The product which separated crystallised from alcohol, m.p.303°. Yield 0.6 g.

Analysis	: Found	: C,57.11 ; H,3.66 %.
$C_{10}H_8O_2NCl$	requires	: C,57.28 ; H,3.81 %.

Oxidation of 7-chloro-4-hydroxymethylcarbostyril with alkaline potassium permanganate : 7-Chloro-2-hydroxycinchoninic acid :

The above hydroxymethyl derivative (1.5 g.) was dissolved in aqueous sodium hydroxide (60 ml. ; 10 %) and potassium permanganate (5 g.) in about 50 ml. water was added portion wise. It was stirred mechanically for 2 hr. and left overnight. On working up as usual the acid crystallised from dilute acetic acid, m.p.331°. Melting point after heating in vacuum at 110° for 4 hr. was 342-4°. Yield 0.5 g.

Analysis	: Found	: C,53.61 ; H,2.51 ; Cl,16.30 %.
$C_{10}H_6O_3NCl$	requires	: C,53.69 ; H,2.68 ; Cl,15.88 %.

6,8-Dimethyl-2-hydroxycinchoninic acid :
6,8-Dimethyl-4-acetoxymethylcarbostyril :

6,8-Dimethyl-4-bromomethylcarbostyril (1 g.) was treated with acetic anhydride (10 ml.) and freshly fused sodium acetate (1.5 g.). It was refluxed for 2 hr. and poured over ice water. The product which separated crystallised from benzene, m.p.224°. Yield 0.7 g.

Analysis	: Found	: C,68.44 ; H,6.03 %.
$C_{14}H_{15}O_3N$	requires	: C,68.56 ; H,6.12 %.

6,8-Dimethyl-4-hydroxymethylcarbostyril :

The above acetoxymethyl derivative (1 g.) was treated with sodium hydroxide solution (60 ml. ; 10 %) and heated on a water bath for 6 hr. On working up as usual the product crystallised from alcohol, m.p.258°. Yield 0.6 g.

Analysis	: Found	: C,70.89 ; H,6.22 %.
$C_{12}H_{12}O_2N$	requires	: C,70.97 ; H,6.40 %.

Oxidation of 6,8-dimethyl-4-hydroxymethylcarbostyril with alkaline potassium permanganate : 6,8-Dimethyl-2-hydroxycinchoninic acid :

The above hydroxymethyl derivative (1.5 g.) was dissolved in sodium hydroxide solution (50 ml. ; 10 %) and potassium permanganate (3 g.) in 50 ml. water was added and stirred for 2 hr. On working up as usual the acid crystallised from glacial acetic acid, m.p.372-5°.

M.P. after heating in vacuum at 110° for 4 hr. was 396-400°(decomp.). Yield 0.3 g.

Analysis	: Found	: C,66.27 ; H,4.92 ; N,6.10 %.
$C_{12}H_{11}O_3N$	requires	: C,66.34 ; H,5.06 ; N,6.45 %.

6-Bromo-2-hydroxycinchoninic acid

6-Bromo-4-acetoxymethylcarbostyril :

6-Bromo-4-bromomethylcarbostyril (1 g.) was refluxed with acetic anhydride (10 ml.) and freshly fused sodium acetate (1.5 g.) for 2 hr. On working up as usual the product which separated crystallised from acetic acid, m.p.219°. Yield 0.7 g.

Analysis	: Found	: C,48.99 ; H,3.72 %.
$C_{12}H_{10}O_3NBr$	requires	: C,48.65 ; H,3.33 %.

6-Bromo-4-hydroxymethylcarbostyril :

The above acetoxymethyl derivative (1 g.) was heated on a water bath with sodium hydroxide solution (50 ml. ; 10 %) . On working up as usual the product which separated crystallised from alcohol,m.p.315°. Yield 0.6 g.

Analysis	: Found	: C,47.70 ; H,3.16 %.
$C_{10}H_8O_2NBr$	requires	: C,47.25 ; H,3.15 %.

Oxidation of 6-bromo-4-hydroxymethylcarbostyril with alkaline potassium permanganate : 6-Bromo-2-hydroxycinchoninic acid :

The above hydroxymethyl derivative (1.5 g.) was dissolved in sodium hydroxide solution (60 ml. ; 10 %)

and potassium permanganate (5 g.) in 50 ml. water was added. It was stirred for 2 hr. and left overnight. On working up as usual the acid crystallised from alcohol, m.p.356°. M.P. after heating in vacuum at 110° for 4 hr. was 367-8°. Yield 0.4 g.

Analysis : Found : C,44.51 ; H,2.22 ; Br,29.40 %.
$C_{10}H_6O_3NBr$ requires : C,44.78 ; H,2.24 ; Br,29.71 %.

8-Chloro-2-hydroxycinchoninic acid

8-Chloro-4-acetoxymethylcarbostyril :

8-Chloro-4-bromomethylcarbostyril (1 g.) was refluxed with acetic anhydride (10 ml.) and fused sodium acetate (1.5 g.) for 2 hr. On working up as usual the product which separated crystallised from dilute acetic acid in needles,m.p.200-2°. Yield 0.7 g.

Analysis : Found : C,52.57 ; H,4.68 %.
$C_{12}H_{10}O_3NCl$ requires : C,52.74 ; H,4.39 %.

8-Chloro-4-hydroxymethylcarbostyril :

The above acetoxymethyl derivative (1 g.) was heated on a water bath with sodium hydroxide solution (50 ml. ; 10 %) for 4 hr. On working up as usual the product which separated crystallised from alcohol,m.p. 244°. Yield 0.7 g.

Analysis : Found : C,57.28 ; H,4.09 %.
$C_{10}H_8O_2NCl$ requires : C,57.28 ; H,3.81 %.

Oxidation of 8-chloro-4-hydroxymethylcarbostyril with alkaline potassium permanganate : 8-Chloro-2-hydroxycinchoninic acid :

The above hydroxymethyl derivative (1.5 g.) was dissolved in sodium hydroxide solution (60 ml. ; 10 %) and potassium permanganate (4 g.) in 50 ml. water was added and stirred for 2 hr. On working up as usual the product which separated crystallised from acetic acid, m.p.344-6°. M.P. after heating in vacuum at 110° for 4 hr. was 360-2°. Yield 0.4 g.

Analysis	: Found	: C,53.44 ; H,2.55 ; Cl,15.44 %.
$C_{10}H_6O_3NCl$	requires	: C,53.69 ; H,2.68 ; Cl,15.88 %.

8-Methyl-4-acetoxymethylcarbostyril :

continued from page 146 → 8-Methyl-4-bromomethylcarbostyril was treated with acetic anhydride (8 ml.) and freshly fused sodium acetate (1.5 g.) and was refluxed for 2 hr. It was poured over ice water with stirring. The separated product was filtered and crystallised from alcohol, m.p. 234°. Yield 0.7 g.

Analysis	: Found	: C,67.44 ; H,5.88 ; N,5.96 %.
$C_{13}H_{13}O_3N$	requires	: C,67.53 ; H,6.06 ; N,5.62 %.

8-Methyl-4-hydroxymethylcarbostyril → continued on page 146

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