SUMMARY OF THE WORK

The objective of the present work is to prepare properly oriented quinolino-quinoline derivatives as possible antiamoebic agents, having activity against both the intestinal and extra-intestinal forms of the infection in order to see if the presence of both the units of 4-aminoquinoline and halogenated oxyquinoline in such a single molecule would exhibit any behaviour indicative of synergistic effect. Suitably substituted dibenzo [b,h][1,6] naphthyridine offers a model which may serve this dual objective. Cyclodehydration of 4-anilino 3-carboxyquinoline derivatives would afford the desired skeleton.

In view of the utility of carbethoxyaceto m-chloroanilide (Compound 2) as intermediate for 4-anilino 3-carboxyquinolines, the reaction of diethyl malonate and m-chloroaniline, which affords a mixture of carbethoxyaceto m-chloroanilide (Compound 2) and malon di-m-chloroanilide, was studied. It was subsequently observed that the two anilides interconverted to one another with suitable choice of reaction conditions.

Attempted cyclodehydration of β-o-methoxyanilino α-cyanoacrylo m-chloranilide (Compound 5) and β-o-methoxy-anilino α-ethoxycarbonylacrylo m-chloroanilide (Compound 3) with either polyphosphoric acid or polyphosphoric ester failed

to effect the ring closure to the desired quinoline nucleus. Phosphorous oxychloride, however, effected cyclodehydration of the latter to ethyl 4-m-chloroanilino 8-methoxyquinoline 3-carboxylate (Compound 4), the yield being rather low. In another sequence of reactions, N:N' bis-(o-methoxyphenyl) formamidine and diethyl malonate were reacted with excess of ethyl orthoformate to afford ethyl α-carbethoxy β-o-methoxy-anilino acrylate which on cyclisation in diphenyl oxide gave ethyl 4-hydroxy 8-methoxyquinoline 3-carboxylate (Compound 8). The corresponding 4-chloro derivative (Compound 9) was condensed with m-chloroaniline to furnish ethyl 8-methoxy 4-m-chloroanilino-quinoline 3-carboxylate (Compound 4). This was saponified to 8-methoxy 4-m-chloroanilinoquinoline 3-carboxylic acid(Compound 10). Hydrolysis of the ester (Compound 4) with constant boiling hydrobromic acid, however, effected simultaneous demethylation to the corresponding 8-hydroxy derivative (Compound 12).

Cyclodehydration of 4-m-chloroanilino 8-methoxyquinoline 3-carboxylic acid (Compound 10) and the corresponding 8-hydroxy compound (Compound 12) in conc. sulfuric acid yielded 4-methoxy 7-hydroxy 10-chloro dibenzo /b,h/1,6/ naphthydridine (Compound 16) and the corresponding 4-hydroxy compound(Compound 18) respectively. The assigned structure was confirmed by an unequivocal cyclodehydration of 8-methoxy 4-(2-carboxy 5-chloro)

anilinoquinoline (Compound 15) to 4-methoxy 7-hydroxy 10-chloro dibenzo [b,h][1,6] naphthyridine (Compound 16). Treatment with phosphorous oxychloride converted 8-methoxy 4-m-chloroanilino-quinoline 3-carboxylic acid (Compound 10) and the corresponding 8-hydroxy compound (Compound 12) to 4-methoxy 7,10-dichloro dibenzo [b,h][1,6] naphthyridine (Compound 17) and the corresponding 4-hydroxy compound (Compound 19) respectively. The 7-chloro compounds (Compounds 17 and 19) were alternately obtained from the 7-hydroxy derivatives (Compounds 16 and 18) by treatment with phosphorous oxychloride. The chlorine atom at the 7-position was found to be exceedingly reactive.

Condensation of 4-hydroxy 7,10-dichloro dibenzo [b,h][1,6] naphthyridine (Compound 19) with 2-amino 5-diethylamino-pentane (Novaldiamine) gave 4-hydroxy 7-(4-diethylaminomethyl 1-methyl-butylamino) 10-chloro dibenzo [b,h][1,6] naphthyridine (Compound 20). Similar condensation with p-aminophenol gave the corresponding 7-(4-hydroxyanilino) derivative (Compound 22). Mannich condensation with the latter (Compound 22) resulted in the recovery of the starting material. It is of interest to note that the presence of 4-hydroxy group in this tetracyclic ring is also unable to induce a Mannich condensation to occur at the vulnerable 3-position. 4-Hydroxy 7-(4-hydroxy 3-diethylamino-methylanilino) 10-chloro dibenzo [b,h][1,6] naphthyridine

(Compound 23) was, however, obtained by the direct condensation of 4-amino 2-diethylaminomethylphenol with 4-hydroxy 7,10-dichloro dibenzo /b,h/1,6/ naphthyridine (Compound 19).

The amino substituents at the 7-position are susceptible to ready displacement in acid solution. Thus 4,7-dihydroxy 10-chloro dibenzo /b,h/1,6/ naphthyridine (Compound 18) slowly precipitates out as hydrochloride from an aqueous solution of either 4-hydroxy 7-(4-diethylamino 1-methylbutylamino) 10-chloro dibenzo /b,h/1,6/ naphthyridine hydrochloride (Compound 20) or the related 7-(4-hydroxy 3-diethylaminomethyl-anilino) derivative. Ready acid labile nature of these 7-amino compounds puts limitations for iodochlorination which is generally carried out by treatment with iodine trichloride in hydrochloric acid solution. Our preliminary attempts to effect iodochlorination below $0^{o}C$ gave a compound which soon transformed into an intractible pasty mass.