PART I

Syntheses of 4-(1-imidazolyl) quinolines

Chloroquin, a 4-substituted-7-chloroquinoline, possesses antiamebic activity (118). 8-Hydroxyquinolines have variable antiamebic and trichomonacidal activity (119). These effects may be either due to chelation with ferrous iron necessary for the growth of amebae (120) or for killing amebae by inhibiting the supporting micro-organisms or by direct action (14). Metronidazole also is a direct acting antiamebic agent and it possesses high antitrichomonal activity (121). Imidazole dicarboxamide was found to possess other interesting antiprotozoal activity (122). Many 1-substituted 4- or 5-imidazole derivatives have activity against T. vaginalis and T. foetus (123).

In this present work some 4-substituted quinolines have been prepared. Imidazole, 2-methylimidazole, 4 or 5-nitroimidazole and 2-methyl 5-nitroimidazole moieties have been substituted at 4-position. The choice of quinoline moiety has been restricted to 7-chloroquinoline, 2-methyl-8-hydroxyquinoline and 2-methyl-3-n-propyl-8-hydroxyquinoline.

Synthesis of 4-(1-imidazolyl)-7-chloroquinolines (LXXI) have been effected by the interaction of 4,7-dichloroquinoline (124) with an appropriate imidazole derivative (LXX) in presence of phenol.

Similarly condensation of appropriate 4-chloro-8-hydroxyquinolines with a desired imidazole has yielded 4-(1-imidazolyl)-8-hydroxyquinolines (LXXV). O-Anisidine has been condensed with acetoacetic ester or its derivatives (126) to
yield 2-methyl-4-hydroxy-8-methoxyquinolines. 4-Hydroxyquinolines (LXXII) thus obtained have been converted to 4-chloroquinolines (LXXIII) by the interaction of a mixture of POCl₃ and PCl₅. Demethylation of 8-methoxy-4-chloroquinolines have been effected using 65 per cent sulfuric acid to yield 4-chloro-8-hydroxyquinolines (LXXIV) (126,127).

The above scheme has been shown below:
Amebicidal testing was carried out at Central Drug Research Institute, Lucknow, India. Trichomonacidal testing was carried out at Messrs Bristol Laboratories, Syracuse, N.Y., U.S.A.

In vitro amebicidal activity was determined in the following procedure.

The testing was done in horse-serum-Ringer's solution (1:8) supplemented with a loopful of starch. The solution was buffered with 0.2% sodium hydrogen phosphate, the pH being adjusted to 7-7.4. P-1 strain of *S. histolytica* with a mixed bacterial flora was used as the test organism. The compounds were dissolved in Ringer's solution and diluted to different concentrations. Three ml of solutions of different dilutions were added to tubes containing 2.5 ml of the test medium. All materials used were sterile and the operation was carried out in sterile condition. They were inoculated with 0.5 ml of amoeba bacteria inoculum and incubated for 24 hrs at 37°C. The contents of each tube were then examined microscopically for the viability of amoeba. The amebicidal end points were determined on the basis of absence of viable amoeba in the test tube.

In vitro trichomonacidal activity was determined in the following procedure.

The testing was done in sterile cystein-peptone-liver-maltose (CPLM) liquid medium at pH 6 (128). Strains of *T. vaginalis* and *T. foetus* were used as the test organisms. Experiment was carried out in test tubes, in which tubes contained 4.5 ml of sterile liquid media (CPLM). The compounds were dissolved in distilled water and five ml of sterile solutions of different dilutions were added to the above test tubes. The test medium has been inoculated with 0.5 ml of trichomonas inoculum and the size of inoculum was 15,000 parasites/ml. The test tubes were incubated for 24 hrs at 37°C. Trichomonacidal end point was determined on
observation of motility and morphological changes in hanging drop preparations (129).

None of the compounds described in this part were found to be significantly active in vitro against T. vaginalis, T. foetus and E. histolytica at a concentration of 12.5 mcg/ml.

EXPERIMENTAL

4-[1-Imidazolyl]-7-chloroquinoline (LXXI: X = Y = H) :

A mixture of imidazole (LXX: X = Y = H; 0.68 g), 4,7-dichloroquinoline (1.98 g), and phenol (8 ml) was heated under reflux at 200°C for 24 hrs in an oil bath. After the reaction was over, it was acidified with dilute HCl and the mass was extracted with ether to remove phenol. Aqueous hydrochloric acid layer was separated out, the acid solution was decolourised with activated charcoal, filtered, and the cooled clear filtrate was basified with NH₄OH (liquor), where a yellow solid separated out. The solid was collected by filtration, washed with water and dried. The yield was 50% (1.15 g). It was crystallised from aqueous ethanol in pale yellow needles, m.p. 266-68°C.

(Found: N, 18.45. C₁₂H₁₀N₂Cl requires N, 18.65%).

4-(5-Nitro-1-imidazolyl)-7-chloroquinoline (LXXI: X = H; Y = NO₂) :

The experimental procedure was the same as was described in the case of the compound (LXXI: X = Y = H). A mixture of 4 or 5-nitroimidazole (LXX: X = H; Y = NO₂; 1.13 g), 4,7-dichloroquinoline (1.98 g) and phenol (8 ml) gave the title compound
in 55% (1.5 g) yield. It was crystallized from aqueous ethanol in light pink
needles, m.p. 263-64°.
(Found: N, 20.15. C_{12}H_{7}N_{4}O_{2}Cl requires N, 20.4%).

4-(2-Methyl-1-imidazolyl)-7-chloroquinoline (LXXI: X = Me; Y = H):

The experimental procedure was the same as was described in the case of the
compound (LXXI: X = Y = H). A mixture of 2-methylimidazole (LXX: X = Me; Y = H;
0.82 g), 4,7-dichloroquinoline (1.98 g) and phenol (8 ml) was allowed to react in
the usual way. It was crystallized from aqueous ethanol in yellow crystals,
m.p. 271-2°. The yield was 65.2% (1.58 g).
(Found: N, 17.1. C_{15}H_{10}N_{3}Cl requires N, 17.2%).

4-(2-Methyl-5-nitro-1-imidazolyl)-7-chloroquinoline (LXXI: X = Me; X = NO_{2}):

The experimental procedure was the same as was described in the case of the
compound (LXXI: X = Y = H). A mixture of 2-methyl 4 or 5-nitroimidazole (LXX;
X = Me; Y = NO_{2}; 1.27 g), 4,7-dichloroquinoline (1.98 g) and phenol (8 ml) was
allowed to react in the usual way. The product was crystallized from aqueous
ethanol in yellow needles, m.p. 273-73.5°. The yield was 40% (1.15 g).
(Found: N, 19.1. C_{13}H_{9}N_{4}O_{2}Cl requires N, 19.41%).

4-(1-Imidazolyl)-2-methyl-8-hydroxyquinoline (LXXV: X = X = H; R' = H):

The experimental procedure was the same as described in the case of the
compound (LXXI: X = Y = H). Imidazole (0.68 g), 2-methyl-4-chloro-8-hydroxy-
quinoline (1.93 g) and phenol (8 ml) were reacted together in the usual way. The
product obtained was crystallized from aqueous ethanol in yellow needles, m.p. 109-10°.
The yield was 20% (0.45 g). ir (KBr) 3245(0H), cm^{-1}.
(Found: N, 18.36. C_{18}H_{11}N_{3}O requires N, 18.63%).
4-(6-Nitro-1-imidazolyl)-2-methyl-8-hydroxyquinoline (LXXV: X = H; Y = \textit{NO}_2; R' = \textit{H}) :

The experimental procedure was the same as described in the case of the compound (LXXI: X = Y = H). 4 or 5-Nitroimidazole (1.13 g), 2-methyl 4-chloro-8-hydroxyquinoline (1.93 g) and phenol (3 ml) were reacted together in the usual way. The product obtained was crystallised from aqueous acetone in yellow needles, m.p. 110-11°C. The yield was 70% (1.89 g). ir (KBr) 3205(OH), cm⁻¹.

(Found: N, 20.44. \textit{C}_{13}\textit{H}_{10}\textit{N}_{4}\textit{O}_3 \text{ requires N, 20.74%}).

4-(2-Methyl-1-imidazolyl)-2-methyl-8-hydroxyquinoline (LXXV: X = Me; Y = H; R' = H) :

A mixture of 2-methylimidazole (0.82 g), 2-methyl-4-chloro-8-hydroxyquinoline (1.93 g), xylene (40 ml) and a few drops of pyridine, taken in 100 ml round bottomed flask fitted with a reflux condenser, was heated at about 200°C for 24 hrs in an oil bath. The contents were acidified with dilute HCl and was extracted with ether to remove xylene. The aqueous hydrochloric acid layer after charcoalisation was basified with \textit{NH}_3(liquor) when a yellow solid separated out. It was collected by filtration, washed with water and dried. The yield was 40% (0.96 g). It was crystallised from aqueous acetone in yellow needles, m.p. 115-16°C. ir (KBr) 3240(OH), cm⁻¹.


4-(2-Methyl-5-nitro-1-imidazolyl)-2-methyl-8-hydroxyquinoline (LXXV: X = Me; Y = \textit{NO}_2; R' = \textit{H}) :

The experimental procedure was the same as was described in the case of the compound (LXXV: X = Me; Y = H; R' = H). A mixture of 2-methyl 4 or 5-nitroimidazole (1.27 g), 2-methyl-4-chloro-8-hydroxyquinoline (1.93 g), xylene (40 ml) and a few drops of pyridine was allowed to react in the usual way. The product obtained was crystallised from a mixture of benzene-petroleum ether (1:1) in
yellow needles, m.p. 187-88°. The yield was 40% (1.13 g). \(\text{ir(KBr)} 3200(\text{OH}) \text{cm}^{-1}\).

(Found: N, 197.23. \(\text{C}_{14}\text{H}_{12}\text{N}_{4}\text{O}_{3}\) requires N, 19.71%).

2-Methyl-3-n-propyl-4-chloro-8-hydroxyquinoline (LXXIV: \(R' = n-C_{3}H_{7}\)):

2-Methyl-3-n-propyl-4-chloro-8-methoxyquinoline (127) (6.8 g) was refluxed with sulphuric acid (89 ml of 63%) taken in 150 ml round bottomed flask provided with refluxing condenser for 7 hours. The content of the flask was basified with \(\text{NH}_{3}(\text{liquor})\) and the solid was collected by filtration. The residue was redissolved in dilute HCl (1:1) and the solution was basified with \(\text{NH}_{3}(\text{liquor})\) after charcoalisation and the separated solid was filtered and washed well with water. The solid was dried in air and was crystallised from dilute alcohol. Yield was 39% (5.7 g); m.p. 50-51°. \(\text{ir(KBr)} 3250(\text{OH}) \text{cm}^{-1}\).

(Found: N, 55.52. \(\text{C}_{15}\text{H}_{14}\text{ONCl}\) requires N, 55.9%).

4-(1-Imidazolyl)-2-methyl-3-n-propyl-8-hydroxyquinoline (LXXV: \(X=X=\text{H}; R'= n-C_{3}H_{7}\)):

The experimental procedure was the same as described in the case of the compound (LXXV: \(X = \text{Me}; Y = R' = \text{H}\)). A mixture of imidazole (0.68 g), 2-methyl-3-n-propyl-4-chloro-8-hydroxyquinoline (2.55 g), xylene (40 ml) and a few drops of pyridine was allowed to react in the usual way. The product obtained was crystallised from benzene-pet.ether (1:1) in yellow needles, m.p. 155-56°. The yield was 84% (2.2 g). \(\text{ir(KBr)} 3230(\text{OH}) \text{cm}^{-1}\).

(Found: N, 15.25. \(\text{C}_{15}\text{H}_{17}\text{N}_{2}\) requires N, 15.7%).

4-(5-Nitro-1-imidazolyl)-2-methyl-3-n-propyl-8-hydroxyquinoline (LXXV: \(X = \text{H}; Y = \text{NO}_{2}; R' = n-C_{3}H_{7}\)):

A mixture of 4 or (5)-nitroimidazole (1.13 g) and 2-methyl-3-n-propyl-4-chloro-8-hydroxyquinoline (2.55 g) was gently heated in an oil bath at about 200°C.
under reduced pressure for half an hour. The contents were washed with ether to remove unreacted quinoline compound, and the residual mass was acidified with 2(N)
HCl. The acid solution was clarified with charcoal and then basified with NH₃(liquor) when a solid separated out. The solid obtained on filtration was washed with water and dried. The yield was 63% (1.9 g). It was recrystallised from aqueous ethanol in yellow needles, m.p. 165-66°. \text{ir(KBr)} 3210(\text{OH}),\text{cm}^{-1}.

(Found: N,17'48. C₁₆H₁₆N₄O₃ requires N,17'94%).

4-(2-Methyl-1-imidazolyl)-2-methyl-3-\text{a}-propyl-8-hydroxyquinoline (LXXV: X = Me; Y = H; R' = n-C₃H₇):

The experimental procedure was the same as was described in the case of the compound (LXXV: X = H; Y = NO₂; R' = n-C₃H₇). 2-Methylimidazole (0.82 g) and 2-
methyl-3-\text{a}-propyl-4-chloro-8-hydroxyquinoline (2.35 g) were reacted together in the usual way. The product obtained was crystallised from aqueous ethanol in yellow needles, m.p. 152-53°. The yield was 55% (1.5 g). \text{ir(KBr)} 3235(\text{OH}),\text{cm}^{-1}.

(Found: N,14'64. C₁₇H₁₈N₄O₃ requires N,14'94%).

4-(2-Methyl-5-nitro-1-imidazolyl)-2-methyl-3-\text{a}-propyl-8-hydroxyquinoline (LXXV:
X = Me; Y = NO₂; R' = n-C₃H₇):

The experimental procedure was the same as was described in the case of the compound (LXXV: X = H; Y = NO₂; R' = n-C₃H₇). 2-Methyl-4 or (5)-nitroimidazole (1.27 g) and 2-methyl-3-\text{a}-propyl-4-chloro-8-hydroxyquinoline (2.35 g) were reacted together in the usual way. The product obtained was crystallised from aqueous ethanol in yellow needles, m.p. 195-96°. The yield was 30% (1.08 g). \text{ir(KBr)} 3215(\text{OH}),\text{cm}^{-1}.

(Found: N,16'92. C₁₇H₁₈N₄O₃ requires N,17'17%).