S U M M A R Y

The synthesis and chemistry of 2,4-dihydroxyquinolines and 2,4-dichloroquinolines, which provide useful intermediates for the preparation of a series of 2-arylamino-4-aminoalkyl aminoquinolines used as antimalarials, have become important in recent years (Drake et al., J. Amer. Chem. Soc., 1946, 68, 1208 ; Curd, Raison and Rose, J. Chem. Soc., 1947, 899). The preparation of 2,4-dihydroxyquinolines have been carried out by a number of processes. One process involves the reduction and simultaneous cyclisation of o-nitrobenzoylmalonic ester (Bischoff, Ann., 1889, 251, 360), later on modified by others (Gabriel, Ber., 1918, 51, 1500 ; Asahina, ibid., 1930, 63, 2057) ; the second involves the cyclisation of the anilide of malonic ester (Baumgarten et al., Ber., 1927, 60, 832 ; Kammerer German Patent, 505,798 ; Chem. Zentr., 1931, 102, 2679 ; Andre Meyer et al., Compt. rend., 1937, 204, 1204) ; the third involves condensation of malonic ester with anthranilic ester (Koller, Ber., 1927, 60, 1108) ; Brooker and Smith (J. Amer. Chem. Soc., 1937, 59, 67) also prepared quinolinediols by the method of Ashley et al.(J. Chem. Soc., 1930, 382) by heating methyl acetyl anthranilate with sodium in toluene ; the fourth involves the cyclisation of N-acetyl anthranilic acid (Bad. Anilin-Soda Fabr., German Patent, 117167). The condensation of alkyl malonic esters with anilines to give 3-alkyl quinolinediols has been carried out by Baker et al. (J. Amer. Chem.Soc., 1946,68,1284) by heating the reactants in diphenyl ether or nitrobenzene (Kammerer, Chem.Abst.,

1931, 25, 525) or in vacuo at 300°C (Baumgarten et al., loc.cit.). W.R.Vaughan (J. Amer.Chem.Soc., 1946, 68,324) carried out the preparation of quinolinediols by a number of methods and reported that the method of cyclisation of anilide of malonic ester was most suitable. Recently, Ziegler and Gelfort (Mh. Chem., 1959, 90,822) have reported a new and simple method of cyclisation of malonic acid dianilide using phosphorus oxychloride as the condensing agent.

In the work incorporated in Part I, it was found during the course of investigation that cyanacet arylamides underwent partial hydrolysis on treatment with polyphosphoric acid or with sulphuric acid (75 %) to form corresponding malon mono arylamides. It is interesting to note that both these reagents bring about partial hydrolysis quantitatively in the initial stage. The present work was undertaken to partially hydrolyse cyanacet arylamides in order to search for the useful intermediates, viz., malon mono arylamides in good yields by simpler methods (Mehta and Patel, Curr. Sci., 1959, 28, 200 ; J. Sci. Industr. Res., 1961, 20B, 457). Again, malon mono arylamides, thus produced, when further treated with polyphosphoric acid underwent cyclisation giving 2,4-dihydroxyquinolines (described in part II) ; whereas sulphuric acid as cyclising agent with these amides was found to be ineffective.

The following cyanacet arylamides have, therefore, been partially hydrolysed to the corresponding malonmono arylamides, viz., cyanacet-(-anilide ; -o.m. and p-toluidides ;

-p-chloroanilide ; -o-anisidide ; -benzylamide ; -1:3:4-xylidide ; -α- and -β-naphthyl amides). The cyanacet arylamides have been attempted to further hydrolyse by means of alcoholic alkali, giving the corresponding malonmono arylacids, but the yields are found to be very poor , hence the latter by the method of complete hydrolysis are not prepared from the former.

Moreover, it is significant to note that, malonmono arylacids, prepared by the method of Ahluwalia et al. (J. Chem.Soc., 1931, 2059), when cyclised by means of polyphosphoric acid, gave much higher yields of quinolinediols, compared to those obtained from the corresponding malonmono arylamides. Ethyl malonate, on condensation with arylamines, gave a mixture of malon dianilides and malon arylamates, from which the former is separated and the latter, on hydrolysis gave the following malonmono arylacids :

Malon-(-anilic acid ; -o,-m-and -p-toluidic acids ; -m-and -p-chloroanilic acids ; -o-and-p-anisidic acids ; -1:3:4-xylidic acid ; -α-and -β-naphthyl anilic acids).

In the work incorporated in Part II, the above mentioned malonmono arylacids and three of the above arylamides, viz., malonmono phenylamide ; -p-toluidide and 1:3:4-xylidide, have been cyclised to give the corresponding 2,4-dihydroxyquinolines, using freshly prepared polyphosphoric acid as the cyclising agent. The marked antimalarial activity of a number of quinoline derivatives having an alkylamino side-chain attached in the 4-position has led to an investigation of new procedures for the preparation

of 4-hydroxyquinolines, which are also important intermediates and can readily be converted to desired drugs. The present work was, therefore, undertaken to synthesise 2,4-dihydroxyquinolines from malon arylacids and malonmono arylamides respectively (Mehta and Patel, J.Sc.Industr. Res., 1959, 18B, 391 ; ibid., 1960, 19B, 436).

The following dihydroxyquinolines and their derivatives are synthesised : 2,4- dihydroxyquinoline ; (-6-methyl-; 6-chloro-; 6-methoxy- ; 7-methyl- ; 7-chloro- ; 8-methyl- ; 8-methoxy- ; 6,7-dimethyl-) -2,4-dihydroxy-quinolines ; (7:8)- and (5:6)-benzoquinolinediols-(2,4) ; 2,4-dichloroquinoline ; 8-methoxy-2,4-dichloroquinoline ; 2,4,7-trichloroquinoline and 6,7-dimethyl-2,4-diacetoxy-quinoline.

It may here be mentioned that diphenyl ether, sulphuric acid and a mixture of acetic anhydride and sulphuric acid proved ineffective as cyclising agents; however, malon arylacids in boiling diphenyl ether were decarboxylated and the corresponding N-acetyl arylamines were obtained.

Reactions with potassium hydroxy methane sulphonate with compounds containing reactive methylene group have been found to give mono sulphomethylated products. (Raschig and Prahl, Ann., 1926, 448, 265). This work gave an impetus to investigate the reaction of sodium hydroxy methane sulphonate with acetoacet arylamides, where the expected sulphonation of the reactive methylene group was not observed, but instead the products obtained were found to be methylene

bis-(-acetoacet arylamides). Shearing and Smiles (J. Chem. Soc., 1937, 1348), by the interaction of formaldehyde and sodium sulphite with 2-naphthol and 6-bromo-2-naphthol, obtained bis-(2-hydroxynaphthyl)- and bis-(-6-bromo-2-hydroxynaphthyl)-1-methanes respectively together with the sulphonates of the reactants. K.G.Naik et al.(J.Ind.Chem. Soc., 1930, 7, 145 ; ibid., 1932, 9, 471) studied the interaction of thionyl chloride with malon diarylamides and acetoacet arylamides, giving the corresponding thio-bis- derivatives of these amides. The condensation of dimethylaniline with formaldehyde has been found to form p-p'-tetramethyl diaminodiphenyl methane (Yoshiro Ogata and Masaya Okano, J.Amer.Chem.Soc., 1950, 72, 1459).

In the present work described in Part III, sodium hydroxy methane sulphonate was made to react with acetoacet arylamides, viz., acetoacet-(-anilide ; -o-m-and-p-chloro-anilides ; -o- and -p-toluidides ; -o-anisidide ; -p-phenetidide ; -1,2,4-and -1,3,4-xylidides ; -α-and-β-naphthylamides). All these amides with sodium hydroxy methane sulphonate gave the corresponding methylene bis-(-acetoacet arylamides). It may be added that bis-(-2-hydroxy-1-naphthyl)methane and bis-(-dimedon) methane have been obtained by the interaction of sodium hydroxy methane sulphonate with 2-naphthol and dimedone(5,5-dimethyl-cyclohexenedione-1,3-) respectively (Mehta and Patel, Curr.Sci., 1960,29, 95).

Schuller (J.prakt.Chem., 1913,(2),88,180) prepared 5,5'-methylene bis-8-hydroxyquinoline by treatment of

8-hydroxyquinoline with-formaldehyde in con.sulphuric acid. Borsche and Meyer, (Ber., 1921, 54, 2841) synthesised 6,6'-methylene bis-2-methylquinoline by the action of alcoholic alkali and acetone on 5,5'-diisatylmethane. Monti and Verona (Gazz.chim.ital., 1932, 62, 878) obtained methylene bis-6-hydroxyquinoline. Kaslow and Reck (J. Amer. Chem. Soc., 1947, 69, 864) reported on the synthesis of several 6,6'-methylene bis lepidine derivatives from corresponding 6,6'-methylene-bis-acetoacetanilides through the carbostyrils and chlorolepidine derivatives. Edgerton et al. (J. Amer. Chem. Soc., 1954, 76, 4902) obtained 7,7'-methylene bis-(-5-chloro-8-quinolinol) during the preparation of 5-chloro-7-diethylaminomethyl-8-quinolinol. Price et al. (J. Amer. Chem. Soc., 1946, 68, 1256) obtained 1,1-bis-(-7-chloro-4-hydroxy-3-quinolyl)-ethane from β-m-chloro-anilino acrylates in hgih dilution of boiling diphenyl ether. A number of 3,3'-methylene bis-(-4-hydroxycarbostyrils) have been obtained by the interaction of 1-substituted carbostyrils with carbonyl compounds at high temperatures (Chem. Abst., 1959, 53,11415 e). 3,3'-Methylenebis-(-4-hydroxycarbostyril) obtained by the action of formaldehyde on 4-hydroxy carbostyril, has been reported as one of the anticoagulant substances (Chem. Abst., 1951, 45, 10245 g.). But it may be pointed out that the 3,3'-methylene bis-(-4-methyl carbostyrils) have not been so far reported.

In the work incorporated in part IV, methylene bis-(-acetoacet arylamides) have been cyclised using acetic anhydride and con.sulphuric acid, when the corresponding

diquinolyl methanes, i.e., 3,3'-methylene-bis-(-2-hydroxy-4-methylquinolines) have been obtained (Mehta and Patel, Curr.Sci., loc.cit.). A number of 3,3'-diquinolyl methanes are prepared as follows:

3,3'-METHYLENE bis-2-hydroxy-(-4-methyl- ; -4,6-dimethyl- ; -4,8-dimethyl- ; -4-methyl-7-chloro ; -4,6,7-trimethyl- ; -4,6,8-trimethyl)-QUINOLINES ; 3,3'-METHYLENE bis- -2-hydroxy-4-methyl-(-benzo-7:8- and benzo-5:6) -QUINOLINES.

In Part V the absorption spectra of a number of acetoacet arylamides, 2-hydroxy-4-methylquinolines and their corresponding methylene bis-derivatives have been studied with a view to relatively throw light on the confirmation of their structures. But the specific purpose of the present study was to observe the insulation effect in a number of bis-compounds, in which one half of the molecule is a replica of the other half, bridged by a reactive methylene-CH_2-group. R.S.Corley and E.R.Blout (J. Amer. Chem. Soc., 1947, 69, 755) gave the spectrum of dinaphthyl methane in comparision with that of the equimolecular mixture of β-naphthol and β-naphthylamine and that of bis-(-2-hydroxy-1-naphthyl)-methane and observed that the curve of dinaphthyl methane is nearly identical with that of dinaphthol(effect of -CH_2-linkage) and that of β-naphthol plus β-naphthylamine (effect of coexistent amino plus phenol functions). T.N. Ghosh et al. (J. Ind. Chem. Soc., 1960, 37, 287) studied the spectrum of 1,1'-methylene bis-3,4-dihydroisoquinoline and observed that it resembled that of 1-methyl-3,4-

dihydroisoquinoline.

It is well known that if two or more chromophores or auxochromes exist in the same molecule, but are separated from each other by insulating groups, there is no effective conjugation between them ; and their spectral characteristic will be the same as if they were in the separate molecules. In the present work the general characteristics and the spectral behaviour of the methylene bis- derivatives of acetoacet arylamides and methylene bis-hydroxyquinolines should respectively correspond to those of acetoacet arylamides and hydroxyquinolines because of the insulation effect due to the presence of methylene bridge in the bis-compounds. This expectation has been realized by the study of the said absorption spectra.

The absorption spectra of the following acetoacet-arylamides, hydroxyquinolines and their corresponding methylene bis-derivatives have been studied : viz., aceto-acet-(-anilide ; -o-and-p-toluidides ; -1:2:4-xylidide ; -o-and -m-chloroanilides ; -α-and β-naphthylamides) along with their corresponding methylene bis-derivatives ; as well as 2-hydroxy-(-4-methyl- ; 4,6-dimethyl- ; 4,8-dimethyl-; 4,6,8-trimethyl- ; -4-methyl-7-chloro- ; and -4-methyl-benzo-7:8)-quinolines along with their corresponding methylene bis-derivatives (Plates I-VIII).

The average hyperchromic effect of the bis-compounds relative to their corresponding mono compounds is being shown from the extinction coefficient values in log E difference and in log E ratio (Tables 4-a and 8-a).

The bathochromic or the hypsochromic effects are comparatively small in the pairs examined ; and the hyperchromic effect is visible by the rise in the intensity of absorption in the bis-compounds. Accordingly, each pair of compound -bis and simple in the two series may be placed in the order of absorption intensity from minimum to maximum as follows.

Acetoacet arylamide series : 3':3 ; 4':4 ; 7':7 ; 6':6 ; 1':1 ; 8':8 ; 5':5 and 2':2 (Plates I-IV)

Hydroxyquinoline series : 6':6 ; 3':3 ; 2':2 ; 5':5 ; 4':4 and 1':1 (Plates V-VIII)

Thus, a considerable increase in the intensity of absorption takes place, when certain groups like $-CH_3$,-Cl, etc. are substituted in the ortho position in presence of another group in the para position in benzene or in quinoline nucleus. Similar difference due to the presence and proximity of certain groups would be observed on the comparision of the hyperchromic effect with the corresponding pairs of compounds in both the series. The hyperchromic effect as seen from some known pair of compounds is small and more comparable to the effect shown by compounds investigated in the present work (Plates IX-XI).

Riegel et al. (J. Amer. Chem. Soc., 1946, 68, 1229) prepared 3-bromo-4-quinolinol on bromination of 4-quinolinol with bromine in glacial acetic acid. Surrey and Cutler (J. Amer. Chem. Soc.,1946, 68, 2570) have reported the preparation of 3-halo-2,4-substituted quinolines by means of sulphuryl chloride, bromine or iodine monochloride in glacial acetic acid. Meyer et al.(Compt.rend., 1936,203,

264 ; Chem.Abst., 1936,30, 7114) by brominating 2,4-substituted quinoline also obtained its 3-bromo derivative. Chick and Wilsmore (J. Chem. Soc., 1910, 97, 1990) by direct bromination prepared 3-bromo-2-hydroxy-4-methyl-quinoline and established that the bromine atom had entered the 3-position in the pyridine part of the quinoline nucleus.

Here in Part VI the halogenation of hydroxy-quinolines has been carried out, by means of bromine and sulphuryl chloride in acetic acid, for respective bromination and chlorination in presence of a trace of iodine as catalyst ; while iodination of these quinolinols has been attempted, using iodine and iodic acid, iodine and liquor ammonia or iodine monochloride in acetic acid. In each case bromine or chlorine atom entered only into the 3-position of qiinolinols, giving 3-bromo-(or 3-chloro)-quinolinols, which are shown to be identical with the cyclised products of mono bromo(or mono chloro) derivatives of acetoacet and malonmono arylamides respectively. Further, 3-iodo-4-methylcarbostyrils have been prepared ; but the iodination of 4-hydroxycarbostyrils is found to be ineffective.(Mehta and Patel, Curr.Sci., 1961,15,30 ; Mehta et al., J.Sci. Industr. Res., 1961, 29B, 460).

By direct halogenation the following 3-halo derivatives of 4-methylcarbostyrils ; as well as 3-bromo and 3-chloro derivatives of 4-hydroxycarbostyrils have been prepared: 3-bromo-2-hydroxy-,(-4,6-dimethyl-; 4,8-dimethyl-; 4,6,8-trimethyl and -6-ethoxy-4-methyl-)-quinolines ; 3-chloro-2-hydroxy-,(-4,8-dimethyl-; -4-methyl-benzo-7:8-and -4-methyl-

benzo-5:6-)-quinolines ; 3-iodo-2-hydroxy-,(-4-methyl-: 4,6-dimethyl-; -4,8-dimethyl-and -4,6,7-trimethyl-)-quinolines ; 3-bromo-,(-6-methyl-; -7-methyl-; -6-chloro-; -6-methoxy-; 6,7-dimethyl-and -benzo-5:6-)-2,4-quinolinols; 3-chloro-,(-6-methyl-;-6-methoxy-and -6,7-dimethyl-)-2,4-quinolinols.

A number of monohalo derivatives of acetoacet arylamides and malonmono arylamides have also been prepared, wherein, the former with acetic anhydride and sulphuric acid, and the latter with polyphosphoric acid have undergone cyclisation,giving the corresponding 3-bromo and 3-chloro derivatives of hydroxyquinolines. In the case of monoiodo arylamides, which being very unstable, the copious fumes of iodine have been evolved,during the process of cyclisation with the result that the 3-iodo-hydroxyquinolines are not formed or decomposed if at all they are formed.

The following monohalo derivatives of the respective arylamides are prepared and cyclised:viz., monobromo aceto-acet-(-p-and -o-toluidides ; -p-chloro-anilide ; -p-phenetidide ; 1:2:4 and 1:3:4-xylidides) ; monochloro acetoacet-(-o-toluidide ; -α-and β-naphthylamide); monoiodo acetoacet-(-anilide;o-toluidide; -p-toluidide and -1:3:4-xylidide);monobromo malonmono-(-p-and-m-toluidides ;-p-chloroanilide ; -p-anisidide ; -1:3:4-xylidide and -β-naphthylamide); monochloro malonmono-(-p-toluidide ; -p-anisidide and -1:3:4-xylidide);monoiodo malonmono-(-anilide and -p-toluidide).

The fact that the halogen enters only into the 3-position of hydroxyquinolines has been amply confirmed from the corresponding cyclised products of monohalo arylamides, which are shown to be identical respectively with the former.