SUMMARY

Studies in the synthesis of quinoline derivatives

Quinoline derivatives are found to occur in nature in the form of alkaloids, in coal tar and in petroleum. Many furoquinoline derivatives are isolated from Australian plant species. Quinine was the standard drug for the suppression and treatment of malaria for centuries. Chloroquine, camoquin etc. are examples of synthetic drugs.

The present work was undertaken with a view to synthesise furoquinolines from suitably substituted quinoline derivatives, to synthesise quinolino-lactone derivatives and pyranoquinolines, to study the pattern of substitution in the bromination of acetoacetarylamides and their subsequent cyclisation to 2-hydroxyquinoline derivatives and to study the reactivity of 4-bromomethylquinoline derivatives.

In chapter I, section I, the synthesis of furo (3,2-c)quinoline and furo(2,3-b)quinoline derivatives has been described.

2-Methyl-3-allyl-4-hydroxyquinoline was subjected to ozonolysis to give2-methyl-3-acetaldehydo-4-methyl-quinoline. This was then cyclised with polyphosphoric acid to 4-methylfuro(3,2-c)quinoline. 2,8-Dimethyl-4-hydroxy-quinoline on allylation and migration gave 3-allyl derivative which on ozonolysis and hydrogenation with palladised charcoal gave 2,8-dimethyl-3-acetaldehydo-4-

hydroxyquinoline. This on cyclisation with polyphosphoric acid gave 4,6-dimethyl furo(3,2-c)quinoline. 6-Methoxy-2-methyl-3-allyl-4-hydroxyquinoline on a similar series of reaction gave 8-methoxy-4-methyl furo(3,2-c)quinoline.

Another method which has been used for building up of unsubstituted furan ring makes the use of o-hydroxy-aldehydes with ethyl bromoacetate or ethyl bromomalanate. 2-Methyl-3-formyl-4-hydroxyquinoline was condensed with ethyl bromoacetate to give 2-methyl-3-formyl-4-carboethoxy-methoxyquinoline from which 4-methyl furo(3,2-c)quinoline can be prepared by hydrolysis followed by ring closure with acetic anhydride and fused sodium acetate. But on hydrolysis the condensed product failed to give the corresponding acid derivative and gave the original 4-hydroxyquinoline derivative back. 2,8-Dimethyl-3-formyl-4-hydroxyquinoline was prepared by Reimer-Tiemann reaction on 2,8-dimethyl-4-hydroxyquinoline and was condensed with ethyl bromoacetate, but on hydrolysis it also gave the original product.

2-Methyl-3-formyl-4-hydroxyquinoline on condensation with ethyl bromomalonate in the presence of anhydrous potassium carbonate in refluxing ethyl methyl ketone for 35 hr. gave 4-methyl-2-carboethoxy furo(3,2-c)quinoline which was hydrolysed with alcoholic potassium hydroxide to 4-methyl furo(3,2-c)quinoline-2-carboxylic acid. This underwent decarboxylation when heated with copper bronze above its melting point and gave the same 4-methyl furo-(3,2-c)quinoline described earlier. Similarly 2,8-dimethyl-3-formyl-4-hydroxyquinoline on condensation with

ethyl bromomalonate gave 4,6-dimethyl-2-carboethoxy furo (3,2-c)quinoline which on hydrolysis and subsequent decarboxylation gave 4,6-dimethyl furo(3,2-c)quinoline which was compared with the product prepared by ozonolysis method. 8-Methoxy-4-methyl furo(3,2-c)quinoline was also prepared by this route and was found to be identical on comparison with the product obtained earlier from ozonolysis method. IR spectra of 2-carboethoxy furo(3,2-c)quinoline derivatives showed the characteristic ester carbonyl band at 1730 cm^{-1}.

In view of the fact that naturally occurring furoquinoline derivatives have furo(2,3-b)quinoline structure, it was thought of interest to study these reactions with 4-methylcarbostyril. But 4-methylcarbostyril neither gave 3-formyl nor 3-allyl derivative, therefore, α-allyl derivatives of acetoacetarylamides were prepared. α-Allylacetoacetanilide on ozonolysis followed by hydrogenation failed to give corresponding acetaldehydo derivative but instead α-propyl derivative was obtained which was also prepared by hydrogenation in the presence of palladised charcoal. This on cyclisation with sulphuric acid gave 2-methyl-3-propyl-4-hydroxyquinoline. Similarly 2,8-dimethyl-3-propyl-,6-methoxy-2-methyl-3-propyl-4-hydroxyquinolines were prepared.

α-Allylacetoacetanilide on cyclisation with concentrated sulphuric acid gave 2,3-dihydro-2,4-dimethyl furo(2,3-b)quinoline. Using this procedure few unknown dihydro furo(2,3-b)quinoline derivatives were prepared in

the present work. Thus 2,3-dihydro-2,4-dimethyl-benzo(h)-, -2,4,8-trimethyl-, -2,4,5,8-tetramethyl-, -6-methoxy-2, 4-dimethyl-, and -6-chloro-2,4-dimethyl furo(2,3-b)quinoline derivatives were prepared from the corresponding α-allyl-acetoacetarylamides. 2,3-Dihydro-2,4,6-trimethyl furo (3,2-c)quinoline and 2,3-dihydro-2,4-dimethyl-benzo(h) furo(3,2-c)quinoline were also prepared using sulphuric acid as cyclising agent from 2,8-dimethyl-3-allyl-4-hydroxyquinoline and 2-methyl-3-allyl-4-hydroxy-benzo(h) quinoline respectively.

Condensation of sodium salt of acetoacetanilide with ethyl bromoacetate gave a product which on cyclisation with concentrated sulphuric acid afforded 4-methyl-2-hydroxyquinoline-3-acetic acid. This on heating with acetic anhydride gave a lactone of 4-methyl-2-hydroxyquinoline-3-acetic acid. In this manner 4,8-dimethyl-, 4,6-dimethyl-, 4,6,8-trimethyl- and 7,8-benzo-4-methylquinolino-lactones were prepared. This work is incorporated in sec. II. IR spectra of few lactone derivatives were also studied. Sodium salt of acetoacetanilide was condensed with ethyl bromopropionate, which after cyclisation with sulphuric acid gave 4-methyl-2-hydroxyquinoline-3-propionic acid. Cyclisation of this to a lactone was unsuccessful. In a similar manner 4,8-dimethyl and 4,6-dimethyl-2-hydroxy-quinoline-3-propionic acids were prepared. 2-Methyl-3-formyl-4-hydroxyquinoline and 2,8-dimethyl-3-formyl-4-hydroxyquinoline on Perkin reaction with acetic anhydride and triethylamine gave 5-methyl- and 5,8-dimethyl-2-oxo-

2H-pyrano(3,2-c)quinoline derivatives respectively. When phenylacetic acid was used in this reaction the corresponding 3-phenyl derivatives were obtained. These structures were supported by IR spectra.

Chapter II, section I deals with the synthesis of bromoquinolines. Acetoacetanilide on bromination with bromine in acetic acid as well as with bromine in chloroform gave ω-bromoacetoacetanilide. The structure was confirmed by NMR spectrum. ω-Bromoacetoacetanilide on cyclisation with sulphuric acid gave 4-bromomethylcarbostyril. In a similar manner acetoacet- (i) o-toluidide, (ii) p-anisidide, (iii) p-chloroanilide, (iv) m-chloroanilide, (v) m-xylidide, (vi) p-bromoanilide, (vii) o-chloroanilide, (viii) α-naphthylamide, (ix) p-phenetidide and (x) p-toluidide were brominated and ω-bromo derivatives were obtained. All these ω-bromo derivatives were cyclised with concentrated sulphuric acid to the corresponding 4-bromomethylcarbostyril derivatives.

4-Methyl, 4,8-dimethyl, 6-methoxy-4-methyl, 6-chloro-4-methyl and 6-bromo-4-methylcarbostyril derivatives were brominated to the corresponding 3-bromo derivatives with bromine in acetic acid and were found to be different from 4-bromomethylcarbostyril derivatives.

4-Methylcarbostyril on treatment with excess of N-bromosuccinimide gave 3-bromo-4-bromomethylcarbostyril which was identical with the product obtained on bromination of 4-bromomethylcarbostyril with bromine in acetic acid.

In a similar manner 8-methyl-3-bromo-4-bromomethylcarbostyril was also prepared.

Chapter II, section II is the continuation of the work carried out in section I. 4-Bromomethylcarbostyril on treatment with acetic anhydride and fused sodium acetate gave 4-acetoxymethylcarbostyril. This was then hydrolysed with aqueous sodium hydroxide to 4-hydroxymethylcarbostyril which on oxidation with alkaline potassium permanganate gave 2-hydroxycinchoninic acid. This series of reactions undoubtedly confirmed the structure of 4-bromomethylcarbostyril and at the same time gave a good method for the preparation of 2-hydroxycinchoninic acid.

Using this procedure 8-methyl, 6-methoxy, 6,8-dimethyl, 6-chloro, 6-bromo, 7-chloro and 8-chloro-2-hydroxycinchoninic acids were prepared.

In chapter III, the reactivity of 4-bromomethylcarbostyril derivatives prepared in chapter II section I has been studied.

In section I, various Mannich bases were prepared by condensing primary and secondary amines with 4-bromomethylcarbostyril derivatives. 4-Bromomethylcarbostyril on treatment with dimethylamine, piperidine and morpholine in alcohol gave the corresponding 4-dimethylaminomethyl, 4-piperidinomethyl and 4-morpholinomethyl derivatives. This reaction was studied by taking different substituents such as methyl, methoxy, chloro and bromo in benzene nucleus of the quinoline ring system. This reaction was

also extended to the primary amine such as aniline and sulphanilamide.

Section II deals with the synthesis of 1,2-bis (2-chloro-4-quinolyl)ethane derivatives. 4-Bromomethylcarbostyril on treatment with potassium cyanide in alcohol gave 1-cyano-1,2-bis (2-hydroxy-4-quinolyl)ethane which on treatment with phosphorus oxychloride gave the corresponding 2-chloro derivative. The structure was supported by IR and NMR spectra. 4-Bromomethylcarbostyril on treatment with phosphorus oxychloride gave dichloro derivative to which 2-chloro-4-chloromethylquinoline structure was assigned on the basis of analytical results. This on refluxing with alcoholic potassium cyanide gave a product identical with the one described above.

1-Cyano-1,2-bis (2-chloro-4-quinolyl)ethane on hydrolysis with 70 % sulphuric acid gave directly 1,2-bis (2-chloro-4-quinolyl)ethane. This was also prepared by treating 1-cyano-1,2-bis(2-hydroxy-4-quinolyl)ethane with 70 % sulphuric acid followed by reaction with excess of phosphorus oxychloride.

Similarly 8-methyl-4-bromomethylcarbostyril on refluxing with potassium cyanide in alcohol gave 1-cyano-1,2-bis(8-methyl-2-hydroxy-4-quinolyl)ethane which was converted into 1-cyano-1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane by treatment with phosphorus oxychloride. This was also obtained by subjecting 8-methyl-4-bromomethylcarbostyril to first with phosphorus oxychloride followed by treatment with alcoholic potassium cyanide. The product was found identical on direct comparison.

Again 1-cyano-1,2-bis(8-methyl-2-chloro-4-quinolyl) ethane with 70 % sulphuric acid gave 1,2-bis(8-methyl-2-chloro-4-quinolyl)ethane which was identical with the product obtained from 1-cyano-1,2-bis(8-methyl-2-hydroxy-4-quinolyl)ethane by reacting it first with 70 % sulphuric acid to give 1,2-bis(8-methyl-2-hydroxy-4-quinolyl)ethane followed by treatment with phosphorus oxychloride.

Using these procedures, 1,2-bis(2,6-dichloro-4-quinolyl)ethane and 1,2-bis(6-bromo-2-chloro-4-quinolyl) ethane have been prepared from 6-chloro-4-bromomethyl-carbostyril and 6-bromo-4-bromomethylcarbostyril respectively.

In section III, the condensation of 2-chloro-4-chloromethylquinoline with sodiomalonic ester is described. The product obtained is assigned 2,2-dicarboethoxy-1,3-bis(2-chloro-4-quinolyl)propane structure which is supported by NMR spectrum. On hydrolysis, it gave 2-carboxy-1,3-bis (2-chloro-4-quinolyl)propane. This when refluxed with alcoholic potassium hydroxide gave 2-carboxy-1,3-bis (2-ethoxy-4-quinolyl)propane wherein 2-chloro group has been replaced by an ethoxy group.

8-Methyl-2-chloro-4-chloromethylquinoline on a similar condensation with sodio malonic ester gave 2,2-dicarboethoxy-1,3-bis(8-methyl-2-chloro-4-quinolyl)propane which on hydrolysis afforded 2-carboxy-1,-3-bis(8-methyl-2-chloro-4-quinolyl)propane.