INTRODUCTION

Amongst the 4-substituted quinolines, chloroquine and camoquine are the two outstanding drugs acting against malaria. Though the treatment of malaria by cinchona preparations dates back as early as seventeenth century, it has only been comparatively recently that an effective drug has been found.

Cinchona alkaloids are found in the bark of cinchona. Use of these alkaloids in medicine were brought into light through the efforts of the Countess of Cinchon, who in 1638 was successfully treated for malaria. Almost two centuries later, Gomes in Portugal isolated a crude mixture of crystalline alkaloids from the bark. Quinine and cinchonine were isolated for the first time by Pelletier and Caventou[1] in 1820. The first insight into the nature of the main framework of the alkaloidal structures was obtained when the bases were subjected to destructive fusion with alkali and the product distilled. Quinoline and methoxy quinoline were thus obtained by Gerhardt[2] in 1842. Rünge[3] is credited for the isolation of quinoline from coal tar a few years earlier, though the identity of the material obtained from two different sources were established after forty years. The correct

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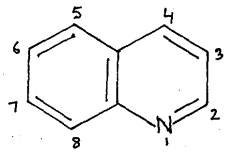
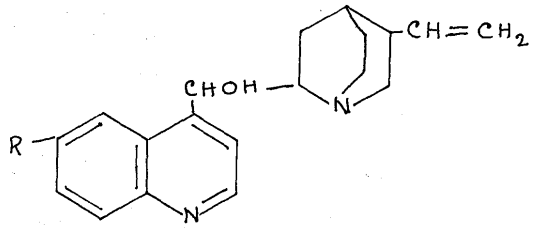
1. Pelletier and Caventou, Ann. Chim. Phys., (2), 15, 291, 337, 1820.
2. Gerhardt, Ann. Chem. Phys., (3), 44, 279, 1842.
3. Rünge Ann. Physik und Chem., (2), 31, 65, 1834.

structure for Quinoline (I) - the key degradation product, was proposed by Körner[4] in 1870 and was established through synthesis of the base by Koenigs[5], by Baeyer[6] and by Friedlander[7].



I

Further studies on cinchona alkaloid revealed the structure of cinchonine and quinine as II.



II

where R = IIa - OCH_3, quinine

R = IIb - H , cinchonine

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4. Körner, Ann., 155, 321, 1870.
5. Koenigs, W., Ber., 12, 453, 1879.
6. Baeyer, A., Ber., 12,460, 1320,(1879); 16, 2207,1883.
7. Friedlander. P., Ber.,15, 2572, 1882.

Since the presence of this ring system in the cinchona alkaloid, tremendous amount of work has been carried out in this field. It would be of interest to recall that after the discovery of quinine, its constitution remained a mystery for 88 years and after 124 years, it was synthesised in 1944 by Woodward and Doering[8], the work of Rabe[9] pioneering the route.

The chemotherapeutic properties associated with very many alkaloids having the quinoline ring system led to the further investigation and interest on the natural and isoteric compounds. The bark of Angostura comprises of numerous alkaloids, apart from some simpler quinoline bases (viz. substituted 4-methoxy quinoline) contains N-methyl quinolines. Echinopsine, Dictamine, Skimmianine, Acronycidine, Addendum etc. are important members of the group of alkaloids containing quinoline ring system have augmented the importance of quinoline moeity in the search of chemotherapeutic agents.[10]

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8. Woodward and Doering, Jour. Amer. Chem. Soc.,67, 860, 1945.
9. Rabe and Volger, Ber., 64, 2487, 1931.
10. The Alkaloids; Manskey and Holmes, Academic press inc., New York, Vol III, 1953, p.66.

An excellent treatise on the chemistry of quinoline and its derivatives have been published.[11] Besides, several reviews, monographs, and books contain discussion on the chemistry of this important ring system.[12,13]

During the last fifty years a large number of quinoline derivatives having a variety of substituents at the different positions of the ring have been synthesised. Many of them are pharmacologically effective. The efficacy of the compounds depends not only on the substituents but also on the position where it is attached to the quinoline ring. The pharmacologically active compounds may be classified in the following categories.

1) 8-Aminoquinoline derivatives
2) 4-Aminoquinoline derivatives
3) 8-Hydroxy quinoline derivatives
4) Miscellaneous quinoline derivatives.

1) 8-Aminoquinoline derivatives

The idea that led to the discovery of plasmoquine,[14,15] the first synthetic antimalarial drug, is a classic account

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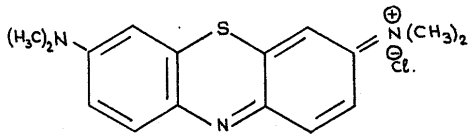
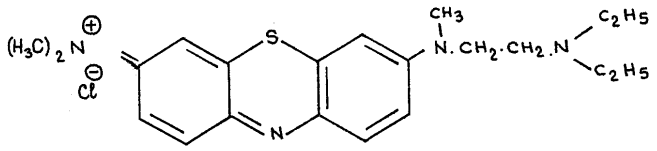
11. Heterocyclic Compounds; R.C.Elderfield, John Wiley & Sons, 1952, Vol.IV, p.1.
12. R.H.Manske, Chem. Reviews, 30, 113, 1942.
13. Burgstrom, ibid., 35, 150, 1944.
14. Schulemann W., Proc. Roy. Soc. Med.,25, 897, 1932.
15. Schulemann and Wingler, Klin. Wochschr., 11, 381,1932.

in the history of the development of chemotherapy. From his work on selective staining of micro organism by dyestuffs Ehrlich noted that Methylene blue (III) possessed some antimalarial activity.



III

Replacement of the dimethylamino group in the methylene blue molecule, by dialkylamino-alkyl group (IV) led to an enhancement of antimalarial activity.[16]



IV

The intense colour of the compound along with other inherent drawbacks led to the replacement of the chromophoric system by the other suitable heterocyclic nuclei.

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16. Schulemannand Kingler, U.S. Pat., 1, 766, 403, 1930.