PART II

Synthesis of 2,4-dihydroxyquinolines by cyclisation of malon arylacids and malonmono arylamides using polyphosphoric acid as the cyclising agent.

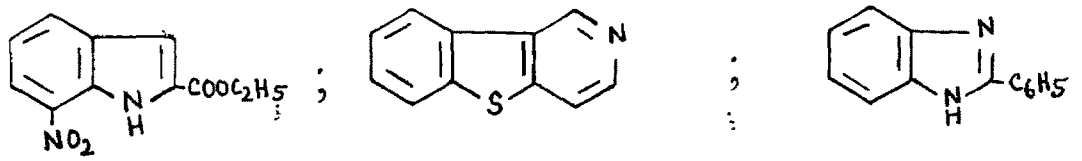
PART II

Theoretical

Polyphosphoric acid has been found to be a very effective reagent so far employed in organic synthesis as is seen from the review made by F.D.Popp and W.E.McEwen (loc.cit.). Polyphosphoric acid has been widely used as a condensing agent in the synthesis of numerous heterocyclic compounds, e.g., in the Fischer indole synthesis and pomeranz-Fritsch reaction ; in the preparation of cyclic ketones by intra molecular acylation reactions ; in the cyclodehydration reactions of aldehydes, ketones and alcohols ; in the Beckmann, Lossen, Wagner-Meerwein and Schmidt-rearrangements ; in the intra molecular acylation and alkylation and in some other miscellaneous uses, viz., nitration, bromination, dehydration, hydrolysis, polymerization and phosphorylation reactions.

Witkop et al. (J. Amer. Chem. Soc., 1952, 74, 3948) used polyphosphoric acid and obtained 2-phenylindole in good yield, not only from acetophenone phenylhydrazone but also from a mixture of phenylhydrazine and acetophenone by the method of Fischer indole synthesis. Singer H. and Shive W. (J. Org. Chem., 1957, 22, 84) carried out similar Fischer cyclisation of ethyl pyruvate-o-nitrophenylhydrazone with polyphosphoric acid and obtained ethyl-7-nitro-2-indole carboxylate (I). Herz and Tsai (J. Amer. Chem. Soc., 1953, 75, 5122) carried out the Pomeranz-Fritsch reaction on thiophenecarboxaldehyde and aminoacetal using polyphosphoric

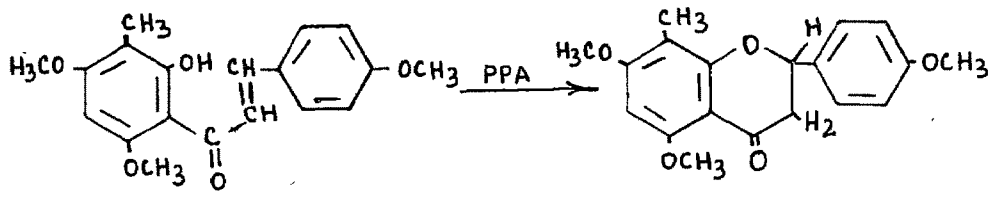
acid and obtained thianaphtheno (2,3-c) pyridine (II) derivatives. A mixture of polyphosphoric acid and phosphorus oxychloride here was used with better yield than that obtained with concentrated sulphuric acid. Leavitt et al. (J. Amer. Chem. Soc., 1957, 79, 427) carried out the Phillips benzimidazole synthesis using polyphosphoric acid with o-phenylenediamine and benzoic acid to give 2-phenylbenzimidazole (III). (Miss) E.F.M. Stephenson (J. Chem. Soc., 1957, 1928) obtained 3-methyl-3-phenyloxindole by cyclisation of (±)-atrolacetanilide with polyphosphoric acid. Hill R.K. (J. Org. Chem., 1957, 22, 830) cyclised nitrocycloalkanes into spirolactams using polyphosphoric acid.



(I) (II) (III)

Koo, J. (Chem. and Ind., 1955, 445) condensed resorcinol with each of the β-ketoesters, ethyl acetoacetate, ethyl α-methylacetoacetate and ethyl benzoylacetate in polyphosphoric acid and obtained respectively 4-methyl-7-hydroxycoumarin, 3-4-dimethyl-7-hydroxycoumarin and 4-phenyl-7-hydroxycoumarin in 80-95 % yield. The chalcone (IV) has been converted by Nakazawa and Matsuura (J. Pharm. Soc., Japan, 1955, 75, 469) into the flavanone derivative (V)

in 80 % yield by the action of polyphosphoric acid.



(IV) (V)

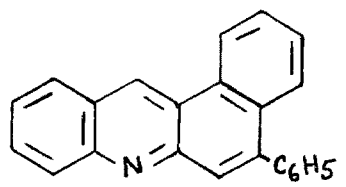
Elston (Doctoral Dissertation, University of Illinois, 1954) prepared 4,7-dimethylcoumarin in 76 % yield from m-cresol and ethylacetoacetate using polyphosphoric acid and found that polyphosphoric acid is about as effective a catalyst as sulphuric acid.

Sukh Dev (loc.cit.) converted βγ-or γδ -unsaturated acids to cyclenones with the aid of polyphosphoric acid, viz.,cycloheptylidenesuccinic acid was cyclised to cycloheptenocyclopentanone (VI) by treatment with polyphosphoric acid. Cope and Smith (J. Amer. Chem. Soc., 1955, 77, 4596) carried out the cyclisation of o-(β-phenethyl)phenylacetic acid to 1,2,5,6-dibenz-1,5-cyclooctadiene-3-one (VII) in 93 % yield using polyphosphoric acid.

(VI) (VII)

Phillips (J. Amer. Chem. Soc., 1955, 77, 3658) prepared 4,7-dimethyl-1-tetralone from γ-p-tolylvaleric

acid by polyphosphoric acid catalyzed cyclisation. Hauser and Murray (J. Amer. Chem. Soc., 1955, 77, 3858) synthesised 5-phenyl-benz-acridine (VIII) in 87 % yield from 2-phenacyl-3-phenylquinoline using polyphosphoric acid. Poller et al. (J. Chem. Soc., 1956, 1195) carried out several conversions of diarylarsinic acids into 9-arsafluorene oxides (IX) by polyphosphoric acid at 160°C for 3 hours.



(VIII)

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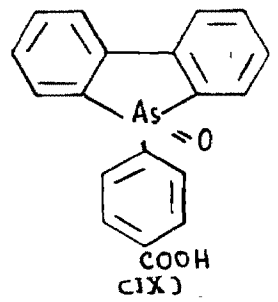


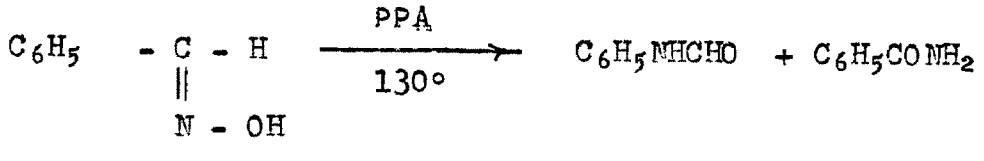
(IX)

Pratt, Rice and Luckenbaugh (J. Amer. Chem. Soc., 1957, 79, 1212) prepared 3,4-dihydroisoquinoline from N-formylphenethylamine by Bischler-Napieralski synthesis with polyphosphoric acid. Further, Proctor and Thomson (J. Chem. Soc., 1957, 2302) carried out the synthesis of 2-tosyl-1,2,3,4-tetrahydroisoquinoline. Snyder and Werber (loc.cit.) subjected the Bischler-Napieralski reaction to N-acetyl-phenylalanine with a mixture of polyphosphoric acid and phosphorus oxychloride and obtained 1-methylisoquinoline.

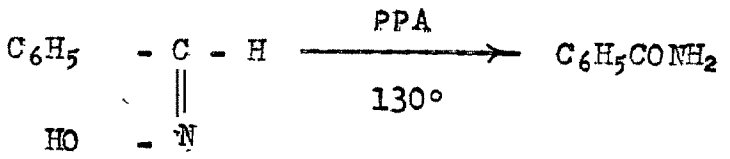
Ghosh, Bhattacharya and Dutta (J. Ind. Chem. Soc., 1958, 35, 758) studied the process, involving cyclodehydration probably followed by decarboxylation and dehydrogenation, when α-methyl-α-acetamido-β-phenyl-propionic acid was treated with a mixture of polyphosphoric acid and phosphorus oxychloride yielded 1,3-dimethyliso-

quinoline. Popp and McEwen (J. Amer. Chem. Soc., 1957, 79, 3773) also used a mixture of polyphosphoric acid and phosphorus oxychloride for preparing 6,7-dimethoxyisoquinoline from veratrylideneaminoacetal.

Horning et al. (loc.cit.) studied the Beckmann rearrangement of oximes with polyphosphoric acid e.g. when syn benzaldoxime treated with polyphosphoric acid at 130° gave formanilide and benzamide, while anti form at the same temperature gave only benzamide.



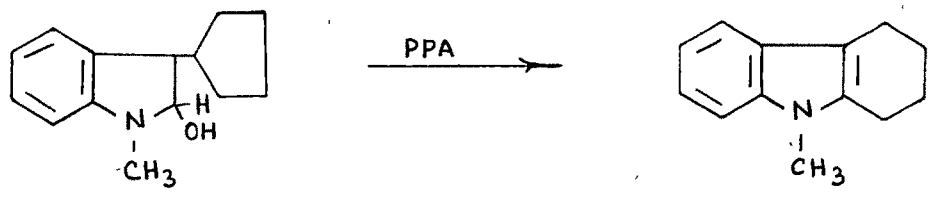
(Syn)



(Anti)

Hence, it was concluded that the syn-isomer undergoes partial isomerization to the anti-form in contact with polyphosphoric acid. The conversion of aromatic carboxylic acids to arylamines commonly called Lessen rearrangement has been carried out by the reaction with acid and hydroxylamine hydrochloride in polyphosphoric acid. Ketones are also converted to amines by this method. Polyphosphoric acid is also applied to Wagner-Meerwein rearrangement, and in this case when spiro(cyclopentane-1,3'-N-methyl-2'-hydroxyindole) (X) is treated with the

above reagent gave 9-methyltetrahydrocarbazole (XI).

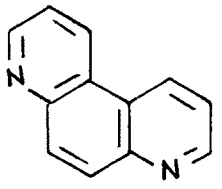


(X) (XI)

Klager et al. (J. Amer. Chem. Soc., 1955, 77, 5433) carried out the nitration of diethyl alkylmalonate with polyphosphoric acid and obtained a high yield of diethyl alkylnitromalonate. Polyphosphoric acid is also used as a dehydrating agent for the preparation of olefins from alcohols. Benzyl esters of amino acids, useful intermediates for the synthesis of peptides, have been prepared in high yields with polyphosphoric acid solution. Cherbuliez and Weniger (Helv. Chim. Acta., 1946, 29, 2006) carried out the phosphorylation of alcohols, e.g., methyl phosphate, benzyl phosphate and cetyl phosphate have been prepared by reaction of the respective alcohols with polyphosphoric acid. Schaad (U.S.Patent, 2557924 ; 1951) prepared alkylazides by the acid-catalyzed addition of hydrogen azide to alkenes. Breuer and Hofferth (U.S.Patent, 2740767 ; 1956) observed that coumarone-indene resins, having low softening points may be upgraded by treatment with polyphosphoric acid and a source of formaldehyde. Finally, polyphosphoric acid has been found to be of use in the catalytic reforming of petroleum stocks, containing significant amounts of nitrogen compounds

and here ammonia formed, during the cracking operation, is removed.

Kermack et al. (J. Chem. Soc., 1940, 1164 ; ibid., 1942, 213) synthesised number of p-phenanthroline (XII) derivatives from 6-aminoquinolines by Skraup reaction. Moreover, Kermack and Halcrow (J. Chem. Soc., 1946, 155) subjected o-phenylenediamine to Skraup reaction and obtained o-phenanthroline (XIII) derivatives, while Kermack and Tebrich (J. Chem. Soc., 1945, 375) prepared 4-hydroxy-m-phenanthroline (XIV) from 5-amino-4-hydroxy-quinoline by Skraup reaction.



(XII)

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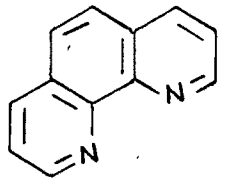

(XIII)

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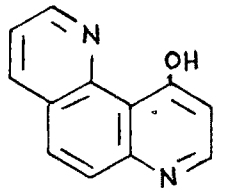
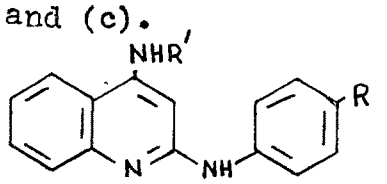


(XIV)

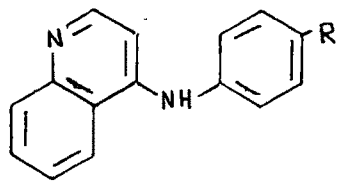
4-Hydroxyquinolines have been obtained by Conrad and Limpach (Ber., 1887, 20, 944 ; ibid., 1888, 21, 521 ; Limpach Ber., 1931, 64, 969 ; Price and Roberts, J. Amer. Chem. Soc., 1946, 68, 1204) on thermal cyclisation of several ethyl β-arylamino-α-β-unsaturated esters obtained from ethyl acetoacetate and primary arylamines. Ewins and King (J. Chem. Soc., 1913, 103, 104) synthesised 2-hydroxyquinolines by a modified method of Knorr (Ber., 1884, 17, 540), using concentrated sulphuric acid as a cyclising agent. Bangdiwala and Desai (J. Ind. Chem. Soc.,

1953, 30, 655) obtained 4-hydroxyquinolines on cyclisation of crotonates and acrylates, using a mixture of acetic anhydride and concentrated sulphuric acid as a cyclising agent. Hauser and Murrey (loc.cit.) used polyphosphoric acid for the preparation of 4-hydroxy-quinolines. (Miss) Stephenson (loc.cit.) synthesised 2-hydroxyquinoline derivatives from N-(benzoylacetyl) aniline with polyphosphoric acid in good yield.

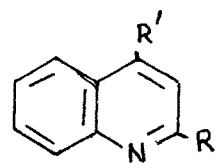
The synthesis and chemistry of 2,4-dihydroxy-quinolines and 2,4-dichloroquinolines, which provide the useful intermediates for the preparation of a series of 2-arylamino-4-aminoalkylaminoquinolines used as antimalerials, have been important in recent years (Drake et al. J. Amer. Chem. Soc., 1946, 68, 1208 ; Curd, Raison and Rose, J. Chem. Soc., 1947, 899). The differential reactivities of the substituent groups in 2,4-dihydroxy-quinolines and 2,4-dichloroquinolines have been investigated and utilized for the preparation of a series of 2-arylamino-4-aminoalkylaminoquinolines (a) and their derivatives (b) and (c).



(a)



(b)



(c)

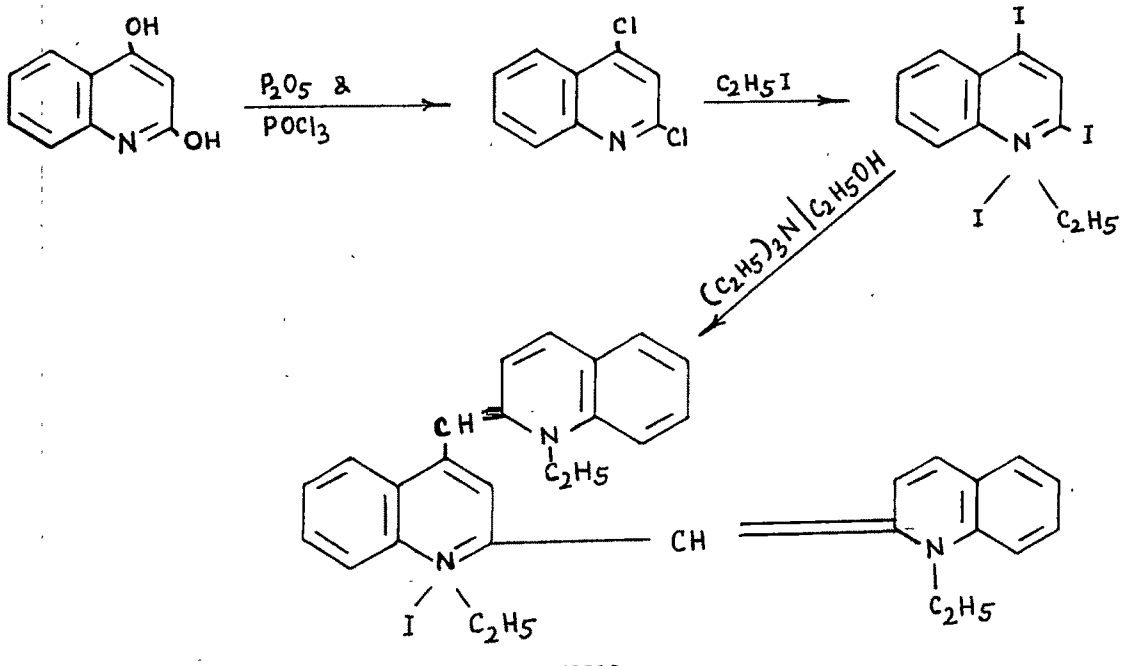
To achieve the synthesis of compounds of types (a) and (b), the possibility of a stepwise replacement of the groups R and R' in a quinoline derivatives of type (c),

where R=R'=OH or halogen, was first considered because the simplest of such compounds, namely 2,4-dihydroxyquinolines, was available as an intermediate. The reaction of 2,4-dihydroxyquinoline with a number of primary and secondary aliphatic amines at 150-250°C to give 4-aminoquinolines or 4-alkylaminoquinolines has been described in Germann Patent No. 681980, which makes no mention of the condensation of 2,4-dihydroxyquinoline with arylamines to obtain 4-anilino-2-hydroxyquinolines.

Further, V.Niementowski (Ber., 1907, 40, 4285) and Dziewonski and Dymek (Chem. Zentr., 1937, 1, 1153) obtained 4-anilino-2-hydroxyquinoline from benzoyl acetic ester with anthranilic acid, noted its insolubility in alkali, and obtained 4-anilinoquinoline ; whereas on distillation with zinc dust obtained 2,4-dianilinoquinoline which on heating with potassium hydroxide, obtained 4-anilino-2-hydroxyquinoline with its isomer 4-hydroxy-2-anilinoquinoline, which is soluble in alkali.

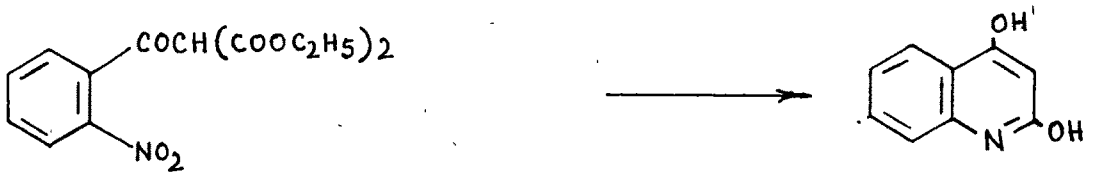
Brooker and Smith (loc.cit.) prepared 2,4-dihydroxyquinoline by the method of Ashley et al.(loc.cit.) by treating methyl acetyl-anthranilate with sodium in toluene. 2,4-Dihydroxyquinoline on treatment with phosphorus pentoxide and phosphorus oxychloride gave 2,4-dichloro-quinoline from which a new type of cyanine dye, viz., 2,4-Di-[1-ethyl-2(1)-quinolylidene)-methyl] -quinoline ethiodide (XV), containing three hetrocyclic nuclei, has

been obtained. Thus:

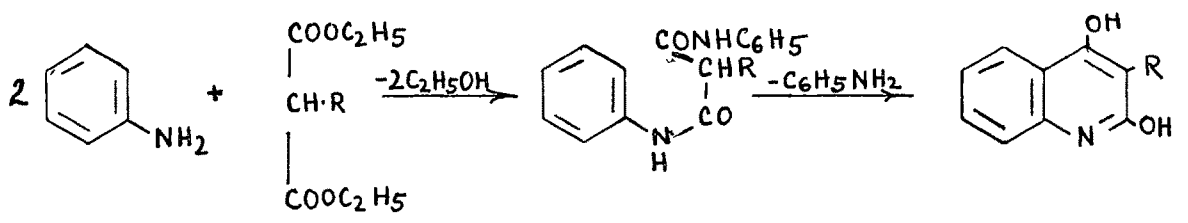


(XV)

Various workers have carried out the preparation of 2,4-dihydroxyquinolines, involving a number of processes. One process involves the reduction and simultaneous cyclisation of o-nitro-benzoylmalonic ester (Bischoff, loc.cit.), latter on modified by others (Gabriel, loc.cit.; Asahina, loc.cit.). Thus;



The second process involves the cyclisation of the anilide of malonic ester (Baumgarten et al., loc.cit.; Kammerer, loc.cit.), as follows:

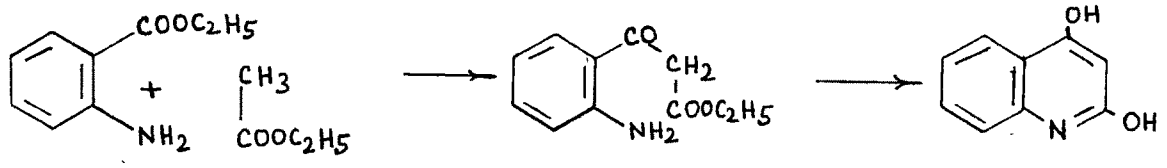


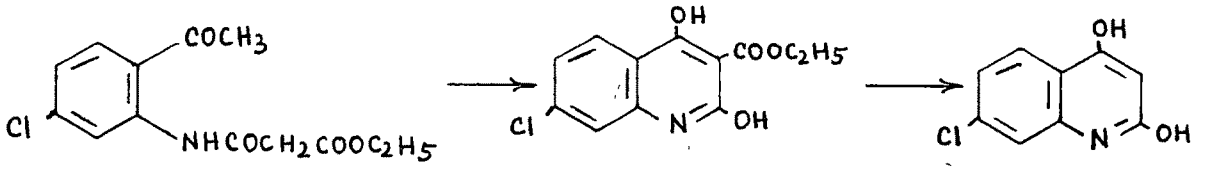
The third process involves the condensation of malonic ester with anthranilic ester in order to obtain 2,4-dihydroxyquinoline-3-carboxylate methyl ether (Koller, loc.cit.). The fourth process involves the cyclisation of N-acetyl anthranilic acid (Bad.Anilin-Soda Fabr., German Patent, 117167), while the fifth one is a relatively simple reaction between quinoline and anhydrous potassium hydroxide in the presence of barium oxide (Tschitschibabin, J.Russ.Phys.Chem.Soc., 1924,55,7). E. Ziegler and H. Juenk (Chem. Abst., 1957, 51, 3598 ; Monatsh., 1956, 87, 503) carried out the reaction of malon acid dianilide with anhydrous $AlCl_3$ and obtained 4-anilinocarbostyril, from which 4-hydroxycarbostyril was obtained by hydrolysis with hydrochloric acid (Nimentowski, Chem. Abst., 2,279).

Recently, Ziegler and Gelfert (loc.cit.) have reported a new and simple method for the preparation of 2,4-dihydroxyquinoline by cyclisation of malonic acid dianilide using phosphorus oxychloride as the cyclising agent. Baumgarten and Kargel (loc.cit.) prepared 2,4-dihydroxyquinolines by the simple method of heating malonic ester with an aromatic primary amine. But this method can

only be used for the preparation of the 3-substituted-2, 4-dihydroxyquinolines. Shah et al. (J. Sci. Industr. Res., 1960, 19B, 176) also prepared quinolinediols using a mixture of anhydrous zinc chloride and phosphorus oxychloride. W.R.Vaughan (loc.cit.) carried out the preparation of 2,4-dihydroxy-3-quinolyl methylketones by heating a solution of primary arylamine and acetylmalonic ester in nitrobenzene in a metal-bath at 230-245°C for one hour and reported that the method of cyclisation of anilide of malonic ester was most suitable.

Erdmann (Ber., 1899,32, 3570) carried out the Claisen condensation of ethyl anthranilate and ethyl acetate, followed by a closure of the quinoline ring and obtained 2,4-dihydroxyquinoline. Lutz and co-workers (Lutz et al., J. Amer. Chem. Soc., 1946, 68, 1285) improved the method of Ashley et al. (loc.cit.) by starting from the more reactive malonyl anthranilic ester and prepared 7-chloro-2,4-dihydroxyquinoline (Koller., loc.cit.). These reactions are expressed as :-





In an attempt to find a new type of compound, which might prove effective in the treatment of malaria, Baker, Lappin and Riegel (loc.cit.) prepared some 3-alkyl-2,4-quinolinediols. The condensation of alkyl-malonic esters with anilines to give 3-alkylquinolinediols has been carried out by heating the reactants in vacuo to 300°C (Baumgarten and Kurgl., loc.cit.) or by heating in nitrobenzene as a solvent (Kammerer., loc.cit.). Neither of these methods proved satisfactory when applied to cyclohexylpropylmalonic ester with aniline or to p-dimethyl-aminoaniline with any alkylmalonic ester. However, when equimolecular quantities of cyclohexylpropyl-malonic ester and aniline was heated in refluxing diphenyl ether a quantitative yield of 3-alkyl-2,4-quinolinediol was obtained. This method was also successful with p-dimethylaminoaniline, but not with o-nitroaniline alkylmalonic ester nor with 3-diethylaminopropyl malonic ester.

Berinzaghi, Muruzabal, Labriola and Deulofeu (J.Org.Chem., 1945, 10, 181) obtained 2,4-dihydroxymethoxy-quinoline by drgradation of γ-fagarine, which was shown by independent synthesis to be 2,4-dihydroxy-8-methoxyquinoline. Again, 2,4-dihydroxy-8-methoxyquinoline was prepared from ethyl malonate and methoxy-o-nitrobenzyl chloride in dry ether and sodium ethoxide, and finally the product was dissolved in alcohol, which was refluxed for 12 hours with tin and hydrochloric acid. By the above method 2,4-dihydroxy-6-methoxyquinoline, 2,4-dihydroxy-7-methoxyquinoline and 2,4-dihydroxy-8-methoxyquinoline have been prepared.

Moreover, the 3-nitroso derivatives of 2,4-dihydroxy-methoxyquinolines were prepared with sodium nitrite in a 8 % solution of aqueous sodium hydroxide.

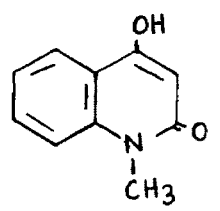
Buchmann and Hamilton (J. Amer. Chem. Soc., 1942, 64, 1357) treated 2,4-dichloroquinoline with alcoholic potassium hydroxide and obtained two isomeric chloroethoxyquinolines. The 4-chloro-2-ethoxyquinoline and 2-chloro-4-ethoxyquinoline from which 4-chloro-2-hydroxy-quinoline and 2-chloro-4-hydroxyquinoline have been obtained by hydriodic acid. The marked antimalerial 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 (Price and Roberts, loc.cit.) for the preparation of 4-hydroxyquinolines from m-chloroaniline and ethoxy methylene malonic ester in boiling diphenyl ether and thus the quinolinols may be converted to the desired drugs.

Further, the constitution of 4-hydroxycarbostyril was proved by Fritz Arndt et al. (Chem. Ber., 1953,86,951 ; Chem. Abst., 1954, 48, 11417). The structure of 4-hydroxycarbostyril was proved by its methyl derivatives. The technical sodium salt of 4-hydroxy-carbostyril is decomposed with hydrochloric acid, the solution extracted with sodium carbonate and the extraction, on acidification, gave 4-hydroxycarbostyril. 4-Hydroxycarbostyril is also prepared from o-aminophenylacetylenecarboxylic acid on heating with concentrated sulphuric acid for 5 minutes at 140°C, according to Baeyer and Bloem (Ber., 1882,15,2151) and

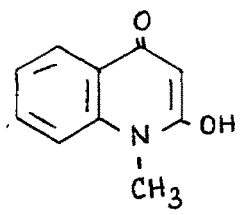
adding diazomethane (CH_2N_2) in ether to 4-hydroxy-carbostyril gave 4-methoxycarbostyril. From the original mother liquor 2,4-dimethoxyquinoline was also isolated. 4-Methoxycarbostyril did not give colour with ferric chloride and this when heated with 20 % hydrochloric acid gave 4-hydroxycarbostyril.

4-Methoxy-1-methyl-carbostyril was obtained from 4-methoxycarbostyril and methyl iodide with sodium hydroxide solution. Refluxing 4-methoxy-1-methylcarbostyril with hydrochloric acid gave 4-hydroxy-1-methylcarbostyril, which also obtained from the sodium salt of 4-hydroxycarbostyril with dimethyl sulphate in sodium hydroxide solution.

2-Methoxy-1-methylkynurin obtained from 4-hydroxy-1-methylcarbostyril and CH_2N_2 in ethereal solution. From the mother liquor 4-methoxy-1-methylcarbostyril was obtained. Betaine is obtained on heating 4-hydroxycarbostyril with concentrated sulphuric acid, and on heating betaine with dry CH_2N_2 gave trimethylbetaine, and from the filtrate 2,4-dimethoxy-1-methylquinolinium-6-sulphonate was obtained.



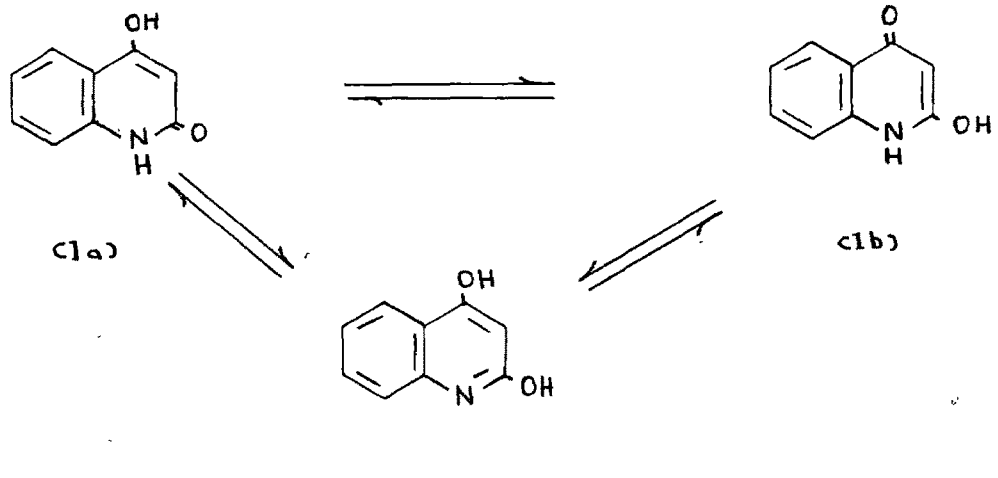
(Id)



(Ie).

4-Hydroxy-1-methylcarbostyril exists in the carbostyril form (Id) or in the kynurin form (Ie) and therefore on methylation gives 4-methoxy-1-methyl-carbostyril and 2-methoxy-1-methylkynurin. Now (Ie) is

more acid and is preferentially methylated ; while 2-methoxy-1-methylkynurin (methoxy of Ie) is more basic than 4-methoxy-1-methylcarbostyril. The transannelar tautomerism of 4-hydroxycarbostyril is as follows:



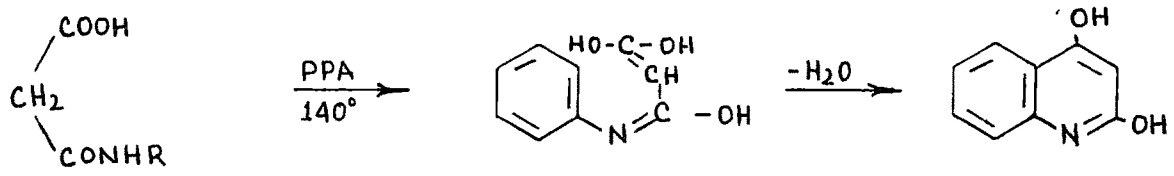
4-Hydroxycarbostyril in a solid state has the 4-hydroxy-2-(1H)-quinoline structure (Ia), and in this form with diazomethane gives 4-methoxycarbostyril exclusively. In solution 4-hydroxycarbostyril undergoes α-γ-tautomerism changing to the kynurin structure (Ib), which on methylation with diazomethane gives 2-methoxy of (Ib), which is not stable and undergoes transannelar tautomerism to 4-hydroxy-2-methoxyquinoline, which on methylation gives 2,4-dimethoxyquinoline.

It is assumed that the transannelar tautomerism occurs first after the kynurin structure (Ib) is fixed by methylation to 2-methoxykynurin and that a dihydroxyquinoline structure (Ic) as such does not exist.

2,4-Dihydroxyquinolines :

The present work was undertaken with a view to prepare 2,4-dihydroxyquinolines, which are found to be important intermediates, used for the preparation of a series of antimalerials. Hence, quinolinediols have been synthesised from malon arylacids and malon mono arylamides respectively, using polyphosphoric acid as the cyclising agent. For this purpose malon arylacids and malon mono arylamides, described in part I, have served as useful intermediates in the preparation of 2,4-quinolinediols.

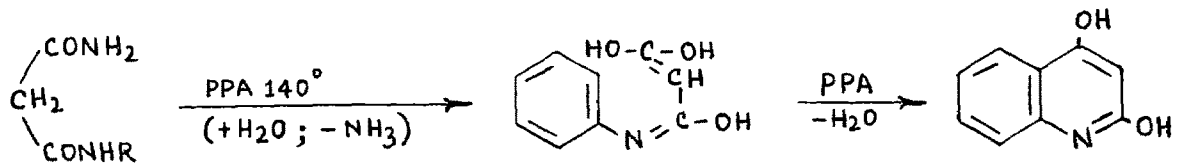
The required malon arylacid was dissolved in a clear solution of polyphosphoric acid which was prepared by dissolving 10 g. phosphorus pentoxide in 6 ml. phosphoric acid of density 1.75 and the reaction mixture was kept at 140°C for 3 hours with a calcium chloride guard tube. It was then worked out by treating with hydrochloric acid followed by sodium hydroxide solution at pH_4 . The crude product was filtered and crystallised from acetic acid gave 2,4-quinolinediol. The course of reaction is expressed as under:



(Where R is phenyl, tolyl, xylyl, naphthyl, etc. groups)

2,4-Dihydroxyquinolines were also obtained from cyanacet arylamides ($RNHCOCH_2CN$) in two steps using polyphosphoric acid, when it acted first as a hydrolytic agent to give malon mono arylamides ($RNHCOCH_2CONH_2$), which, when further treated with polyphosphoric acid gave 2,4-dihydroxyquinolines.

During the course of reaction malon mono arylamides, further hydrolysed to malon arylacids with the elimination of ammonia and then these acids simultaneously underwent cyclisation to give 2,4-dihydroxyquinolines eliminating water as under:

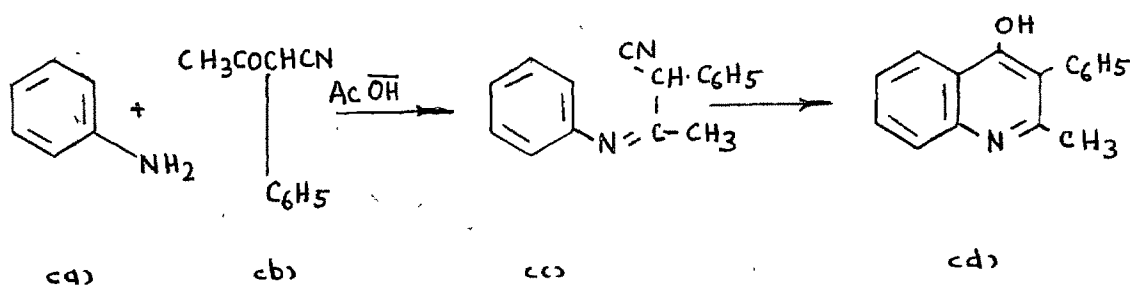


(Where R is phenyl, tolyl, xylyl, naphthyl, etc. groups).

It is to be noted that 2,4-quinolinediols were not obtained directly in a single step from cyanacet arylamides with polyphosphoric acid at 140°. However, the preparation of 2,4-quinolinediols from malon mono arylamides by means of polyphosphoric acid is similar to that employed for malon arylacids (Mehta and Patel., J. Sci. Industr. Res., 1959, 18B, 391 ; ibid., loc.cit.). The yields in the case of quinolinediols obtained from malon arylacids were quantitative, while those obtained

from malonmono arylamides were fair. Most of the quinolinediols have high melting points, and insoluble in most of the organic solvents. They are sparingly soluble in acetic acid but fairly soluble in alkali.

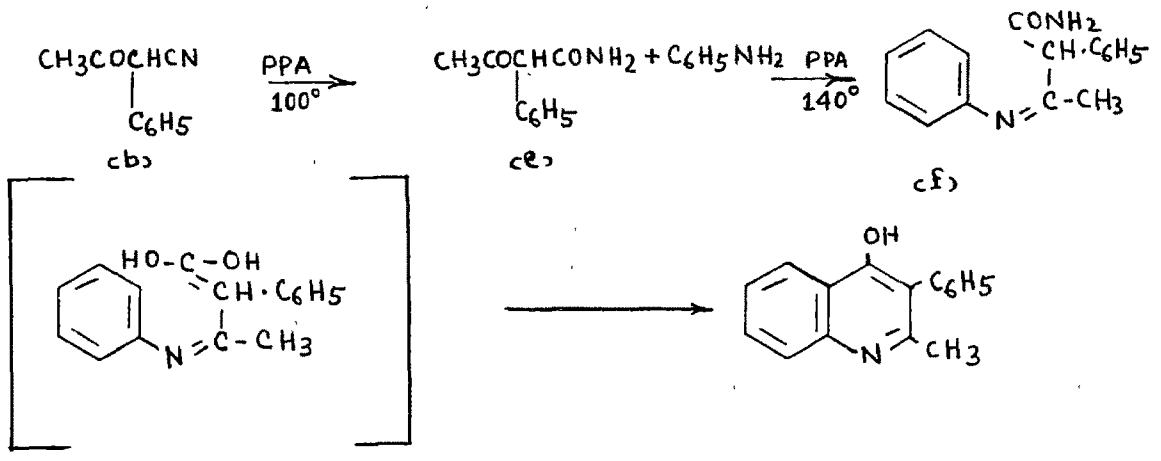
It may here be pointed out that Hauser and Murray (loc.cit.) obtained 2-methyl-3-phenyl-4-quinolinol (d) by Conrad-Limpach type of cyclisation from aniline and acetoacetic ester in 4 % yield. But the same compound (d) from aniline (a) and α-tolunitrile (b) was prepared in good yield employing acetic acid to catalyze the formation of anil (c) and with polyphosphoric acid to effect its cyclisation as under:



(a) (b) (c) (d)

This above method appears to involve the conversion of the anil-nitrile (c) to the corresponding anil-amide (f), which undergoes cyclisation eliminating ammonia. Thus, not only nitriles known to be converted to amides by polyphosphoric acid, but anil-amide (f) obtained from β-ketoamide (e) and aniline was shown to undergo cyclisation to form 2-methyl-3-phenyl-4-quinolinol (d). Here it is possible that some amount of the anil-amide, with the elimination of ammonia, was hydrolysed to the

corresponding carboxylic acid, which underwent cyclisation eliminating water ; at the same time β-ketoamide (e) was formed on partial hydrolysis of β-ketonitrile (b) with polyphosphoric acid at 100°C as under:



(b) (e) (f)

(d).

Again, β-m-chloroanilino-α-cyanoacrylate, when refluxed with diphenyl ether, gave 7-chloro-3-cyano-4-hydroxyquinoline (Price, Leonard and Herbrandson, J. Amer. Chem. Soc., 1946, 68, 1251); while 3-cyclohexyl-2,4-quinolinediols have been obtained by Baker, Lappin and Riegel (loc.cit.) on refluxing a solution of diethyl cyclohexylmalonate and aniline in diphenyl ether.

It may further be pointed out that over and above polyphosphoric acid, other cyclising agents namely, diphenyl ether, concentrated sulphuric acid and a mixture of acetic anhydride and concentrated sulphuric acid have also been tried with malon arylacids and malon mono arylamides without success. Malon arylacids, on refluxing in diphenyl ether, gave the corresponding N-acetyl arylamines (CH_3CONHR), instead of the expected quinolinediols due to decarboxylation taking place during the course of

reaction. Thus, malon anilic acid and malon-p-chloroanilic acid when respectively refluxed with diphenyl ether for 2 hours gave acetanilide, m.p. 114°C., and p-chloroacetanilide, m.p. 179°C., due to their subsequent decarboxylation of the acids. Similarly, malon mono arylamides, when refluxed in diphenyl ether, gave the corresponding cyanacet arylamides ($RNHCOCH_2CN$) due to the dehydration of the former amides. Moreover, concentrated sulphuric acid as well as a mixture of acetic anhydride and concentrated sulphuric acid were also tried with malon arylacids, but it was found that none of these condensing agents was effective in cyclising the acids to quinolinols.

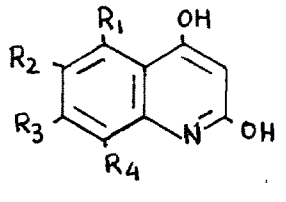
Some dichloro-, and trichloro- derivatives of 2,4-dihydroxyquinolines have also been prepared using phosphorus oxychloride as the chlorinating agent, as well as a diacetoxy derivative of a quinolinol has been prepared using acetic anhydride in presence of a few drops of pyridine.

Thus, 2,4-dichloroquinoline ; 2,4,7-trichloroquinoline ; 8-methoxy-2,4-dichloroquinoline and 6,7-dimethyl-2,4-diacetoxyquinoline have been prepared.

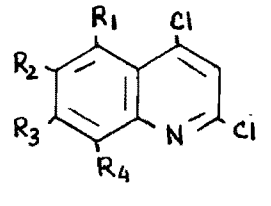
The following malon arylacids and malon mono arylamides have, thus, been cyclised (1) Malon-anilic acid (2) Malon-o-toluidic acid (3) Malon-m-toluidic acid (4) Malon-p-toluidic acid (5) Malon-m-chloroanilic acid (6) Malon-p-chloroanilic acid (7) Malon-o-anisidic acid (8) Malon-p-anisidic acid (9) Malon-1:3:4-xylidic acid (10) Malon α-naphthylanilic acid (11) Malon-β-naphthylanilic

acid (12) Malon mono anilide (13) Malon mono-p-toluidide and (14) Malon mono-1:3:4-xylidide.

It may be pointed out that no work was reported on the synthesis of 2,4-dihydroxyquinolines, using polyphosphoric acid, before the publication of the present work described in this thesis. The compounds marked with (*) asterisks have been reported for the first time. Thus, 2,4-dihydroxyquinolines and some of their chloro-and acetoxy derivatives are given below:



(IV)



(V)

1. 2,4-Dihydroxyquinoline
   (IV, $R_1=R_2=R_3=R_4=H$)
2. 2,4-Dichloroquinoline
   (V, $R_1=R_2=R_3=R_4=H$)

*3. 8-Methyl-2,4-dihydroxyquinoline
   (IV, $R_1=R_2=R_3=H$; $R_4=CH_3$)

*4. 7-Methyl-2,4-dihydroxyquinoline
   (IV, $R_1=R_2=R_4=H$; $R_3=CH_3$)

*5. 6-Methyl-2,4-dihydroxyquinoline
   (IV, $R_1=R_3=R_4=H$; $R_2=CH_3$)

6. 7-Chloro-2,4-dihydroxyquinoline
   (IV, $R_1=R_2=R_4=H$; $R_3=Cl$)

7. 2,4,7-Trichloroquinoline

(V, $R_1=R_2=R_4=H$; $R_3=Cl$)

*8. 6-Chloro-2,4-dihydroxyquinoline

(IV, $R_1=R_3=R_4=H$; $R_2=Cl$)

9. 8-Methoxy-2,4-dihydroxyquinoline

(IV, $R_1=R_2=R_3=H$; $R_4=OCH_3$)

10. 8-Methoxy-2,4-dichloroquinoline

(V, $R_1=R_2=R_3=H$; $R_4=OCH_3$)

11. 6-Methoxy-2,4-dihydroxyquinoline

(IV, $R_1=R_3=R_4=H$; $R_2=OCH_3$)

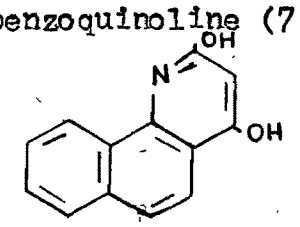
*12. 6,7-Dimethyl-2,4-dihydroxyquinoline

(IV, $R_1=R_4=H$; $R_2=R_3=CH_3$)

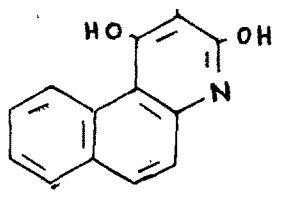
*13. 6,7-Dimethyl-2,4-diacetoxyquinoline

(IV, $OH=OCOCH_3$; $R_1=R_4=H$; $R_2=R_3=CH_3$)

14. 2,4-Dihydroxybenzoquinoline (7:8)



*15. 2,4-Dihydroxybenzoquinoline (5:6)



E X P E R I M E N T A L

2,4-Dihydroxyquinoline :

Malon-anilic acid (1.8 g.) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d. 1.75), and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutraliged with sodium hydroxide solution (pH 4), when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 360°C. Yield 1.4 g.

Malon monoanilide (2.0 g.) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6.0 ml.; d. 1.75) and the mixture was heated in an oil-bath at 140°C for 3 hr. with a calcium chloride guard tube. After cooling hydrochloric acid (30.0 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4), when the crude product precipitated. It was then filtered, crystallised from glacial acetic acid, m.p.360°C. Yield 0.9 g.

2,4-Dihydroxyquinoline, obtained from malon anilic acid or from malon monoanilide, was found to be identical by comparing the melting point, mixed melting point and by the analysis.

Analysis :

6.62 mg. of the substance gave 0.495 ml. of nitrogen at 31°C and 761 mm. pressure.

Found : N = 8.41 %.

$C_9H_7O_2N$ requires : N = 8.70 %.

2,4-Dichloroquinoline :

2,4-Dihydroxyquinoline (1.0 g.) was refluxed with phosphorus oxychloride (10.0 ml.) for an hour with a calcium chloride guard tube. After cooling to 60°C the mixture was poured on crushed ice (250 g.) and neutralised with 20 % sodium hydroxide solution (100 ml.). The separated crude product was filtered, washed with water and crystallised from alcohol, m.p.65°C. It was, then, identified by comparing the melting point and mixed melting point with that of the authentic sample.

8-Methyl-2,4-dihydroxyquinoline :

Malon-o-toluidic acid (1.95 g.) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d. 1.75), and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4), when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 360°C(dec.). Yield 1.5 g.

Analysis :

6.56 mg. of the substance gave 0.451 ml. of

nitrogen at 31°C and 760 mm. pressure.

Found : N = 7.72 %.

$C_{10}H_9O_2N$ requires : N = 8.00 %.

7-Methyl-2,4-dihydroxyquinoline :

Malon-m-toluidic acid (3.0 g.) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (15.0 g.) in phosphoric acid (9.0 ml. ; d. 1.75), and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.) when the crude product precipitated. It was, then, filtered and crystallised from glacial acetic acid, m.p. 388°C(dec.). Yield 2.4 g.

Analysis :

7.98 mg. of the substance gave 0.560 ml. of nitrogen at 33°C and 755 mm. pressure.

Found : N = 7.73 %.

$C_{10}H_9O_2N$ requires : N = 8.00 %.

6-Methyl-2,4-dihydroxyquinoline :

Malon-p-toluidic acid (3.0 g.) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (15.0 g.) in phosphoric acid (9.0 ml.; d. 1.75), and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.) when the crude product precipitated. It

was then filtered and crystallised from glacial acetic acid, m.p. 342°C.(dec.). Yield 2.20 g.

Malon mono-p-toluidide (1.0 g.) was dissolved in a clear solution of polyphosphoric acid, obtained by dissolving phosphorus pentoxide (5.0 g.) in phosphoric acid (3.0 ml. ; d. 1.75) and the reaction mixture was heated in an oil bath at 140°C for 3 hr. with a calcium chloride guard tube. After cooling, hydrochloric acid (15.0 ml. ; 1 N) was added, and the mixture was neutralised with sodium hydroxide solution (pH 4.), when the crude product was precipitated. It was then filtered, crystallised from glacial acetic acid, m.p. 342°C. Yield 0.4 g.

6-Methyl-2,4-dihydroxyquinoline, obtained from malon p-toluidic acid or from malon mono-p-toluidide, was found to be identical by comparing the melting point, mixed melting point and by the analysis.

Analysis :

8.74 mg. of the substance gave 0.644 ml. of nitrogen at 25°C and 750 mm. pressure.

Found : N = 8.32 %.

$C_{10}H_9O_2N$ requires : N = 8.00 %.

7-Chloro-2,4-dihydroxyquinoline :

Malon-m-chloroanilic acid (2.10 g.) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d. 1.75) and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling hydrochloric acid (30 ml. ; 1 N)

was added and the mixture was neutralised with sodium hydroxide solution (pH 4.), when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 339-40°. Yield 1.8 g.

Analysis :

6.94 mg. of the substance gave 0.416 ml. of nitrogen at 29°C and 761 mm. pressure.

Found : N = 6.78 %.

$C_9H_6O_2NCl$ requires : N = 7.20 %.

2,4,7-Trichloroquinoline :

7-Chloro-2,4-dihydroxyquinoline (0.5 g.) was refluxed with phosphorus oxychloride (6.5 ml.) for an hour with a calcium chloride guard tube. After cooling to 60°C, the mixture was poured on crushed ice (100 g.) and neutralised with 20 % sodium hydroxide solution (55 ml.). The separated crude product was filtered, washed with water and crystallised from alcohol ; m.p. 105°C. It was, then, identified by comparing the melting point and mixed melting point with that of the authentic sample.

6-Chloro-2,4-dihydroxyquinoline :

Malon-p-chloroanilic acid (2.10 g.) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d. 1.75) and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.) when the crude product

precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 370°C (dec.). Yield 1.80 g.

Analysis :

6.42 mg. of the substance gave 0.436 ml. of nitrogen at 25°C and 750 mm. pressure.

Found : N = 7.67 %.

$C_9H_6O_2NCl$ requires : N = 7.20 %.

8-Methoxy-2,4-dihydroxyquinoline :

Malon-o-anisidic acid (2.0 g.) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d. 1.75), and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.), when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 248°C. Yield 1.6 g.

Analysis :

9.26 mg. of the substance gave 0.614 ml. of nitrogen at 30°C and 755 mm. pressure.

Found : N = 7.42 %.

$C_{10}H_9O_3N$ requires : N = 7.30 %.

8-Methoxy-2,4-dichloroquinoline :

8-Methoxy-2,4-dihydroxyquinoline (1.0 g.) was refluxed with phosphorus oxychloride (10.0 ml.) for an hour with a calcium chloride guard tube. After cooling to 60°C, the mixture was poured on crushed ice (250 g.) and

neutralised with 20% sodium hydroxide solution (100 ml.). The separated crude product was filtered, washed with water and crystallised from alcohol, m.p. 92°C. It was, then, identified by comparing the melting point and mixed melting point with that of the authentic sample.

6-Methoxy-2,4-dihydroxyquinoline :

Malon-p-anisidic acid (2.0 g.) was dissolved in a clear solution of polyphosphoric acid, prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d.1.75)and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH. 4.) when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 308°C. Yield 1.8 g.

Analysis :

4.288 mg. of the substance gave 9.822 mg. of carbon dioxide and 1.846 mg. of water.

6.60 mg. of the same substance gave 0.426 ml. of nitrogen at 29°C and 761 mm. pressure.

Found : C = 62.51 % ; H = 4.81 % ; N = 7.30 %.

$C_{10}H_9O_3N$ requires : C = 62.82 % ; H = 4.75 % ; N = 7.30 %.

6,7-Dimethyl-2,4-dihydroxyquinoline :

Malon-1:3:4-xylidic acid (2.0 g.) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric

acid (6 ml. ; d. 1.75), and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.) when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 345°C (dec.). Yield 1.7 g.

Malon mono-1:3:4-xylidide (1.0 g.) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (5.0 g.) in phosphoric acid (3.0 ml. ; d. 1.75) and the mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (15 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.) when the crude product was precipitated. It was then filtered, crystallised from glacial acetic acid, m.p. 345°C (dec.). Yield 0.45 g.

6,7-Dimethyl-2,4-dihydroxyquinoline, obtained from malon 1:3:4-xylidic acid or from malon mono 1:3:4-xylidide, was found to be identical by the melting point, mixed melting point and by the analysis.

Analysis :

4.160 mg. of the substance gave 10.642 mg. of carbon dioxide and 2.164 mg. of water.

8.50 mg. of the same substance gave 0.550 ml. of nitrogen at 30°C and 754 mm. pressure.

Found : C = 69.81 % ; H = 5.82 % ; N = 7.23 %.

$C_{11}H_{11}O_2N$ requires : C = 69.82 % ; H = 5.86 % ; N = 7.40 %.

6,7-Dimethyl-2,4-diacetoxyquinoline :

6,7-Dimethyl-2,4-dihydroxyquinoline (0.2 g.) was refluxed with acetic anhydride (4 ml.) in presence of 3 to 4 drops of pyridine for 2 hours. The reaction mixture was then added to water, the product was filtered crystallised from alcohol, m.p. 212°C. Yield 0.15 g.

Analysis :

5.590 mg. of the substance gave 0.247 ml. of nitrogen at 34°C and 756 mm. pressure.

Found : N = 4.88 %.

$C_{15}H_{15}O_4N$ requires : N = 5.12 %.

2,4-Dihydroxybenzoquinoline (7:8) :

Malon-α-naphthylanilic acid (2.3 g.) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d. 1.75) and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.) when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 338-39°C (dec.). Yield 1.9 g.

Analysis :

4.746 mg. of the substance gave 12.884 mg. of carbon dioxide and 1.816 mg. of water.

6.70 mg. of the same substance gave 0.377 ml. of nitrogen at 30°C and 760 mm. pressure.

Found : C = 74.08 % ; H = 4.28 % ; N = 6.34 %.

$C_{13}H_9O_2N$ requires : C = 73.92 % ; H = 4.30 % ; N = 6.63 %.

2,4-Dihydroxybenzoquinoline (5:6) :

Malon-β-naphthylanilic acid (2.3 g.) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (10.0 g.) in phosphoric acid (6 ml. ; d. 1.75) and the reaction mixture was heated in an oil-bath at 140°C for 3 hours with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml. ; 1 N) was added and the mixture was neutralised with sodium hydroxide solution (pH 4.) when the crude product precipitated. It was then filtered and crystallised from glacial acetic acid, m.p. 381°C (dec.). Yield 1.7 g.

Analysis :

6.68 mg. of the substance gave 0.367 ml. of nitrogen at 30°C and 761 mm. pressure.

Found : N = 6.20 %.

$C_{13}H_9O_2N$ requires : N = 6.63 %.

Table 3

2,4-Dihydroxyquinolines

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Nitrogen Found %	Nitrogen Reqd. %	Carbon Found %	Carbon Reqd. %	Hydrogen Found %	Hydrogen Reqd. %
1.	2,4-Dihydroxyquinoline	$C_9H_7O_2N$	360	77.7	8.41	8.70	-	-	-	-
2.	2,4-Dichloroquinoline	$C_9H_5NCl_2$	65	-	-	-	-	-	-	-
3.	8-Methyl-2,4-dihydroxy-quinoline	$C_{10}H_9O_2N$	360	76.8	7.72	8.00	-	-	-	-
4.	7-Methyl-2,4-dihydroxy-quinoline	$C_{10}H_9O_2N$	388	80.0	7.73	8.00	-	-	-	-
5.	6-Methyl-2,4-dihydroxy-quinoline	$C_{10}H_9O_2N$	342	73.3	8.32	8.00	-	-	-	-
6.	7-Chloro-2,4-dihydroxy-quinoline	$C_9H_6O_2NCl$	340	85.7	6.78	7.20	-	-	-	-
7	2,4,7-Trichloroquinoline	$C_9H_4NCl_3$	105	-	-	-	-	-	-	-
8.	6-Chloro-2,4-dihydroxy-quinoline	$C_9H_6O_2NCl$	370	85.7	7.67	7.20	-	-	-	-

Table 3 (Contd)

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Nitrogen Found %	Nitrogen Reqd. %	Carbon Found %	Carbon Reqd. %	Nitrogen Found %	Nitrogen Reqd. %
9.	8-Methoxy-2,4-dihydroxy-quinoline	$C_{10}H_9O_3N$	248	80.0	7.42	7.30	-	-	-	-
10.	8-Methoxy-2,4-dichloro-quinoline	$C_{10}H_7ONCl_2$	92	-	-	-	-	-	-	-
11.	6-Methoxy-2,4-dihydroxy-quinoline	$C_{10}H_9O_3N$	308	90.0	7.30	7.30	62.51	62.82	4.81	4.75
12.	6,7-Dimethyl-2,4-dihydroxy-quinoline	$C_{11}H_{11}O_2N$	345	85.5	7.23	7.40	69.81	69.82	5.82	5.86
13.	6,7-Dimethyl-2,4-diacetoxy-quinoline	$C_{15}H_{15}O_4N$	212	75.0	4.88	5.12	-	-	-	-
14.	2,4-Dihydroxybenzoquinoline (7:8)	$C_{13}H_9O_2N$	339	82.6	6.34	6.63	74.08	73.92	4.28	4.30
15.	2,4-Dihydroxybenzoquinoline (5:6)	$C_{13}H_9O_2N$	381	73.9	6.20	6.63	-	-	-	-