PART VI

Halogenation of 2-hydroxy-4-methyl-quinolines and 2,4-dihydroxyquinolines.

PART VI

Theoretical

Andre ' Meyer and Paul Heimann (loc.cit.) studied the action of bromine on 2,4-dihydroxyquinoline (γ-hydroxy-carbostyril) and obtained the so called a-bromo-2,4-dihydroxyquinoline in cold acetic acid in a quantitative yield ; and with excess of bromine in hot got 3-bromo-2,4-dihydroxyquinoline. Again, bromination without a catalyst in boiling benzene gave c-bromo-2,4-dihydroxyquinoline. Now a-bromo-2,4-dihydroxyquinoline and c-bromo-2,4-dihydroxy-quinoline, on oxidation with hot $KMnO_4$, gave the same 2,4-dihydroxyquinolinic acid, as did 2,4-dihydroxyquinoline. Hence the Br atom in the a-bromo-or c-bromo-2,4-dihydroxy-quinoline are in undetected positions in the benzene ring. But 2,4-dihydroxyquinoline and a-bromo-2,4-dihydroxyquinoline with PBr_5 gave 2,4-dibromoquinoline and 2,3,4-tribromo-quinoline respectively. Therefore the a-bromo-or the c-bromo derivative ? can must not be the same 3-bromo-2,4-dihydroxy-quinoline.

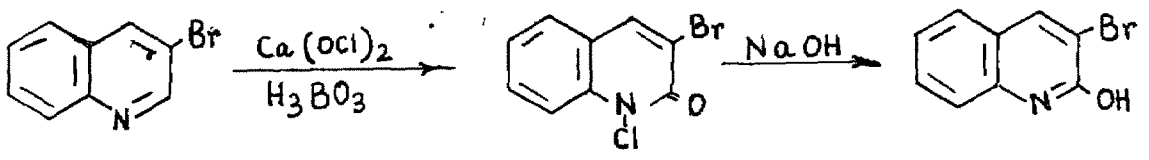
Jansen and Wibaut (Rec.trav.chim., 1937,56,699 ; 708) carried out the bromination of quinoline in gaseous phase between 300-500°C ; and found that the first bromine atom only entered in the pyridine nucleus. But 3-bromo-quinoline was prepared by passing preheated vapours of quinoline and bromine through a tube, filledi with pumice at 300°C while at 450-500° the product was 2-bromoquinoline in 50-60% yield.

Edinger (J.prakt.Chem., 1896,54,[2], 357)

however, prepared 3-bromoquinoline most conveniently by direct bromination of quinoline in the presence of a relatively large amount of sulphur. Presumably sulphuryl bromide is the actual brominating agent. Similarly, Edinger and Lubberger (J.prakt.Chem., 1896, 162 2,340 ; Baker et al., J. Amer. Chem. Soc., 1946, 68, 1532 inter alia) carried out the chlorination of the quinoline at 3-position by refluxing it with sulphur dichloride.

Renshaw and Friedman (J. Amer. Chem. Soc., 1939, 61, 3320) observed that bromination of quinoline with sulphur and bromine gave 3-bromoquinoline. Heating 3-bromoquinoline with concentrated ammonium hydroxide and copper sulphate catalyst in a rocking autoclave at 160°C for 2 hours and after extraction with ether gave 3-aminoquinoline. Mills and Watson (J. Chem. Soc., 1910, 97, 753) prepared 3-quinolinol by diazotization of 3-aminoquinoline, which is in turn prepared by treatment of 3-bromoquinoline with ammonia in the presence of copper (Maier-Bode, Ber., 1936, 69, 1536).

LaCoste (Ber., 1881, 14, 917) obtained a bromoquinoline when a solution of quinoline in hydrochloric acid was warmed with bromine. Claus and Collischonn (Ber., 1886, 19, 2508, 2763) obtained the same compound by heating quinoline dibromide hydrobromide, $C_9H_7N.HBr.Br_2$ and assigned it the structure of 4-bromoquinoline. But Decker (J. prakt. Chem., 1892, 45 [2], 47) found that the above compound was 3-bromoquinoline by converting it into 3-bromocarbostyril as under :



Riegel et al. (loc.cit.) have prepared 3-bromo-4-quinolinol from 4-quinolinol with bromine. Further, 3-bromo-4-quinolinol with phosphorus oxychloride gave 3-bromo-4-chloroquinoline, but this compound was unreactive towards amines in the coupling reaction, so a more reactive compound was prepared. This was accomplished by refluxing the quinolinol with phosphorus tribromide to produce 3,4-dibromoquinoline from which the antimalerial drug was finally obtained.

Hardman and Partridge (J. Chem. Soc., 1958, 614 ; ibid., 1955, 510) studied the bromination of 2-amino-4-hydroxy-7-methylquinolineand observed that the bromine entered into the 3-position. The 3-bromo derivative, on treatment with nitrous acid, furnished the bromo-hydroxyquinoline, and the removal of bromine by reduction with raney alloy gave the dihydroxyquinoline from which the dichloroquinoline was obtained on treatment with phosphorus oxychloride. 2,4-Dihydroxyquinoline was also obtained from 2-amino-4-hydroxyquinoline, which was fused at 250-290° with potassium hydroxide and then acidified with hydrochloric acid. Further bromination of 2-amino-4-hydroxyquinoline in glacial acetic acid gave a monobromo derivative, which on treatment with nitrous acid furnished the same bromo-2,4-dihydroxy-quinoline as was obtained by a similar bromination of 2,4-dihydroxyquinoline. Hence, it is concluded that the bromine

atom has occupied the 3-position both in bromo-2,4-dihydroxy-quinoline and in 2-amino bromo-4-hydroxyquinoline.

Schofield and Swain (J. Chem. Soc., 1950, 384) observed the qualitative comparison with related 4-hydroxy-quinolines and showed that the hydroxyquinolines undergo chlorination and bromination more readily and more efficiently at the 3-position than do analogous cinnolines. For this purpose, they have carried out the bromination of 4-hydroxy-, 6-chloro-4-hydroxy- and 6-bromo-4-hydroxyquinolines and obtained respectively 3-bromo-,6-chloro-3-bromo-, and 3,6-dibromo-4-hydroxyquinolines in good yields. Also they have carried out the chlorination of the above compounds using sulphuryl chloride as the chlorinating agent at 95°C and obtained the 3-chloroquinoline derivatives.

Chick and Wilsmore (loc.cit.) prepared γ-bromo-aceto-acetanilide from aniline dissolved in carbon tetrachloride with a solution of γ-bromoacetoacetylbromide in the same solvent. The anilide was obtained, which melted and decomposed at 138°C as given by Knorr (Annalen., 1886, 236, 79) for the bromoacetoacetanilide which he obtained by brominating acetoacetanilide. On dissolving the bromoacetoacetanilide in cold concentrated sulphuric acid gave 3-bromo-2-hydroxy-4-methylquinoline.

Surrey and Cutler (loc.cit.) carried out the synthesis of several 3-halo-4-aminoquinoline derivatives as a part of a general study on the effect of the position of halogen atom substituents on the antimalerial action of 4-dialkylaminoalkylaminoquinoline compounds. Here,

ethyl-4-hydroxyquinaldate and ethyl 5-(and 7)-chloro-4-hydroxyquinaldates were treated in glacial acetic acid with bromine, sulphuryl chloride, or iodine monochloride, and gave respectively the 3-bromo-3-chloro- or 3-iodo derivatives in practically quantitative yields. A trace of iodine as a catalyst was used in the chlorination and bromination. The structure of 3-bromo-4-hydroxyquinoline was proved by the identity of its melting point with the compound reported by Niementowski and Sucharda (J. prakt. Chem., 1916, 94, 225).

Lydia Monti (Gazz. Chim. ital., 1937, 67, 624) treated the mixture of 2-hydroxy-4,8-dimethylquinoline and methylolchloroacetamide in concentrated sulphuric acid at room temperature and obtained chloroacetyl (2-hydroxy-4,8-dimethyl-3-quinolyl)methylamine. Riegel and his co-workers (loc.cit.) prepared 3-bromo-4-quinolinol and 3-bromo-8-nitro-4-quinolinol from 4-quinolinol and 8-nitro-4-quinolinol respectively by brominating in warm glacial acetic acid.

Fujino et al. (Nippon Daigaku Yakugaku Kenkyu Hokoku., 1958, 2, 36 ; Chem. Abst., 1959, 53, 8137) carried out the bromination of quinaldine in presence of BF_3-AcOH and obtained monobromoquinaldine with a small quantity of ω-dibromoquinaldine.

Schultz, Goldberg, Carsch and Ordas (J. Org. Chem., 1946, XI, 170) carried out the chlorination of 6-methoxy-8-nitroquinoline with sulphuryl chloride and obtained a mixture of polychlorinated compounds, viz. 3,5(or 7)-dichloro-6-methoxy-8-nitroquinoline ; 3,5,7,8-

tetrachloro-6-methoxy-8-nitroquinoline and 5,7,8-trichloro-6-methoxy-8-nitroquinoline. Quinolines carrying halogen in the benzene ring are generally easily prepared by various ring closer methods. Zaruma et al. (Zhur. Obshchei. Khim., 1960, 30, 1614 ; Chem. Abst., 1961, 55, 3590) carried out the synthesis of 5-bromoquinoline, viz., bromination of 8-acetamidoquinoline at 0°C in acetic acid and adjustment to pH 9 with sodium hydroxide gave 92 % yield of 5-bromo-8-acetamidoquinoline, from which 5-bromo-8-aminoquinoline was prepared by hydrochloric acid.

Ridd et al. (Chem. and Ind., London, 1958, 361) carried out the bromination of quinoline at 5 and 8-positions in concentrated sulphuric acid. They pointed out that the bromination of quinoline by direct mixing of the reagents in the presence of sulphur or in hydrochloric acid, the product usually include polybromoquinolines, but the initial substitution appears to be in the heterocyclic ring, for the only mono-substituted product obtained by the above methods, was found to be 3-bromoquinoline. In contrast, the nitration of quinoline in mixtures of nitric acid and sulphuric acid gave exclusively to substitution, in the homocyclic ring, the 5-nitro and 8-nitro isomers being formed in similar amounts (Dewar and Maitlis, J. Chem. Soc., 1957, 2521). So the bromination of quinoline under conditions more nearly related to those employed in the above nitration, was carried out in concentrated sulphuric acid in presence of silver sulphate and the 5-bromo-and 8-bromo-quinolines have been obtained.

Huggill and Plant (J. Chem. Soc., 1939, 784) studied the bromination of 2,3-disubstituted-4-quinolones, viz., 1,2,3,4-tetrahydroacridone, on bromination with one mole of bromine in acetic acid, gave 7-bromotetrahydroacridone ; while with two mols.of bromine it gave 7,9-dibromotetrahydroacridone. The bromination of 2,6,8-trimethyl-4-quinolone was carried out by the above method, and obtained a mono-bromo derivative from which the halogen atom is not removed by pyridine, and since the 3-position is unsubstituted in the starting material, it is likely that the bromine atom has entered at this point.

In the present investigation of Part VI, it is proposed to study the halogenation of 2-hydroxy-4-methylquinolines and 2,4-dihydroxyquinolines respectively with the object of determining the position in which the halogen atom enters the benzene or the pyridine part of the quinoline nucleus. The problem of confirming the position of the halogen atom, occupying the quinoline ring is not only of considerable importance, but of much confusion, as has been observed from their reactions. Because of the low electron density at the 2- and 4-positions of the quinoline ring compared to the 3,5,6,7 and 8-positions, quinoline halogen derivatives with the halogen in the 2- or 4-position differ considerably from the other halogen compounds. These differences involve both methods of synthesis and reactions and in general the 2- and 4-haloquinoline compounds parallel to their pyridine counterparts.

Direct bromination and chlorination of

hydroxyquinolines in acetic acid have, therefore, been carried out and the corresponding 3-bromo- and 3-chloro-derivatives have been prepared. Iodination of hydroxyquinolines is also attempted by the available methods, using iodine and iodic acid, iodine in liquor ammonia and iodine monochloride. It may be pointed out that 3-iodo-2-hydroxy-4-methylquinolines were prepared by direct iodination of 2-hydroxy-4-methylquinolines, using iodine and iodic acid; but attempts at the iodination of 4-hydroxycarbostyrils, were found to be unsuccessful.

The fact that the bromine or the chlorine atom has entered only in the 3-position of hydroxyquinolines is duly confirmed by the preparation of a number of mono bromo and mono chloro derivatives of acetoacet arylamides and of malon mono arylamides, each of which on subsequent cyclisation, has given the corresponding 3-bromo-and 3-chloro-hydroxyquinolines ; also 3-iodo derivatives of 4-methylcarbostyrils are obtained, but not of 4-hydroxy-carbostyrils. Hence, 3-haloquinolines have been prepared by the cyclisation of the corresponding mono halo acetoacet arylamides and mono halo malonmono arylamides ; while the similar cyclisation of the mono iodo derivatives of these amides was not found possible. Thus, to confirm the 3-position occupied by the halogen atom in hydroxyquinolines, a number of mono halo derivatives of the above amides have been prepared and subsequently cyclised.

In the present work the corresponding mono bromo and mono chloro derivatives of acetoacet arylamides and of

malonmono arylamides, in much better yields have been prepared, using bromine and sulphuryl chloride in acetic acid respectively in presence of a trace of iodine as catalyst.

Backe's, West and Whiteley (loc.cit.) prepared monobromo derivatives of the substituted amides of malonic acid by brominating the amides in acetic acid. West (J. Chem. Soc., 1922, 121, 2196) brominated malon diarylamides and found that the hydrogen atom in the para position of the phenyl group and one of the hydrogen atoms of the methylene group were equally susceptible to the attack of bromine. Naik and Shah, (J. Ind. Chem. Soc., 1927, 4, 11) prepared dichloro malon arylamides using sulphuryl chloride in dry benzene. Desai (J. Ind. Chem. Soc., 1955, 32, 592) prepared mono bromo derivatives of cyanacet arylamides using bromine in hot acetic acid. Here, the hydrogen atom of the reactive methylene group, situated between the two carbonyl groups, $-CO.CH_2.CO-$, is replaced by the halogen atom and the mono halogen derivatives of the said arylamides have been prepared by the methods given below:

Bromination method of amides :

Acetoacet arylamide or malonmono arylamide (0.01 M) was dissolved in 10-15 ml. of glacial acetic acid in presence of a trace of iodine as catalyst, to which 10 % solution of bromine in acetic acid (16 ml. 0.01 M) was added with continuous stirring. The flask was, then kept over-night at room temperature and the reaction mixture, on pouring into cold water, gave a white product, which was filtered and crystallised from benzene.

$$CH_3COCH_2CONHR + Br_2 \longrightarrow CH_3COCHBrCONHR + HBr$$

$$H_2NCO\ CH_2\ CO\ NHR + Br_2 \longrightarrow H_2NCOCH_2CONHR + HBr$$

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

The monobromo derivatives of the other members of acetoacet arylamides and of malonmono arylamides in a similar way have been prepared in 70-75 per cent yields. (Mehta, Trivedi and Patel, J. Sci. Industr. Res., 1961, 20B, 460)

Chlorination method of amides :

Acetoacet arylamide or malonmono arylamide (0.01 M) was dissolved in 10-15 ml. of glacial acetic acid in presence of a trace of iodine as catalyst, to which sulphuryl chloride (0.01 M) in cold was added. The reaction mixture was kept for 3 hours at room temperature and on pouring into cold water, it gave a white product, which was filtered and crystallised from alcohol.

$$CH_3COCH_2CONHR + SO_2Cl_2 \longrightarrow CH_3COCHClCONHR + SO_2 + HCl$$

$$H_2NCOCH_2CONHR + SO_2Cl_2 \longrightarrow H_2NCOCHClCONHR + SO_2 + HCl$$

(Where R, is phenyl, tolyl, xylyl and naphthyl radicals).

Similarly, monochloro derivatives of other members of the said amides have been prepared. It may be pointed out that Naik et al., (J. Ind. Chem. Soc., 1943, 20, 384) prepared a few monochloro acetoacet arylamides in cold, using sulphuryl chloride in dry ether ; but the present method furnishes better yields.

Iodination method of amides :

Acetoacet arylamide or malonmono arylamide (0.05 M) was dissolved in alcohol by heating to which was added

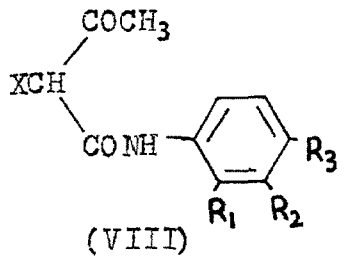
iodine (0.04 M) in presence of concentrated aqueous solution of iodic acid (0.01 M). The reaction mixture, without reflux and on cooling, gave a product, which was filtered and crystallised from alcohol.

$$5CH_3COCH_2CONHR + 2I_2 + HIO_3 \longrightarrow 5CH_3COCHICONHR + 3H_2O$$

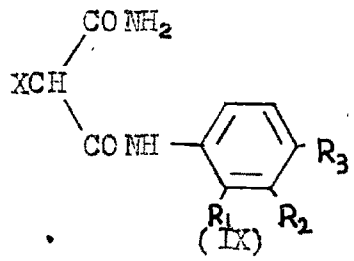
$$5H_2NOCCH_2CONHR + 2I_2 + HIO_3 \longrightarrow 5H_2NOCCHICONHR + 3H_2O$$

In the same way the monoiodo derivatives of other members of acetoacet arylamides and of malonmono arylamides have been prepared. It is to be noted that Avasare et al. (J. Ind.Chem.Soc., 1952,29, 709) have prepared iodo derivatives of acetoacet arylamides and cyanacet arylamides.

Accordingly, the following mono halogen derivatives of acetoacet arylamides and malonmono arylamides have been prepared.



(VIII)



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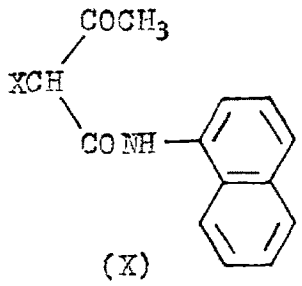

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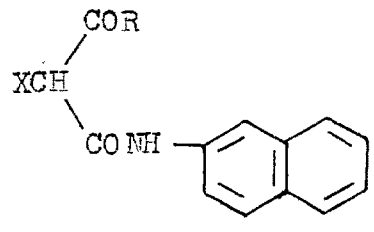


(XI)

*1. Monobromo acetoacet-p-toluidide
(VIII, X=Br ; R_1=R_2=H ; R_3=CH_3)

*2. Monobromo acetoacet-o-toluidide
(VIII, X=Br ; R_2=R_3=H ; R_1=CH_3)

*3. Monobromo acetoacet-p-chloroanilide
(VIII, X=Br ; R_1=R_2=H ; R_3=Cl)

*4. Monobromo acetoacet-p-phenitidide
(VIII, X=Br ; R_1=R_2=H ; R_3=OC_2H_5)

*5. Monobromo acetoacet-1:2:4-xylidide
(VIII, X=Br ; R_2=H ; R_1=R_3=CH_3)

*6. Monobromo acetoacet-1:3:4-xylidide
(VIII, X=Br ; R_1=H ; R_2=R_3=CH_3)

*7. Monochloro acetoacet-o-toluidide
(VIII, X=Cl ; R_2=R_3=H ; R_1=CH_3)

*8. Monochloro acetoacet-α-naphthylamide
(X, X=Cl)

*9. Monochloro acetoacet-β-naphthylamide
(XI, X=Cl ; R=CH_3)

10. Monoiodo acetoacetanilide
(VIII, X=I ; R_1=R_2=R_3=H)

11. Monoiodo acetoacet-o-toluidide
(VIII, X=I ; R_2=R_3=H ; R_1=CH_3)

12. Monoiodo acetoacet-p-toluidide
(VIII, X=I ; R_1=R_2=H ; R_3=CH_3)

13. Monoiodo acetoacet-1:3:4-xylidide
(VIII, X=I ; R_1=H ; R_2=R_3=CH_3)

*14. Monobromo malonmono-p-toluidide
(IX, X=Br ; R_1=R_2=H ; R_3=CH_3)

*15. Monobromo malonmono-m-toluidide
(IX, X=Br ; R_1=R_3=H ; R_2=CH_3)

*16. Monobromo malonmono-p-chloroanilide
(IX, X=Br ; R_1=R_2=H ; R_3=Cl)

*17. Monobromo malonmono-p-anisidide
(IX, X=Br ; R_1=R_2=H ; R_3=OCH_3)

*18. Monobromo malonmono-1:3:4-xylidide
(IX, X=Br ; R_1=H ; R_2=R_3=CH_3)

*19. Monobromo malonmono-β-naphthylamide
(XI, X=Br ; R=NH_2)

*20. Monochloroo malonmono-p-toluidide
(IX, X=Cl ; R_1=R_2=H ; R_3=CH_3)

*21. Monochloro malonmono-p-anisidide
(IX, X=Cl ; R_1=R_2=H ; R_3=OCH_3)

*22. Monochloro malonmono-1:3:4-xylidide
(IX, X=Cl ; R_1=H ; R_2=R_3=CH_3)

*23. Monoiodo malonmono anilide
(IX, X=I ; R_1=R_2=R_3=H)

*24. Monoiodo malonmono-p-toluidide
(IX, X=I ; R_1=R_2=H ; R_3=CH_3)

*25. Monomethyl acetoacetanilide
(VIII, X=CH_3 ; R_1=R_2=R_3=H)

* The compounds marked with asterisks (*) are reported for the first time.

Mehta and Patel, (Curr.Sci., 1961, 15, 30) carried out direct bromination of 2,4-disubstituted quinolines, using bromine in acetic acid in presence of a trace of iodine as catalyst and obtained 3-bromo-2,4-disubstituted quinolines. The 2,4-disubstituted quinolines, thus, selected for study are 2-hydroxy-4-methylquinolines, which are obtained by the method of Ewins and King (loc.cit.) ; whereas 2,4-dihydroxyquinolines have been prepared by Mehta and Patel (loc.cit.). These 2,4-disubstituted quinolines are also chlorinated and the 3-chloroquinoline

derivatives respectively of 4-methylcarbostyrils and 4-hydroxycarbostyrils have been obtained. The 3-iodo-2-hydroxyquinolines likewise prepared ; but the attempts to iodinate 2,4-dihydroxyquinolines were not successful. The direct halogenation of hydroxyquinolines in the 3-position was, thus, carried out by the methods described below :

Bromination of hydroxyquinolines :

2-Hydroxy-4,6-dimethylquinoline or 6-methyl-2,4-dihydroxyquinoline (0.01 M) was dissolved in 25 ml. of glacial acetic acid in presence of a trace of iodine as catalyst, to which 20 % solution of bromine in acetic acid (8 ml.) was slowly added with continuous stirring. The reaction mixture, on dilution with water, gave a white product, which was filtered and crystallised from alcohol. White needles of 3-bromo-2-hydroxy-4,6-dimethylquinoline or of 3-bromo-6-methyl-2,4-dihydroxyquinoline were obtained. Similarly, 3-bromo derivatives of the other members of hydroxyquinolines were prepared.

Chlorination of hydroxyquinolines :

2-Hydroxy-4,8-dimethylquinoline or 6-methyl-2,4-dihydroxyquinoline (0.01 M) was dissolved in glacial acetic acid (15 ml.) to which sulphuryl chloride (0.01 M) in cold was added in presence of a trace of iodine as catalyst. The reaction mixture was stirred for half an hour and the monochloro derivative, which was separated, filtered and crystallised from alcohol. In a similar way 3-chloro derivatives of the other members of hydroxyquinolines

have been prepared.

Iodination of hydroxyquinolines : (With iodine and iodic acid)

2-Hydroxy-4,8-dimethylquinoline (2.16 g.) was dissolved in minimum quantity of hot alcohol, to which iodine crystals (1.27 g.) and concentrated aqueous solution of iodic acid (0.5 g.) were added. The reaction mixture was stirred for one hour at room temperature and on dilution with water gave a product, which was filtered and crystallised from alcohol. The product of crystallisation was identified as 3-iodo-4,6-dimethylquinoline. In a similar way the other 3-iodo derivatives of 4-methylcarbostyrils are prepared ; but 3-iodo-4-hydroxycarbostyrils are, likewise, not obtained.

The yields of iodo derivatives were found to be better by this method than those obtained by the other methods. It may be noted, that the attempts to prepare iodo derivatives of 4-hydroxycarbostyrils have not been successful.

(a) With iodine and iodic acid :

6-Methyl-2,4-dihydroxyquinoline (2.19 g.) was dissolved in hot alcohol, to which iodine (1.27 g.) and iodic acid (0.5 g.) were added and the reaction mixture treated as above. The product was crystallised from alcohol, which was identified as the original 6-methyl-2,4-dihydroxyquinoline. Similarly with other members of 2,4-dihydroxyquinolines, the iodination was, thus,found to be unsuccessful, where only the respective original

2,4-dihydroxyquinoline derivative was obtained from the reaction mixture.

(b) With iodine and liq.ammonia :

6-Methyl-2,4-dihydroxyquinoline (1.75 g.) was dissolved in 40 ml. of 22 % aqueous ammonia, to which a solution of iodine (1.27 g.) in potassium iodide (3 g.) was added with stirring for half an hour. The mixture was then poured into excess of dilute ice cold sulphuric acid. The precipitated white mass was filtered and crystallised from alcohol. The product was identified as the original 6-methyl-2,4-dihydroxyquinoline.

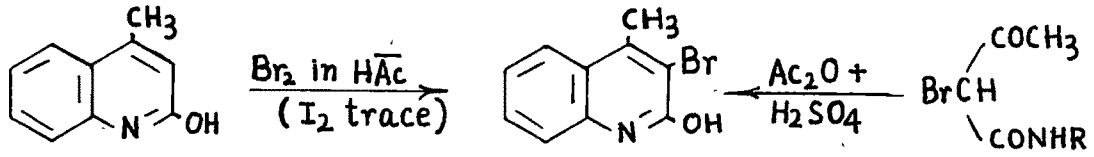
(c) With iodinemonochloride :

6-Methyl-2,4-dihydroxyquinoline (0.01 M) was dissolved in a minimum quantity of acetic acid, to which 15 ml. of hydrochloric acid (d. 1.11) and iodine monochloride (1.62 g.) were added. The reaction mixture was kept over-night in a well stoppered flask at 60°C, then stirred vigorously for two hours. The separated solid was filtered, washed with water and crystallised from acetic acid which was identified as the original 6-methyl-2,4-dihydroxyquinoline.

Now the monobromo- and the monochloro- derivatives of acetoacet arylamides, prepared by the above mentioned methods, which on subsequent cyclisation, gave the corresponding 3-bromo and 3-chloro- derivatives of 2-hydroxy-4-methylquinolines, using a mixture of acetic anhydride and concentrated sulphuric acid in the proportion of 1 : 1 by volume as the cyclising agent (Mehta and Patel,

loc.cit.). Similarly, .the monobromo and the monochloro derivatives of malonmono arylamides, on cyclisation, gave the corresponding 3-bromo and 3-chloro derivatives of 2,4-dihydroxyquinolines using polyphosphoric acid as the cyclising agent at 140°C. (Patel and Mehta, loc.cit.).

The courses of reaction of 2-hydroxy-4-methyl-quinolines (I) and bromo or chloro acetoacet arylamides (II and IV), by direct and indirect methods, confirming the 3-bromo(or 3-chloro) hydroxyquinolines (III and V) are expressed as under:

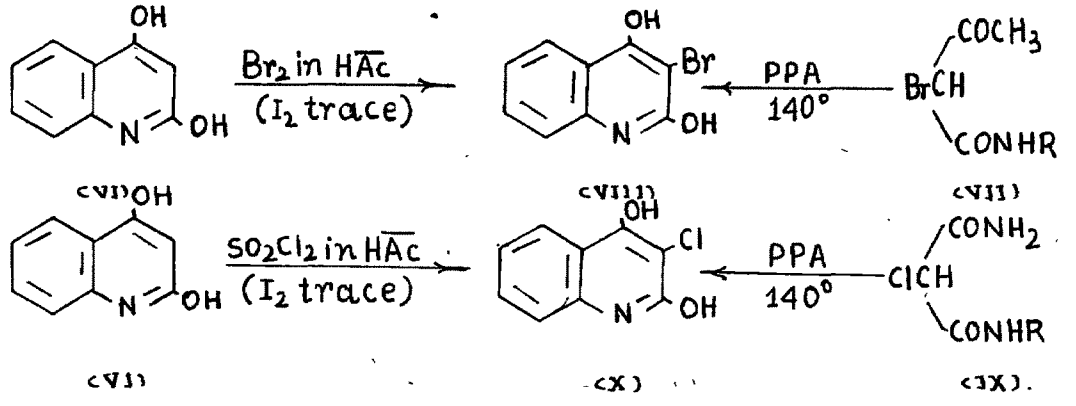


(I) (III) (II)

(V) (IV).

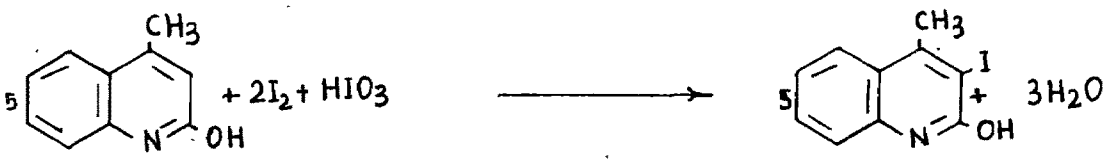
(Where, R = $-C_6H_5$, $-C_7H_7$, $-C_8H_9$ and $-C_{10}H_7$ groups).

Similarly, with 2,4-dihydroxyquinolines (VI) the confirmations of 3-bromo or 3-chloro derivatives of 4-hydroxycarbostyrils (VIII and X), and bromo (or chloro) of malonomono arylamides (VII and IX) are given below:



(Where R = phenyl, tolyl, xylyl and naphthyl groups).

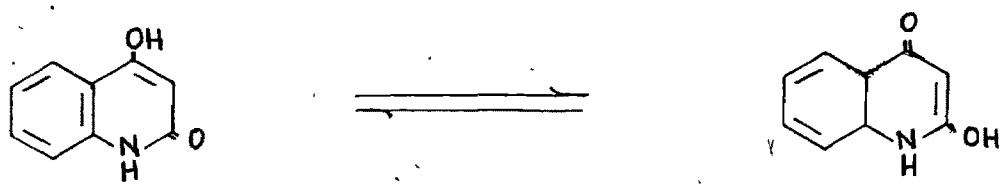
Since, 2-hydroxy-4-methylquinolines, on iodination with iodine crystals and iodic acid, gave the corresponding 3-iodo-2-hydroxy-4-methylquinolines ; but for reasons not known the iodination of 2,4-dihydroxyquinolines was not possible, inspite of the attempts being made by the application of available methods described under (a), (b) and (c) and in each case under investigation it was found that the original dihydroxyquinoline derivative was recovered from the reaction mixture undergoing iodination. Then,



While confirming the position-3 occupied by iodine atom in use of iodo derivatives, prepared by direct iodination of 4-methylcarbostyrils, it can, conveniently, be shown from the analogous behaviour of the formation of 3-bromo and 3-chloro derivatives of hydroxyquinolines ; because the mono iodo acetoacet arylamides are very unstable

and they undergo spontaneous decomposition, evolving copious fumes of iodine vapour from the reaction mixture, with the result that the 3-iodo-4-methyl carbostyrils are not obtained by cyclisation, using a mixture of acetic anhydride and sulphuric acid as the cyclising agent. Such copious fumes of iodine, were similarly, evolved from the reaction mixture of the monoiodo derivatives of malonmono arylamides, during the process of cyclisation, using polyphosphoric acid as the cyclising agent, with the result that 3-iodo-4-hydroxy carbostyrils were not formed or immediately decomposed if at all they were formed.

However, it is difficult to explain the non-formation of 3-iodo-4-hydroxy carbostyrils by the available methods of iodination. The fact that 4-hydroxycarbostyril, as shown in part II, exists in transannelar carbostyril (Ia) and kynurin (Ib) tautomeric structures ; whereas the existence of such a kynurin (Ib) structure in 4-methyl-carbostyril has not become possible. Thus;



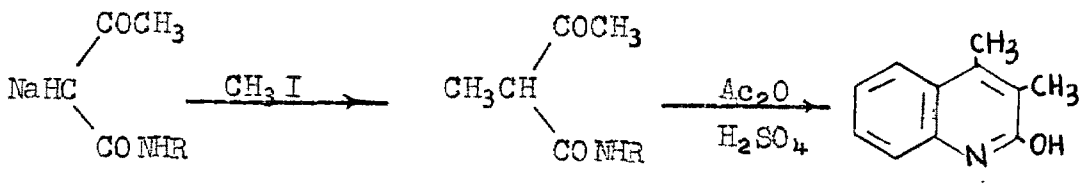
(Ia) (Ib)

On the basis of this phenomenon of tautomerism , it may probably be possible to explain the non-formation of 3-iodo derivatives with 4-hydroxycarbostyrils or the formation of 3-iodo derivatives with 4-methylcarbostyrils. Moreover, it must be remembered that the mode or the mechanism of substitution for bromination and chlorination

does not seem to be of the same type as that of iodination.

It is quite obvious that in the molecule of acetoacet arylamide and malonmono arylamide, containing the reactive methylene (-CO.CH_2.CO-) group of which the hydrogen atom is being replaced by a halogen atom or a monovalent group of atoms, forming its respective reactive H-substituted derivative of the amide, wherein the same halogen atom or the other monovalent group will occupy the 3-position in the newly formed derivative of hydroxy-quinoline, obtained by the cyclisation of the said arylamides.

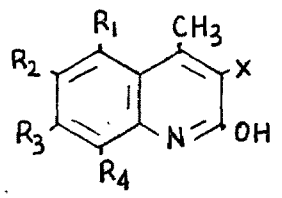
Further, through the interaction of monosodio acetoacetanilide with methyl iodide, the monomethyl acetoacetanilide was prepared, which, on cyclisation with acetic anhydride and sulphuric acid, gave 2-hydroxy-3,4-dimethylquinoline, the identity of which was proved by comparing its melting point with that of the authentic sample (Knorr, Ann., 1888, 245,365). Here, the methyl group of the amide, on cyclisation, is shown to occupy the 3-position in hydroxyquinoline as under:



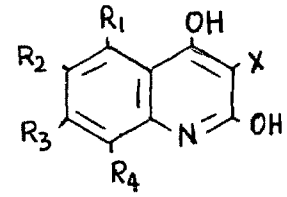
Thus, the direct bromination and chlorination of hydroxyquinolines gave the respective 3-bromo and 3-chloro derivatives, the identity of which was established by means of their melting points, mixed melting points and

analysis with the corresponding products, obtained by the respective cyclisation of monobromo and monochloro derivatives of acetoacet arylamides and malonmono arylamides.

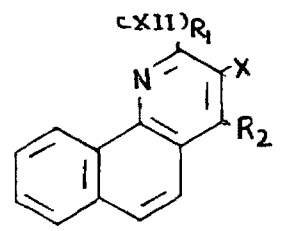
The following 3-halo derivatives of 4-methyl-carbostyrils and 4-hydroxycarbostyrils were prepared.



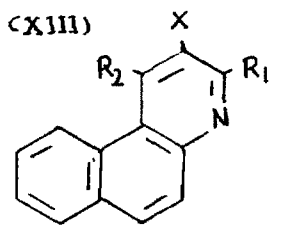
(XII)



(XIII)



(XIV)



(XV)

1. 3-Bromo-2-hydroxy-4,6-dimethylquinoline
   (XII, X=Br ; $R_1=R_3=R_4=H$; $R_2=CH_3$)
2. 3-Bromo-2-hydroxy-4,8-dimethylquinoline
   (XII, X=Br ; $R_1=R_2=R_3=H$; $R_4=CH_3$)
3. 3-Bromo-2-hydroxy-4,6,8-trimethylquinoline
   (XII, X=Br ; $R_1=R_3=H$; $R_2=R_4=CH_3$)
4. 3-Bromo-2-hydroxy-6-ethoxy-4-methylquinoline
   (XII, X=Br ; $R_1=R_3=R_4=H$; $R_2=OC_2H_5$)
5. 3-Chloro-2-hydroxy-4,8-dimethylquinoline
   (XII, X=Cl ; $R_1=R_2=R_3=H$; $R_4=CH_3$)
6. 3-Chloro-2-hydroxy-4-methylbenzoquinoline(7:8)
   (XIV, X=Cl ; $R_1=OH$; $R_2=CH_3$)
7. 3-Chloro-2-hydroxy-4-methylbenzoquinoline(5:6)
   (XV, X=Cl ; $R_1=OH$; $R_2=CH_3$)
8. 3-Iodo-2-hydroxy-4-methylquinoline
   (XII, X=I ; $R_1=R_2=R_3=R_4=H$)

9. 3-Iodo-2-hydroxy-4,8-dimethylquinoline
   (XII, X=I ; R_1=R_2=R_3=H ; R_4=CH_3)
10. 3-Iodo-2-hydroxy-4,6-dimethylquinoline
   (XII, X=I ; R_1=R_3=R_4=H ; R_2=CH_3)
11. 3-Iodo-2-hydroxy-4,6,7-trimethylquinoline
   (XII, X=I ; R_1=R_4=H ; R_2=R_3=CH_3)
12. 3-Bromo-6-methyl-2,4-dihydroxyquinoline
   (XIII, X=Br ; R_1=R_3=R_4=H ; R_2=CH_3)
13. 3-Bromo-7-methyl-2,4-dihydroxyquinoline
   (XIII, X=Br ; R_1=R_2=R_4=H ; R_3=CH_3)
14. 3-Bromo-6-chloro-2,4-dihydroxyquinoline
   (XIII, X=Br ; R_1=R_3=R_4=H ; R_2=Cl)
15. 3-Bromo-6-methoxy-2,4-dihydroxyquinoline
   (XIII, X=Br ; R_1=R_3=R_4=H ; R_2=OCH_3)
16. 3-Bromo-6,7-dimethyl-2,4-dihydroxyquinoline
   (XIII, X=Br ; R_1=R_4=H ; R_2=R_3=CH_3)
17. 3-Bromo-2,4-dihydroxybenzoquinoline (5:6)
   (XV, X=Br ; R_1=R_2=OH)
18. 3-Chloro-6-methyl-2,4-dihydroxyquinoline
   (XIII, X=Cl ; R_1=R_3=R_4=H ; R_2=CH_3)
19. 3-Chloro-6-methoxy-2,4-dihydroxyquinoline
   (XIII, X=Cl ; R_1=R_3=R_4=H ; R_2=OCH_3)
20. 3-Chloro-6,7-dimethyl-2,4-dihydroxyquinoline
   (XIII, X=Cl ; R_1=R_4=H ; R_2=R_3=CH_3)

The above mentioned 3-halo derivatives of hydroxyquinolines are reported for the first time.

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

Monobromo acetoacet-p-toluidide :

Acetoacet-p-toluidide (1.91 g.) was dissolved in 10-15 ml. of glacial acetic acid in presence of a trace of iodine as catalyst, to which 10 % solution of bromine in acetic acid (16 ml.) was slowly added with continuous stirring. The reaction mixture was kept over-night at room temperature and on dilution with excess of cold water it gave a white product which was filtered and crystallised from benzene, m.p. 149°C. Yield 1.25 g.

Analysis :

16.0 mg. of the substance gave 11.20 mg. of silver bromide.

Found : Br = 29.79 %.

$C_{11}H_{12}O_2NBr$ requires : Br = 29.67 %.

Monobromo acetoacet-o-toluidide :

Acetoacet-o-toluidide (1.91 g.) and bromine in acetic acid (1.6 g.) were treated as above, and the monobromo acetoacet-o-toluidide, thus obtained was crystallised from alcohol, m.p. 90°C. Yield 0.95 g.

Analysis :

19.8 mg. of the substance gave 14.16 mg. of silver bromide.

Found : Br = 30.04 %.

$C_{11}H_{12}O_2NBr$ requires : Br = 29.67 %.

Monobromoacetoacet-p-chloroanilide

Acetoacet-p-chloroanilide (2.11 g.) and bromine in acetic acid (1.6 g.) were treated as before and the bromo derivative, thus obtained, was crystallised from alcohol, m.p. 145°C. Yield 1.15 g.

Analysis :

6.134 mg. of the substance gave 0.297 ml. of nitrogen at 29°C and 750 mm. pressure.

Found : N = 5.20 %.

$C_{10}H_9O_2NClBr$ requires : N = 4.82 %,

Monobromo acetoacet-p-phenitidide

Acetoacet-p-phenitidide (2.21 g.) and bromine in acetic acid (1.6 g.) were treated as before and the bromo derivative, thus obtained, was crystallised as above, m.p. 149°C. Yield 1.65 g.

Analysis :

16.38 mg. of the substance gave 10.32 mg. of silver bromide.

Found : Br = 26.81 %.

$C_{12}H_{14}O_3NBr$ requires : Br = 26.66 %.

Monobromo acetoacet-1:2:4-xylidide

Acetoacet-1:2:4-xylidide (2.05 g.) and bromine in acetic acid were treated as above and the monobromo acetoacet-1:2:4-xylidide, thus obtained, was crystallised from alcohol, m.p. 128°C. Yield 1.3 g.

Analysis :

6.402 mg. of the substance gave 4.222 mg. of silver bromide.

Found : Br = 28.06 %.

$C_{12}H_{14}O_2NBr$ requires : Br = 28.16 %.

Monobromo acetoacet-1:3:4-xylidide

Acetoacet-1:3:4-xylidide (2.05 g.) and bromine in acetic acid were treated as above and the monobromo acetoacet-1:3:4-xylidide, thus obtained, was crystallised from alcohol, m.p. 126°C. Yield 1.4 g.

Analysis :

10.750 mg. of the substance gave 7.102 mg. of silver bromide.

Found : Br = 28.11 %.

$C_{12}H_{14}O_2NBr$ requires : Br = 28.16 %.

Monochloroacetoacet-o-toluidide

Acetoacet-o-toluidide (1.91 g.) was dissolved in glacial acetic acid (10 ml.) in presence of a trace of iodine as catalyst, to which sulphuryl chloride (1.35 g.) was added in cold. After two hours, the reaction mixture was diluted with water and when extracted with petroleum ether, it gave a white product, which was crystallised from aqueous alcohol, m.p. 85°C. Yield 1.1 g.

Analysis :

6.372 mg. of the substance gave 3.956 mg. of silver chloride.

Found : Cl = 15.36 %.

$C_{11}H_{12}O_2NCl$ requires : Cl = 15.74 %.

Monochloro acetoacet-α-naphthylamide

Acetoacet-α-naphthylamide (2.27 g.) and sulphuryl chloride (1.35 g.) were treated as before and the product

thus, obtained, was crystallised from alcohol, m.p. 135°C. Yield 1.5 g.

Analysis :

7.962 mg. of the substance gave 4.22 mg. of silver chloride.

Found : Cl = 13.11 %.

$C_{14}H_{12}O_2NCl$ requires : Cl = 13.58 %.

Monochloroacetoacet-β-naphthylamide

Acetoacet-β-naphthylamide (2.27 g.) and sulphuryl chloride (1.35 g.) were treated as before, and the product, thus obtained, was crystallised from aqueous alcohol, m.p. 93°C. Yield 1.6 g.

Analysis :

8.390 mg. of the substance gave 4.44 mg. of silver chloride.

Found : Cl = 13.10 %.

$C_{14}H_{12}O_2NCl$ requires : Cl = 13.58 %.

Monoiodo acetoacetanilide :

Acetoacetanilide (2.22 g.) was dissolved in alcohol (15 ml.), to which iodine (1.27 g.) and iodic acid (0.5 g.) were added with continuous stirring. The monoiodo derivative thus obtained, was filtered and crystallised from alcohol, m.p. 124°C.

Monoiodo acetoacet-o-toluidide :

Acetoacet-o-toluidide (2.4 g.), iodine (1.27 g.) and iodic acid (0.5 g.) were treated as above, and the monoiodo derivative, thus obtained, was filtered and crystallised from alcohol; m.p. 128°C.

Monoiodo acetoacet-p-toluidide :

Acetoacet-p-toluidide (2.4 g.), iodine (1.27 g.) and iodic acid (0.5 g.) were treated as above, and the monoiodo derivative, thus obtained, was filtered and crystallised from alcohol, m.p. 121°C.

Monoiddo acetoacet-1:3:4-xylidide :

Acetoacet-1:3:4-xylidide (2.5 g.), iodine(1.27 g.) and iodic acid (0.5 g.) were treated as above, and the monoiodo derivative, thus obtained, was crystallised from alcohol, m.p. 131°C.

Monobromo malonmono-p-toluidide :

Malonmono-p-toluidide (1.92 g.) and bromine in acetic acid (1.6 g.) were treated as before and the product, obtained, was crystallised from alcohol, m.p. 190°C. Yield 1.25 g.

Analysis :

6.960 mg. of the substance gave 0.562 ml. of nitrogen at 32°C and 757 mm. pressure.

Found : N = 10.51 %.

$C_{10}H_{11}O_2N_2Br$ requires : N = 10.33 %.

Monobromo malonmono-m-toluidide :

Malonmono-m-toluidide (1.92 g.) and bromine in acetic acid (1.6 g.) were treated as before and the product, obtained was crystallised from alcohol, m.p. 122°C. Yield 1.2 g.

Analysis :

16.70 mg. of the substance gave 11.71 mg. of silver bromide.

Found. : Br = 29.73 %.

$C_{10}H_{11}O_2N_2Br$ requires : Br = 29.52 %.

Monobromo malonmono-p-chloroanilide :

Malonmono-p-chloroanilide (2.12 g.) and bromine in acetic acid (1.6 g.) were treated as before and the product, thus obtained, was crystallised from alcohol, m.p. 180°C. Yield 1.4 g.

Analysis :

9.30 mg. of the substance gave 1.20 ml. of nitrogen at 33°C and 754 mm. pressure.

Found : N = 14.30 %.

$C_9H_8O_2N_2ClBr$ requires : N = 14.35 %.

Monobromo malonmono-p-anisidide :

Malonmono-p-anisidide (2.08 g.) and bromine in acetic acid (1.6 g.) were treated as before and the product obtained was crystallised from alcohol, m.p. 165°C. Yield 1.4 g.

Analysis :

15.60 mg. of the substance gave 10.30 mg. of silver bromide.

Found : Br = 28.15 %.

$C_{10}H_{11}O_3N_2Br$ requires : Br = 27.87 %.

Monobromo malonmono-1:3:4-xylidide :

Malonmono-1:3:4-xylidide (2.06 g.) and bromine in acetic acid (1.6 g.) were treated as before and the product, thus obtained, was crystallised from alcohol, m.p. 172°C. Yield 1.2 g.

Analysis :.

14.66 mg. of the substance gave 9.66 mg. of silver bromide.

Found : Br = 28.04 %.

$C_{11}H_{13}O_2N_2Br$ requires : Br = 27.97 %.

Monobromo malonmono-β-naphthylamide :

Malonmono-β-naphthylamide (2.28 g.) and bromine in acetic acid (1.6 g.) were treated as before and the product obtained was crystallised from alcohol, m.p. 215°C. Yield 1.6 g.

Analysis :

6.56 mg. of the substance gave 0.494 ml. of nitrogen at 31°C and 760 mm. pressure.

Found : N = 8.75 %.

$C_{13}H_{11}O_2N_2Br$ requires : N = 9.12 %.

Monochloro malonmono-p-toluidide :

Malonmono-p-toluidide (1.92 g.) and sulphuryl chloride (1.35 g.) were treated as before and the product, thus obtained, was crystallised from alcohol, m.p. 140°C. Yield 1.3 g.

Analysis :

7.94 mg. of the substance gave 5.012 mg.of silver chloride.

Found : Cl = 15.62 %.

$C_{10}H_{11}O_2N_2Cl$ requires : Cl = 15.74 %.

Monochloro malonmono-p-anisidide :

Malonmono-p-anisidide (2.08 g.) and sulphuryl chloride (1.35 g.) were treated as before, and the product,

thus obtained, was crystallised from alcohol, m.p. 142°C. Yield 1.4 g.

Analysis :

8.78 mg. of the substance gave 0.887 ml. of nitrogen at 32°C and 760 mm. pressure.

Found : N = 11.30 %.

$C_{10}H_{11}O_3N_2Cl$ requires : N = 11.54 %.

Monochloro malonmono-1:3:4-xylidide :

Malonmono-1:3:4-xylidide (2.06 g.) and sulphuryl chloride (1.35 g.) were treated as before, and the product thus obtained, was crystallised from alcohol, m.p. 148°C. Yield 1.4 g.

Analysis :

13.92 mg. of the substance gave 8.74 mg. of silver chloride.

Found : Cl = 15.13 %.

$C_{11}H_{13}O_2N_2Cl$ requires : Cl = 14.76 %.

Monoiodo malonmonoanilide :

Malonmonoanilide (2.22 g.), iodine (1.27 g.) and iodic acid (0.5 g.) were treated as before, and the product thus obtained was crystallised from alcohol, m.p. 165°C. Yield 1.5 g.

Analysis :

11.064 mg. of the substance gave 8.490 mg. of silver iodide.

Found : I = 41.76 %.

$C_9H_9O_2N_2I$ requires : I = 41.44 %.

Monoiodo malonmono-p-toluidide :

Malonmono-p-toluidide (2.4 g.), iodine (1.27 g.) and iodic acid (0.5 g.) were treated as before, and the product thus obtained was crystallised from alcohol, m.p. 175°C. Yield 1.9 g.

Analysis :

10.756 mg. of the substance gave 8.028 mg. of silver iodide.

Found : I = 40.35 %.

$C_{10}H_{11}O_2N_2I$ requires : I = 39.93 %.

Monomethyl acetoacetanilide :

Acetoacetanilide (1.77 g.) was dissolved in dry benzene to which pulverised sodium (0.32 g.) was added, and the reaction mixture was refluxed, till the monosodio derivative of the amide was separated out. This was filtered and the product was taken in dry benzene, to which methyl iodide (1.42 g.) was added, and the reaction mixture was again refluxed for two hours. On cooling and adding petrol-ether, the crude product was separated, which was filtered and crystallised from alcohol, m.p.140°C. Yield 1.0 g.

Analysis :

5.008 mg. of the substance gave 0.327 ml. of nitrogen at 32°C and 757 mm. pressure.

Found : N = 7.28 %.

$C_{11}H_{13}O_2N$ requires : N = 7.33 %.

3-Bromo-2-hydroxy-4,6-dimethylquinoline :

2-Hydroxy-4,6-dimethylquinoline (1.73 g.) was dissolved in warm glacial acetic acid (25 ml.), to which a crystal of iodine was added as catalyst. A 20 % solution of bromine in acetic acid (8 ml.) was slowly added to it with continuous stirring. The reaction mixture, on dilution with water, gave a white product, which was filtered and crystallised from alcohol as white needles, m.p. 282°C. Yield 1.5 g.

Again, monobromo acetoacet-p-toluidide (1.0 g.) as described before, was cyclised, using a mixture of acetic anhydride and concentrated sulphuric acid (1 : 1). The crude product obtained on addition of water, was filtered and crystallised from alcohol as white needles, m.p. 282°C. Yield 0.7 g.

The mixed melting point of this cyclised 3-bromo-2-hydroxy-4,6-dimethylquinoline with the above compound was not depressed.

Analysis

4.624 mg. of the substance gave 8.960 mg. of carbon dioxide and 1.620 mg. of water.

17.72 mg. of the same substance gave 13.06 mg. of silver bromide.

Found : C = 52.88 % ; H = 3.92 % ; Br= 31.35 %.

$C_{11}H_{10}ONBr$ requires : C = 52.38 % ; H = 3.97 % ; Br= 31.74 %.

3-Bromo-2-hydroxy-4,8-dimethylquinoline :

2-Hydroxy-4,8-dimethylquinoline (1.73 g.) was brominated by means of bromine in acetic acid (8 ml.; 20 %)

in the presence of a crystal of iodine as catalyst. The reaction mixture was treated as above and the product, thus obtained, was crystallised from alcohol as white needles, m.p. 255°C. Yield 1.6 g.

Again, monobromo acetoacet-o-toluidide (2 g.) as described before, was cyclised using a mixture of acetic anhydride and concentrated sulphuric acid (1 : 1) The crude product was filtered and crystallised from alcohol as white needles, m.p. 255°C. Yield 1.5 g.

The mixed melting point of this cyclised 3-bromo-2-hydroxy-4,8-dimethylquinoline with the above compound was not depressed.

Analysis :

10.76 mg. of the substance gave 7.98 mg. of silver bromide.

Found : Br = 31.56 %.

$C_{11}H_{10}ONBr$ requires : Br = 31.74 %.

3-Bromo-2-hydroxy-4,6,8-trimethylquinoline :

2-Hydroxy-4,6,8-trimethylquinoline (1.87 g.) was brominated by means of bromine in acetic acid (8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo derivative, thus obtained, was crystallised as above in white needles, m.p. 265°C. Yield 1.4 g.

Again, monobromo acetoacet-1:2:4-xylidide (2.0 g.) as described before, was cyclised using a mixture of acetic anhydride and concentrated sulphuric acid (1 : 1). The crude product was filtered and crystallised from alcohol, m.p. 265°C. Yield 1.25 g.

The mixed melting point of the cyclised 3-bromo - 2-hydroxy-4,6,8-trimethylquinoline with the above compound was not depressed.

Analysis :

16.76 mg. of the substance gave 11.72 mg. of silver bromide.

Found : Br = 29.75 %.

$C_{12}H_{12}ONBr$ requires : Br = 30.07 %.

3-Bromo-2-hydroxy-6-ethoxy-4-methylquinoline

2-Hydroxy-6-ethoxy-4-methylquinoline (2.00 g.) was brominated by means of bromine in acetic acid (8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo derivative, thus obtained, was crystallised as usual in white needles, m.p. 252°C. Yield 1.6 g.

Again, monobromo acetoacet-p-phenitidide (1 g.) as described before, was cyclised using a mixture of acetic anhydride and concentrated sulphuric acid (1 : 1). The crude product was filtered and crystallised from alcohol, m.p. 252°C. Yield 0.8 g.

The mixed melting point of the cyclised 3-bromo-2-hydroxy-6-ethoxy-4-methylquinoline with the above compound was not depressed.

Analysis :

15.66 mg. of the substance gave 10.34 mg. of silver bromide.

Found : Br = 28.19 %.

$C_{12}H_{12}O_2NBr$ requires : Br = 28.37 %.

3-Chloro-2-hydroxy-4,8-dimethylquinoline

2-Hydroxy-4,8-dimethylquinoline (1.7 g.) was dissolved in glacial acetic acid (15 ml.) in presence of a trace of iodine as a catalyst to which sulphuryl chloride (1.35 g.) was added in cold. The reaction mixture was stirred for half an hour at room temperature and the chloro derivative, thus obtained, was filtered and crystallised from alcohol, m.p. 205°C. Yield 1.2 g.

The mixed melting point of the cyclised 3-chloro-2-hydroxy-4,8-dimethylquinoline with the above compound was not depressed.

Analysis :

17.26 mg. of the substance gave 15.46 mg. of silver chloride.

Found : Cl = 22.16 %.

$C_{11}H_{10}ONCl$ requires : Cl = 21.69 %.

3-Chloro-2-hydroxy-4-methylbenzoquinoline (7:8)

2-Hydroxy-4-methylbenzoquinoline (2.25 g.) and sulphuryl chloride (1.35 g.) were treated as before and the product, thus obtained, was crystallised from alcohol, m.p. 380°C(dec). Yield 1.2 g.

The mixed melting point of the cyclised 3-chloro-2-hydroxy-4-methylbenzoquinoline(7:8) with the above compound was not depressed.

Analysis :

9.620 mg. of the substance gave 4.816 mg. of silver chloride.

Found : Cl = 14.68 %.

$C_{14}H_{10}ONCl$ requires : Cl = 14.57 %.

3-Chloro-2-hydroxy-4-methylbenzoquinoline (5:6)

2-Hydroxy-4-methylbenzoquinoline (5:6) (2.25 g.) and sulphuryl chloride (1.35 g.) were treated as before and the chloro derivative, thus obtained, was crystallised from alcohol, m.p. 370°C.(dec.). Yield 1.4 g.

The mixed melting point of the cyclised 3-chloro-2-hydroxy-4-methylbenzoquinoline (5:6) with the above compound was not depressed.

Analysis :

11.918 mg. of the substance gave 6.240 mg. of silver chloride.

Found : Cl = 14.75 %.

$C_{14}H_{10}ONCl$ requires : Cl = 14.57 %.

3-Iodo-2-hydroxy-4-methylquinoline

2-Hydroxy-4-methylquinoline (2.0 g.) was dissolved in a minimum quantity of hot alcohol, to which iodine crystals (1.27 g.) and aqueous solution of iodic acid (0.5 g.) were added. The reaction mixture was stirred for one hour and on dilution with water it gave a product, which was filtered and crystallised from alcohol, m.p. 291°C. Yield 1.5 g.

Analysis :

9.458 mg. of the substance gave 7.820 mg. of silver iodide.

Found : I = 44.69 %.

$C_{10}H_8ONI$ requires : I = 44.57 %.

3-Iodo-2-hydroxy-4,8-dimethylquinoline

2-Hydroxy-4,8-dimethylquinoline (2.2 g.), iodine (1.27 g.) and aqueous iodic acid (0.5 g.) were treated as above and the iodo derivative, thus obtained, was crystallised from alcohol, m.p. 232°C. Yield 1.4 g.

Analysis :

6.746 mg. of the substance gave 5.164 mg. of silver iodide.

Found : I = 42.28 %.

$C_{11}H_{10}ONI$ requires : I = 42.47 %.

3-Iodo-2-hydroxy-4,6-dimethylquinoline

2-Hydroxy-4,6-dimethylquinoline (2.2 g.), iodine (1.27 g.) and aqueous iodic acid (0.5 g.) were treated as above and the iodo derivative, thus obtained, was crystallised from alcohol, m.p. 280°C. Yield 1.7 g.

Analysis :

10.098 mg. of the substance gave 7.870 mg. of silver iodide.

Found : I = 42.13 %.

$C_{11}H_{10}ONI$ requires : I = 42.47 %.

3-Iodo-2-hydroxy-4,6,7-trimethylquinoline

2-Hydroxy-4,6,7-trimethylquinoline (2.34 g.), iodine (1.27 g.) and aqueous iodic acid (0.5 g.) were treated as above and the iodo derivative, thus obtained, was crystallised from alcohol, m.p. 273°C. Yield 1.6 g.

Analysis :

10.004 mg. of the substance gave 7.542 mg. of silver iodide.

Found - : I = 40.76 %.

$C_{12}H_{12}ONI$ requires : I = 40.58 %.

3-Bromo-6-methyl-2,4-dihydroxyquinoline

6-Methyl-2,4-dihydroxyquinoline (1.85 g.) was brominated by means of bromine in acetic acid (8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo derivative, thus obtained, was crystallised from glacial acetic acid as white needles, m.p. 260°C. Yield 1.4 g.

Again, monobromo malonmono-p-toluidide (2.0 g.) as described before, was cyclised using polyphosphoric acid on refluxing at 140°C. The crude product was filtered and crystallised from acetic acid m.p. 260°C. Yield 1.1 g.

The mixed melting point of the cyclised 3-bromo-6-methyl-2,4-dihydroxyquinoline with the above compound was not depressed.

Analysis :

4.324 mg. of the substance gave 7.482 mg. of carbon dioxide and 1.314 mg. of water.

16.52 mg. of the same substance gave 12.32 mg. of silver bromide.

Found : C = 47.22 % ; H = 3.40 % ; Br = 31.73 %.

$C_{10}H_8O_2NBr$ requires : C = 47.24 % ; H = 3.15 % ; Br = 31.50 %.

3-Bromo-7-methyl-2,4-dihydroxyquinoline

7-Methyl-2,4-dihydroxyquinoline (1.75 g.) was brominated by means of bromine in acetic acid(8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo derivative, thus obtained, was crystallised as above,

m.p. 237°C. Yield 1.32 g.

The mixed melting point of the cyclised 3-bromo-7-methyl-2,4-dihydroxyquinoline with the above compound was not depressed.

Analysis :

15.26 mg. of the substance gave 11.24 mg. of silver bromide.

Found : Br = 31.34 %.

$C_{10}H_8O_2NBr$ requires : Br = 31.50 %.

3-Bromo-6-chloro-2,4-dihydroxyquinoline

6-Chloro-2,4-dihydroxyquinoline (1.95 g.) was brominated by means of bromine in acetic acid (8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo derivative, thus obtained, was crystallised as above in white needles, m.p. 262°C. Yield 1.2 g.

Again, monobromo malonmono-p-chloroanilide (1 g.) as described before, was cyclised using polyphosphoric acid on refluxing at 140°C. The crude product was filtered and crystallised from acetic acid, m.p. 262°C. Yield 0.48 g.

The mixed melting point of the cyclised 3-bromo-6-chloro-2,4-dihydroxyquinoline with the above compound was not depressed.

Analysis :

9.96 mg. of the substance gave 0.420 ml. of nitrogen at 28°C and 757 mm. pressure.

Found : N = 4.77 %.

$C_9H_5O_2NBrCl$ requires : N = 5.10 %.

3-Bromo-6-methoxy-2,4-dihydroxyquinoline

6-Methoxy-2,4-dihydroxyquinoline(1.91 g.) was brominated by means of bromine in acetic acid (8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo compound, thus obtained, was crystallised from glacial acetic acid as white needles, m.p. 256°C. Yield 1.2 g.

The mixed melting point of the cyclised 3-bromo-6-methoxy-2,4-dihydroxyquinoline with the above compound was not depressed.

Analysis :

4.292 mg. of the substance gave 7.048 mg. of carbon dioxide and 1.288 mg. of water.

18.18 mg. of the same substance gave 12.68 mg. of silver bromide.

Found : C = 44.82 % ; H = 3.35 % ; Br = 29.63 %.

$C_{10}H_8O_3NBr$ requires : C = 44.44 % ; H = 3.15 % ; Br = 29.62 %.

3-Bromo-6,7-dimethyl-2,4-dihydroxyquinoline

6,7-Dimethyl-2,4-dihydroxyquinoline (1.89 g.) was brominated by means of bromine in acetic acid (8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo-derivative, thus obtained, was crystallised as above, m.p. 255°C. Yield 1.4 g.

Again, monobromo malonmono-1,3,4-xylidide (1.0 g.), as described before, was cyclised using polyphosphoric acid on refluxing at 140°C. The crude product was filtered and crystallised from acetic acid, m.p. 255°C. Yield 0.52 g.

The mixed melting point of the cyclised 3-bromo-6,7-dimethyl-2,4-dihydroxyquinoline with the above compound

was not depressed.

Analysis :

17.40 mg. of the substance gave 12.02 mg. of silver bromide.

Found : Br = 29.40 %.

$C_{11}H_{10}O_2NBr$ requires : Br = 29.70 %.

3-Bromo-2,4-dihydroxybenzoquinoline (5:6)

2,4-Dihydroxybenzoquinoline (5:6) ; (2.11 g.) was brominated by means of bromine in acetic acid (8 ml. ; 20 %) and the reaction mixture was treated as above. The bromo compound, thus obtained, was crystallised from acetic acid as white needles, m.p. 270°C. Yield 1.55 g.

The mixed melting point of the cyclised 3-bromo-2,4-dihydroxyquinoline (5:6) with the above compound was not depressed.

Analysis :

16.06 mg. of the substance gave 10.52 mg. of silver bromide.

Found : Br = 27.88 %.

$C_{13}H_8O_2NBr$ requires : Br = 27.60 %.

3-Chloro-6-methyl-2,4-dihydroxyquinoline

6-Methyl-2,4-dihydroxyquinoline (1.75 g.) and sulphuryl chloride (1.34 g.) were treated as above and the chloro derivative, thus obtained, was filtered and crystallised from alcohol, m.p. 296°C. Yield 1.2 g.

The mixed melting point of the cyclised 3-chloro-6-methyl-2,4-dihydroxyquinoline with the above compound was not depressed.

Analysis :

15.22 mg. of the substance gave 10.2 mg. of silver chloride.

Found : Cl = 16.36 %.

$C_{10}H_8O_2NCl$ requires : Cl = 16.90 %.

3-Chloro-6-methoxy-2,4-dihydroxyquinoline

6-Methoxy-2,4-dihydroxyquinoline (1.90 g.) was chlorinated by means of sulphuryl chloride (1.35 g.) in glacial acetic acid in presence of a trace of iodine as catalyst. The reaction mixture was stirred for half an hour at room temperature and the chloro derivative, thus separated, was crystallised from glacial acetic acid, as white needles, m.p. 268°C. Yield 1.15 g.

Again, monochloro malonmono anisidide (1.0 g.), as described before, was cyclised using polyphosphoric acid on refluxing at 140°C. The crude product was filtered and crystallised from acetic acid, m.p. 268°C. Yield 0.55 g.

The mixed melting point of the cyclised 3-chloro-6-methoxy-2,4-dihydroxyquinoline with the above compound was not depressed.

Analysis :

4.102 mg. of the substance gave 8.044 mg. of carbon dioxide and 1.290 mg. of water.

13.92 mg. of the same substance gave 8.74 mg. of silver chloride.

Found : C = 53.51 % ; H = 3.52 % ; Cl = 15.53 %.

$C_{10}H_8O_3NCl$ requires : C = 53.20 % ; H = 3.54 % ; Cl = 15.74 %.

3-Chloro-6,7-dimethyl-2,4-dihydroxyquinoline

6,7-Dimethyl-2,4-dihydroxyquinoline (1.9 g.) and sulphuryl chloride (1.34 g.) were treated as above and the product, thus obtained, was crystallised from alcohol, m.p. 228°C. Yield 1.32 g.

The mixed melting point of the cyclised 3-chloro-6,7-dimethyl-2,4-dihydroxyquinoline with the above compound was not depressed.

Analysis :

11.060 mg. of the substance gave 6.79 mg. of silver chloride.

Found : Cl = 15.54 %.

$C_{11}H_{10}O_2NCl$ requires : Cl = 15.89 %.

Attempted iodination of 2,4-dihydroxyquinoline

2,4-Dihydroxyquinoline (2.0 g.) was dissolved in warm alcohol (50 ml.), to which crystals of iodine (1.27 g.) and aqueous solution of iodic acid (0.5 g.) were added. The reaction mixture was stirred for about four hours and the separated product was filtered and crystallised from acetic acid, m.p. 360°C. It was found to be the same original compound i.e. 2,4-dihydroxyquinoline.

2,4-Dihydroxyquinoline (1.6 g.) was dissolved in 25 % liquor ammonia (40 ml.) to which a solution of iodine in potassium iodide (3.0 g.) was added and the reaction mixture was stirred for about four hours. It was then acidified with cold sulphuric acid, and the separated product was crystallised from acetic acid, m.p. 360°C. This was identified as 2,4-dihydroxyquinoline.

2,4-Dihydroxyquinoline (1.6 g.) and iodine monochloride (1.62 g.) were treated in acetic acid, kept for 24 hours, and then stirred vigorously for two hours . The separated solid was filtered, washed with water, and crystallised from acetic acid, which was identified as the original 2,4-dihydroxyquinoline.

2-Hydroxy-3,4-dimethylquinoline

Monomethyl acetoacetanilide (1 g.), described before, was dissolved in acetic anhydride (3 ml.) to which concentrated sulphuric acid (3 ml.) was slowly added. The reaction mixture was kept for about half an hour at room temperature and on dilution with water it gave a white product, which was filtered and crystallised from alcohol, m.p. 266°C. Yield 0.75 g. The mixed melting point of the compound with the authentic sample of 2-hydroxy-3,4-dimethylquinoline was not depressed.

Analysis :

6.742 mg. of the substance gave 0.505 ml. of nitrogen at 32°C and 756 mm. pressure.

Found : N = 8.34 %.

$C_{11}H_{11}ON$ requires : N = 8.09 %.

Table 6

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Halogen Found %	Halogen Reqd. %	Nitrogen Found %	Nitrogen Reqd. %
1.	Monobromo acetoacet-p-toluidide	$C_{11}H_{12}O_2NBr$	149	65.8	27.79	29.67	-	-
2.	Monobromo acetoacet-o-toluidide	$C_{11}H_{12}O_2NBr$	90	50.0	30.04	29.67	-	-
3.	Monobromo acetoacet-p-chloroanilide	$C_{10}H_9O_2NClBr$	145	61.46	-	-	5.20	4.82
4.	Monobromo acetoacet-p-phenitidide	$C_{12}H_{14}O_3NBr$	149	75.0	26.81	26.66	-	-
5.	Monobromo acetoacet-1:2:4-xylidide	$C_{12}H_{14}O_2NBr$	128	66.0	28.06	28.16	-	-
6.	Monobromo acetoacet-1:3:4-xylidide	$C_{12}H_{14}O_2NBr$	126	70.0	28.11	28.16	-	-
7.	Monochloro acetoacet-o-toluidide	$C_{11}H_{12}O_2NCl$	85	57.6	15.36	15.74	-	-
8.	Monochloro acetoacet-α-naphthylamide	$C_{14}H_{12}O_2NCl$	135	66.0	13.11	13.58	-	-
9.	Monochloro acetoacet-β-naphthylamide	$C_{14}H_{12}O_2NCl$	93	70.5	13.10	13.58	-	-
10.	Monoiodo acetoacetanilide	$C_{10}H_{10}O_2NI$	124	-	-	-	-	-
11.	Monoiodo acetoacet-o-toluidide	$C_{11}H_{12}O_2NI$	128	-	-	-	-	-
12.	Monoiodo acetoacet-p-toluidide	$C_{11}H_{12}O_2NI$	121	-	-	-	-	-
13.	Monoiodo acetoacet-1:2:4-xylidide	$C_{12}H_{14}O_2NI$	131	-	-	-	-	-

Table 7

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Halogen Found %	Halogen Reqd. %	Nitrogen Found %	Nitrogen Reqd. %
1.	Monobromo malon mono-p-toluidide	$C_{10}H_{11}O_2N_2Br$	190	65.1	-	-	10.51	10.33
2.	Monobromo malon mono-m-toluidide	$C_{10}H_{11}O_2N_2Br$	172	62.5	29.73	29.52	-	-
3.	Monobromo malon mono-p-chloroanilide	$C_9H_8O_2N_2ClBr$	180	65.88	-	-	14.30	14.35
4.	Monobromo malon mono-p-anisidide	$C_{10}H_{11}O_3N_2Br$	165	67.31	28.15	27.87	-	-
5.	Monobromo malon mono-1:3:4-xylidide	$C_{11}H_{13}O_2N_2Br$	172	75.0	28.04	27.97	-	-
6.	Monobromo malon mono-β-naphthylamide	$C_{13}H_{11}O_2N_2Br$	215	70.2	-	-	8.75	9.12
7.	Monochloro malon mono-p-toluidide	$C_{10}H_{11}O_2N_2Cl$	140	67.7	15.62	15.74	-	-
8.	Monochloro malon mono-p-anisidide	$C_{10}H_{11}O_3N_2Cl$	142	67.3	-	-	11.30	11.54
9.	Monochloro malon mono-1:3:4-xylidide	$C_{11}H_{13}O_2N_2Cl$	148	69.1	15.13	14.76	-	-
10.	Monoiodo malon monoanilide	$C_9H_9O_2N_2I$	165	67.5	41.76	41.44	-	-
11.	Monoiodo malon mono-p-toluidide	$C_{10}H_{11}O_2N_2I$	175	79.1	40.35	39.93	-	-
12.	Monomethyl acetoacetanilide	$C_{11}H_{13}O_2N$	140	56.5	-	-	7.28	7.33

Table 8

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Halogen Found %	Halogen Reqd. %	Carbon Found %	Carbon Reqd. %	Hydrogen Found %	Hydrogen Reqd. %
1.	3-Bromo-2-hydroxy-4,6-dimethylquinoline	$C_{11}H_{10}ONBr$	282	87.7	31.35	31.74	52.88	52.38	3.92	3.97
2.	3-Bromo-2-hydroxy-4,8-dimethylquinoline	$C_{11}H_{10}ONBr$	255	92.4	31.56	31.74	-	-	-	-
3.	3-Bromo-2-hydroxy-4,6,8-trimethylquinoline	$C_{12}H_{12}ONBr$	265	74.8	29.75	30.07	-	-	-	-
4.	3-Bromo-2-hydroxy-6-ethoxy-4-methylquinoline	$C_{12}H_{12}O_2NBr$	252	80.0	28.19	28.37	-	-	-	-
5.	3-Chloro-2-hydroxy-4,8-dimethylquinoline	$C_{11}H_{10}ONCl$	205	70.6	22.16	21.69	-	-	-	-
6.	3-Chloro-2-hydroxy-4-methylbenzoquinoline(7:8)	$C_{14}H_{10}ONCl$	380	53.3	14.68	14.57	-	-	-	-

Table 8 (Contd.)

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Halogen Found %	Halogen Reqd. %	Carbon Found %	Carbon Reqd. %	Hydrogen Found %	Hydrogen Reqd. %
7.	3-Chloro-2-hydroxy-4-methyl-benzoquinoline(5:6)	$C_{14}H_{10}ONCl$	370	62.2	14.75	14.57	-	-	-	-
8.	3-Iodo-2-hydroxy-4-methylquinoline	$C_{10}H_8ONI$	291	75.0	44.69	44.51	-	-	-	-
9.	3-Iodo-2-hydroxy-4,8-dimethylquinoline	$C_{11}H_{10}ONI$	232	63.6	42.28	42.47	-	-	-	-
10.	3-Iodo-2-hydroxy-4,6-dimethylquinoline	$C_{11}H_{10}ONI$	280	73.3	42.13	42.47	-	-	-	-
11.	3-Iodo-2-hydroxy-4,6,7-trimethylquinoline	$C_{12}H_{12}ONI$	273	68.4	40.76	40.58	-	-	-	-

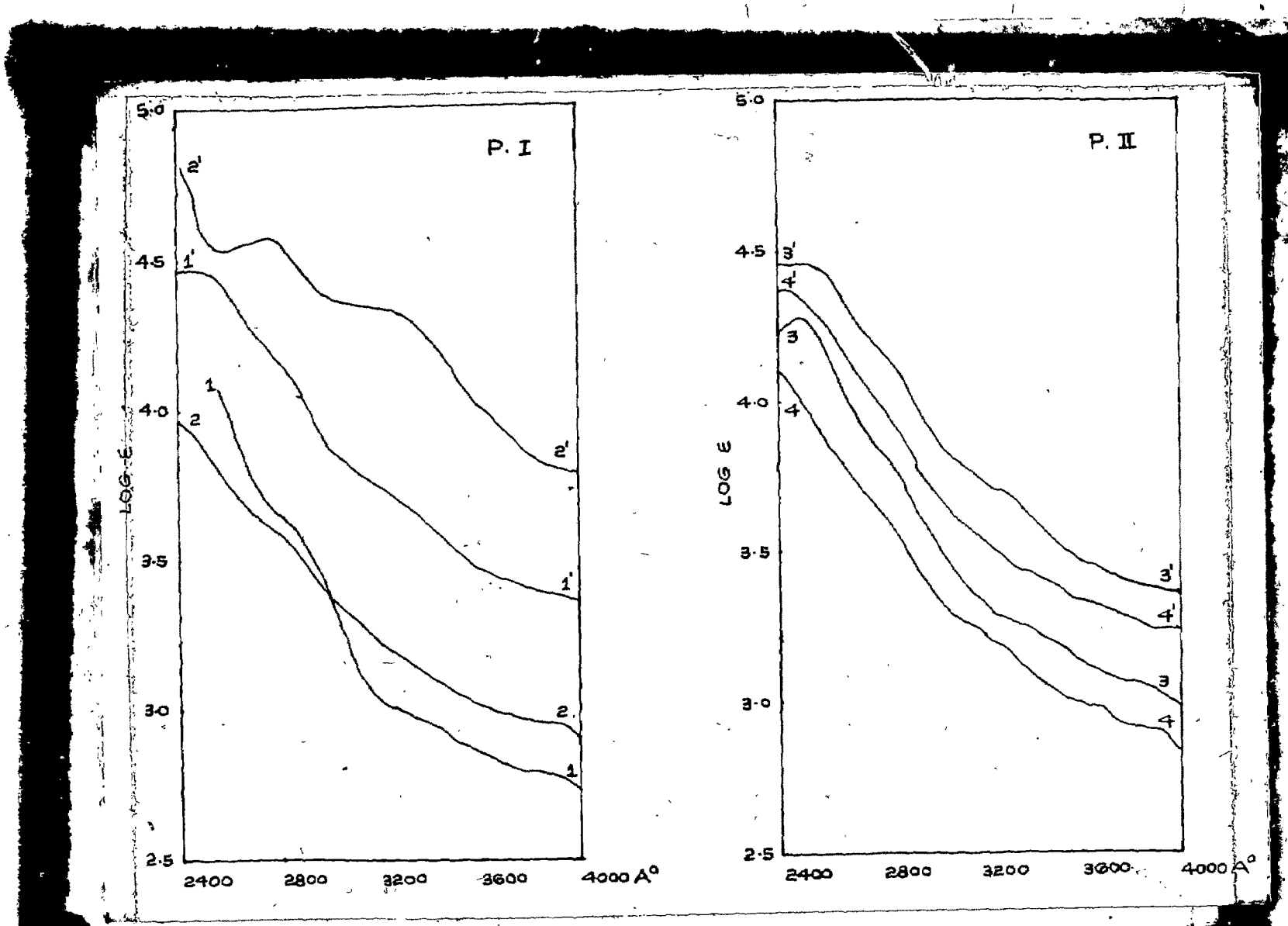
Table 9

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Halogen Found %	Halogen Reqd. %	Carbon Found %	Carbon Reqd. %	Hydrogen Found %	Hydrogen Reqd. %
1.	3-Bromo-6-methyl-2,4-dihydroxyquinoline	$C_{10}H_8O_2NBr$	260	75.6	31.73	31.50	47.22	47.24	3.40	3.15
2.	3-Bromo-7-methyl-2,4-dihydroxyquinoline	$C_{10}H_8O_2NBr$	237	75.4	31.34	31.50	-	-	-	-
*3.	3-Bromo-6-chloro-2,4-dihydroxyquinoline	$C_9H_5O_2NBrCl$	262	61.5	-	-	-	-	-	-
4.	3-Bromo-6-methoxy-2,4-dihydroxyquinoline	$C_{10}H_8O_3NBr$	256	62.8	29.63	29.62	44.82	44.44	3.35	3.15
5.	3-Bromo-6,7-dimethyl-2,4-dihydroxyquinoline	$C_{11}H_{10}O_2NBr$	255	73.6	29.40	29.70	-	-	-	-
6.	3-Bromo-2,4-dihydroxy-benzoquinoline (5:6)	$C_{13}H_8O_2NBr$	270	73.8	27.88	27.60	-	-	-	-

Table 9 (Contd.)

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Halogen Found %	Halogen Reqd. %	Carbon Found %	Carbon Reqd. %	Hydrogen Found %	Hydrogen Reqd. %
7.	3-Chloro-6-methyl-2,4-dihydroxyquinoline	$C_{10}H_8O_2NCl$	296	68.5	16.36	16.90	-	-	-	-
8.	3-Chloro-6-methoxy-2,4-dihydroxyquinoline	$C_{10}H_8O_3NCl$	268	60.5	15.53	15.74	53.51	53.20	3.52	3.54
9.	3-Chloro-6,7-dimethyl-2,4-dihydroxyquinoline	$C_{11}H_{10}O_2NCl$	228	69.4	15.54	15.89	-	-	-	-
*10.	2-Hydroxy-3,4-dimethyl-quinoline	$C_{11}H_{11}ON$	266	75.0	-	-	-	-	-	-

* (3) Found : N = 4.77 % ; requires N = 5.10 % ; (10) Found N = 8.34 % ; requires N = 8.09 %.

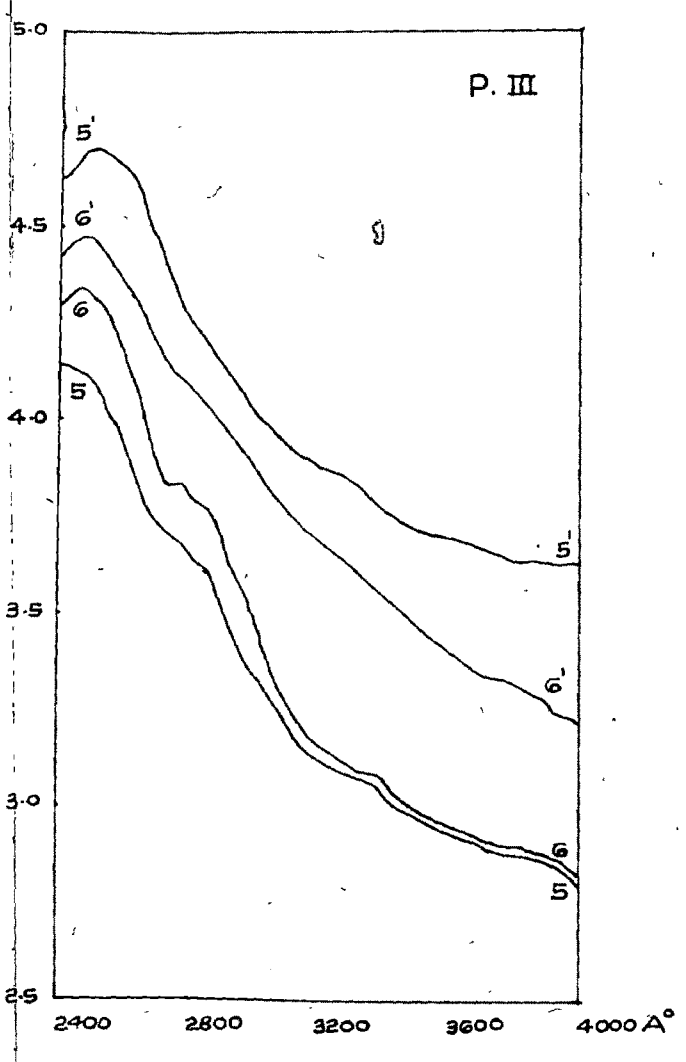


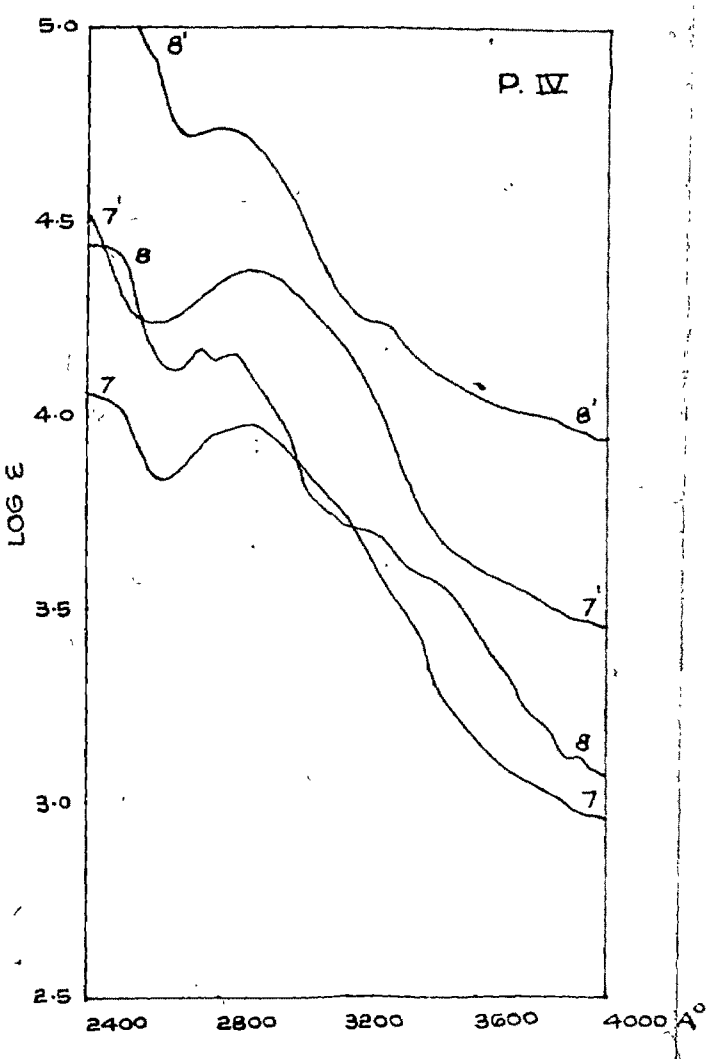
(1) Acetoacet anilide and (1') its methylene bis-derivative;

(2) Acetoacet-o-toluidide and (2') iits methylene bis-derivative.

(3) Acetoacet-p-toluidide and (3') methylene bis-derivative ;

(4) Acetoacet-1:2:4-xylidide and (4') its methylene bis-derivative.



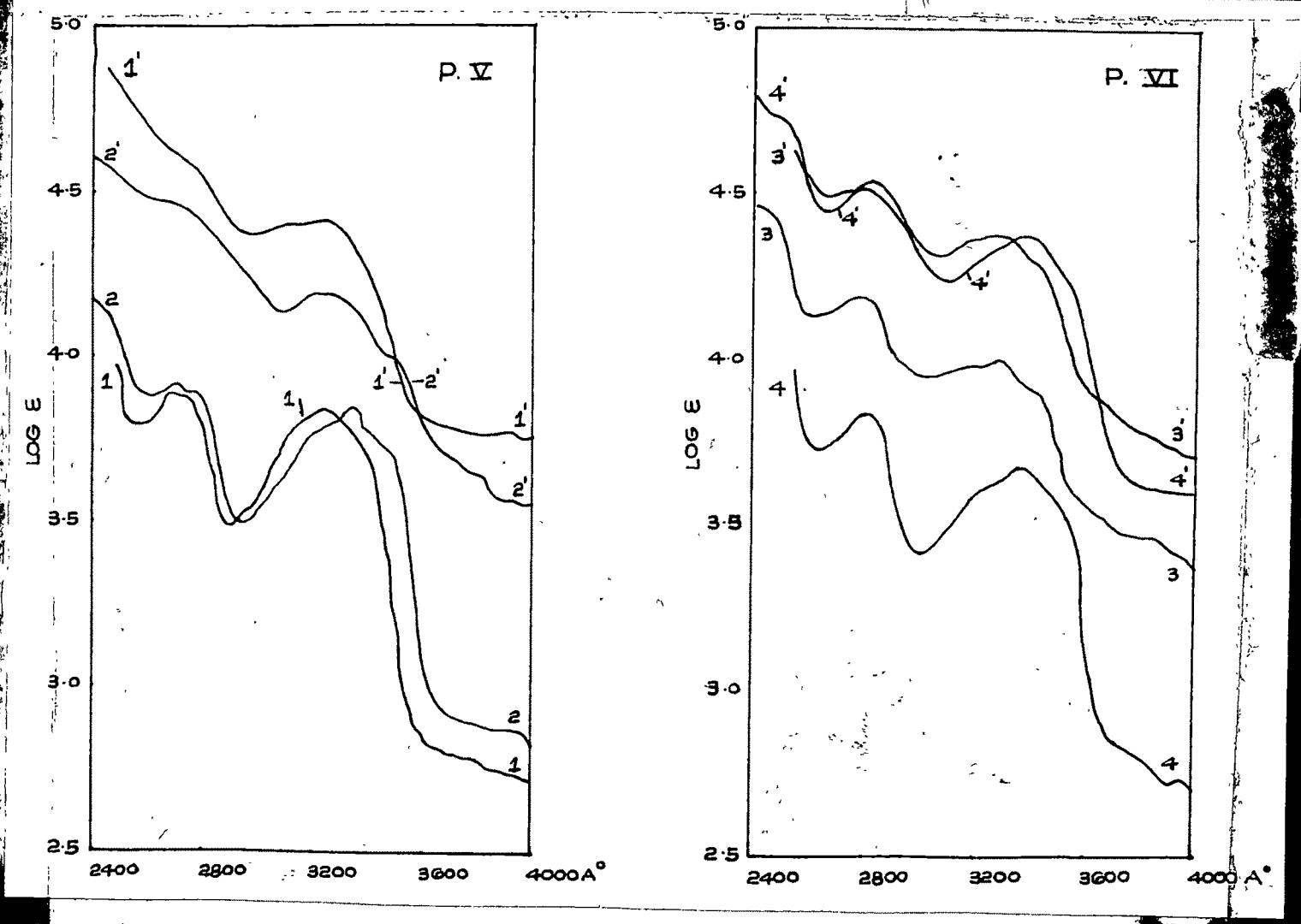


(5') Acetoacet-o-chloroanilide and its methylene bis-derivative ;

(6') Acetoacet-m-chloroanilide and its methylene bis-derivative

(7) Acetoacet-α-naphthylamide and its methylene bis-derivative.

(8) Acetoacet-β-naphthylamide and its methylene bis-derivative.

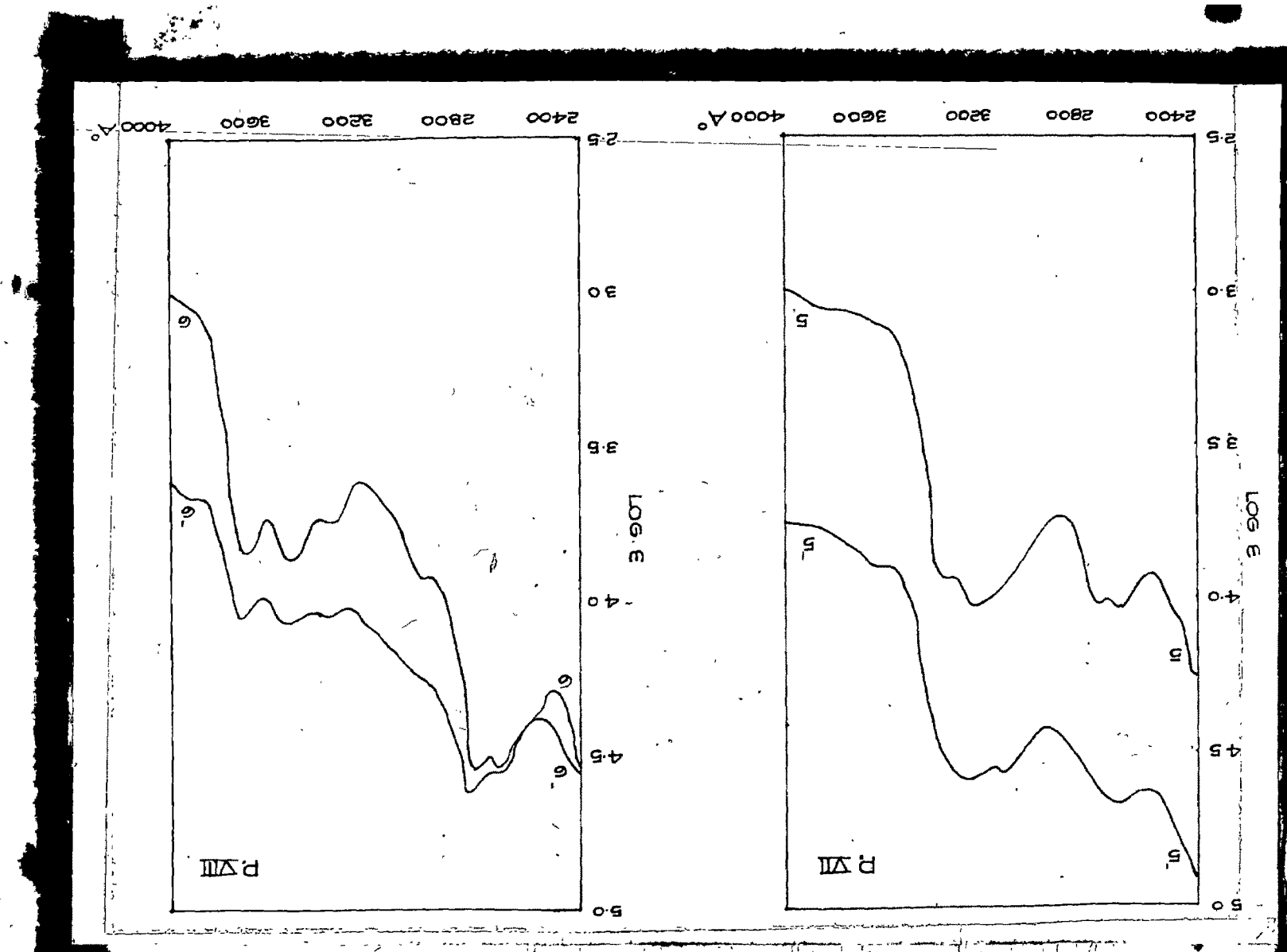


(1) [illegible]roxy-4-methylquinoline and (1') [illegible]ethylene bis-derivative;

(2) [illegible]roxy-4,6-dimethylquinoline and its methylene bis-derivative.

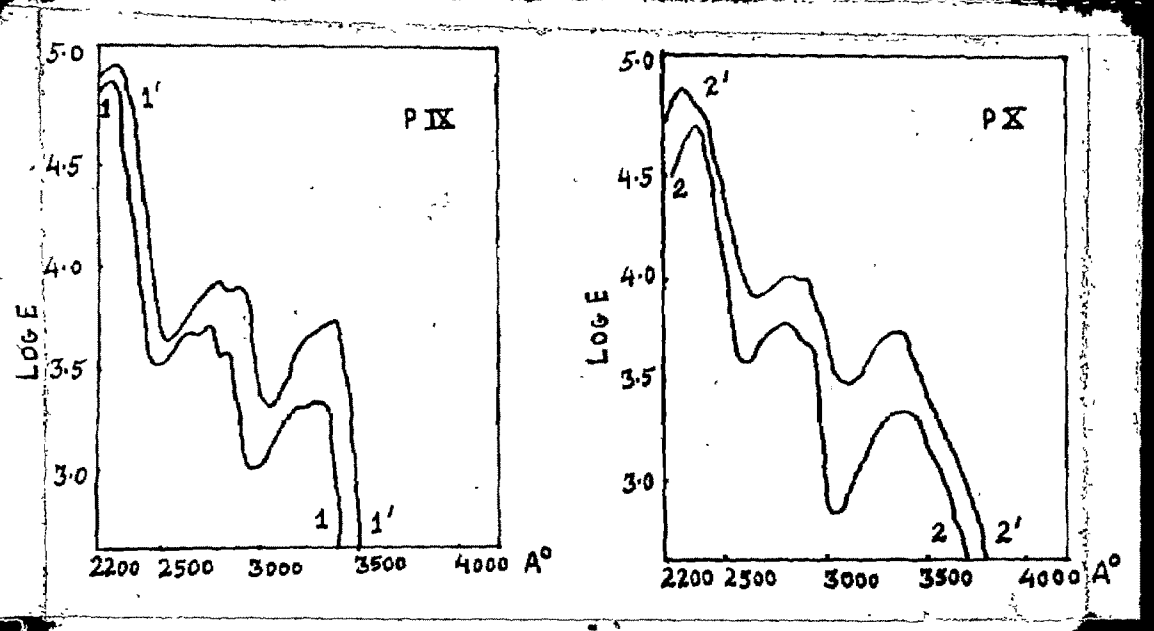
(3) 2-Hydroxy-4,8-dimethylquinoline a[illegible] (3') its methylene bis-derivative.

(4) 2-Hydroxy-4,6,8-trimethylquinolin[illegible] (4') its methylene bis-derivative.



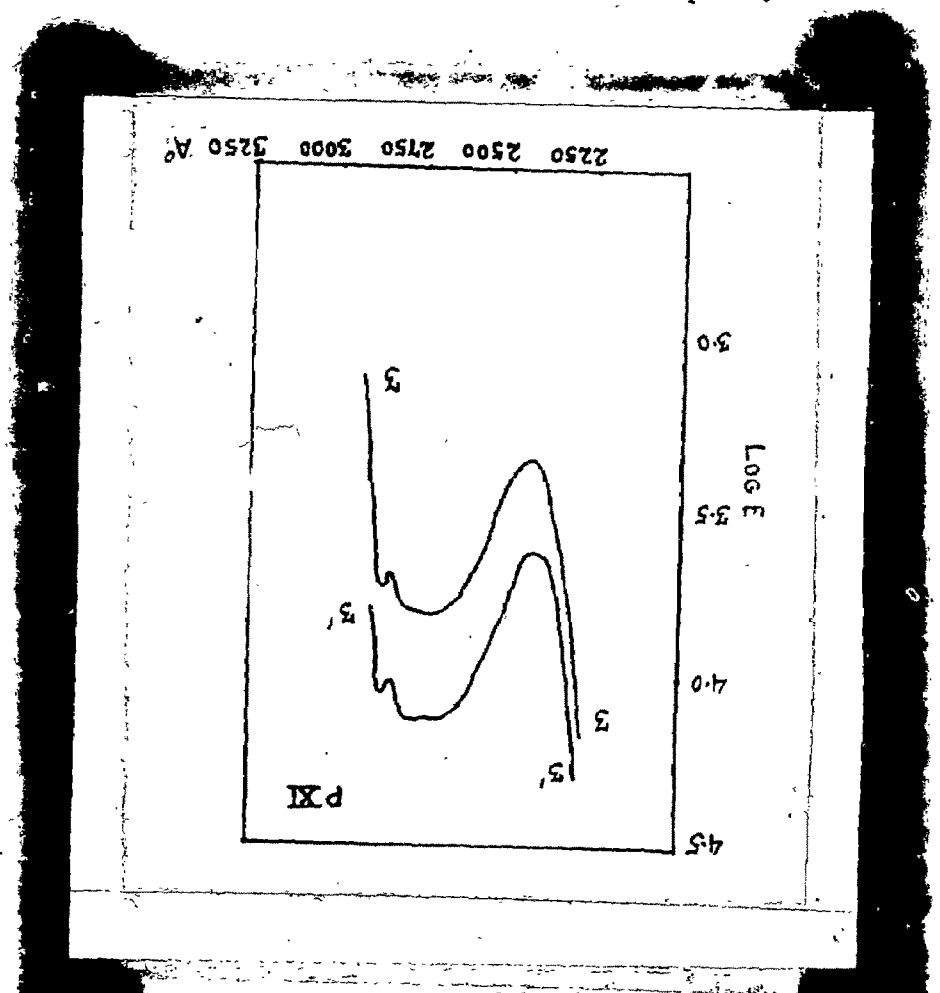
(6) 2-Hydroxy-4-methylbenzoquinol… and (6') its methylene bis-d…

2-Hydroxy-4-methyl-7-chloro-quinoline and (5') its methylene bis-derivative.

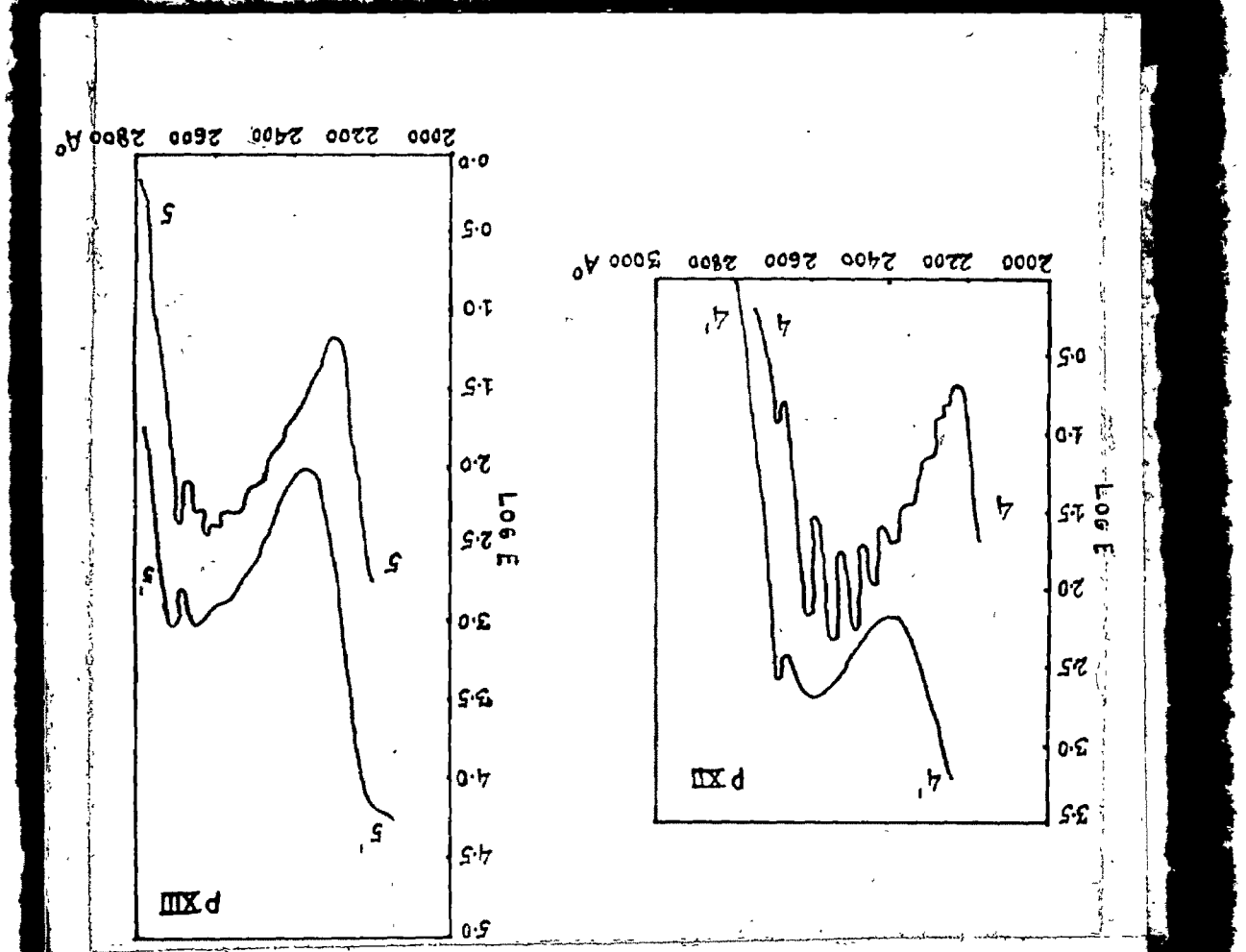


β-Naphthyl and (1') its methylene bis-derivative.

(2) β-Naphthylamine and 2-amino-2'-hydroxy-1-dinaphthylmethane.



(3) Gramine methiodide and (3') its methylene bis-derivative.



(4) Benzene and (4') diphenylmethane.

(5) Toluene and (5') 9,10-dihydroanthracene.

PARTIAL HYDROLYSIS OF SUBSTITUTED AMIDES OF CYANACETIC ACID BY (A) POLYPHOSPHORIC ACID AND (B) SULPHURIC ACID

By
C. M. MEHTA AND G. H. PATEL

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PARTIAL HYDROLYSIS OF SUBSTITUTED AMIDES OF CYANACETIC ACID BY (A) POLYPHOSPHORIC ACID AND (B) SULPHURIC ACID

NITRILES have been hydrolysed to amides by Snyder and Elson[1] using polyphosphoric acid. Sperber *et al.*[2] prepared trisubstituted acid amides from corresponding nitriles using 80% H_2SO_4 at 100° C. Thus, the substituted amides of cyanacetic acid undergoing partial hydrolysis have been converted to corresponding malon mono amides, on separately using (*a*) polyphosphoric acid and (*b*) sulphuric acid. The process is as follows :—

$$CH_2\begin{matrix}CN\\CONHR\end{matrix} \xrightarrow[(b)\ H_2SO_4]{(a)\ PPA} CH_2\begin{matrix}CONH_2\\CONHR\end{matrix}$$

I II

(where, R is phenyl, tolyl, etc., groups).

(*a*) 0·01 M substituted cyanacetamide I, was dissolved in a clear solution of PPA, obtained by dissolving 10 gm. P_2O_5 in 6 c.c. phosphoric acid (1·75 d.) and heated for 2 hours at 110° C. The reaction mixture on pouring in water, gave white product, which was crystallised from alcohol-water and it was found to be corresponding malon mono amide II.

(*b*) 0·01 M same cyanacetamide I, was dissolved in 10 c.c. ice-cold 75% sulphuric acid and the reaction mixture was kept overnight at room temperature. It was then poured in water and white product was obtained. This, on crystallisation as above, gave the same malon mono amide II.

The yields by both methods were almost quantitative; but in (*b*) the products were more clean and this method is relatively simple. These malon mono amides II have been found identical with the authentic samples prepared by Whiteley's[3] method modified by Naik[4] and his collaborators. Further work on the above amides is in progress and details will be published elsewhere.

Chemistry Department,
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M. S. University of Baroda,
Baroda,
December 23, 1958.

C. M. MEHTA.
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TABLE 1 — PARTIAL HYDROLYSIS OF CYANACETARYLAMIDES TO CORRESPONDING MALON MONOARYLAMIDES

Amide	M.P. (uncorrected) °C.	Yield %	Mol. formula	Nitrogen, %	
				Found	Reqd
Malon monoanilide	164; 133†	85	$C_9H_{10}N_2O_2\ \frac{1}{2}H_2O$	14·93	14·97
Malon mono-*p*-toluidide	164; 144†	88	$C_{10}H_{12}N_2O_2\ \frac{1}{2}H_2O$	13·64	13·93
Malon mono-*p*-chloroanilide*	145	82	$C_9H_9ClN_2O_2$	13·43	13·17
Malon mono-*m*-toluidide	165	84	$C_{10}H_{12}N_2O_2$	14·32	14·58
Malon mono-*o*-toluidide	162	80	$C_{10}H_{12}N_2O_2$	14·30	14·58
Malon monobenzylamide*	120	75	$C_{10}H_{12}N_2O_2$	14·88	14 58
Malon mono-1,3,4-xylidide	166	80	$C_{11}H_{14}N_2O_2$	13·84	13·60
Malon mono-α-naphthylamide	145	85	$C_{13}H_{12}N_2O_2$	12·54	12·27
Malon mono-β-naphthylamide	188	82	$C_{13}H_{12}N_2O_2$	12·40	12 27
Malon mono-*o*-anisidide*	162	90	$C_{10}H_{12}N_2O_3$	13·20	13·40

*Reported for the first time.
†Water of crystallization from the hydrated compound was removed by heating at 110°C. under vacuum.

obtained. Hauser and Eby[6] converted β-ketonitriles to β-ketoamides by boron fluoride in aqueous acetic acid and by polyphosphoric acid.

In the present investigation it was found that by using polyphosphoric acid or 75 per cent sulphuric acid, the malon monoarylamides listed in Table 1 can be prepared by partial hydrolysis from the corresponding cyanacetarylamides according to the reaction:

$$NCCH_2CONHR \xrightarrow[(b)\ H_2SO_4]{(a)\ PPA} H_2NOC.CH_2.CONHR$$

where R is phenyl, tolyl, benzyl, xylyl and naphthyl groups.

Hydrolysis using polyphosphoric acid—Cyanacetarylamide (0·01*M*) was dissolved in a clear solution of polyphosphoric acid obtained by dissolving 10 g. P_2O_5 in 6 ml. phosphoric acid (*d*, 1·75) and heated for 2 hr at 110°C. The reaction mixture on pouring into water gave a white product, which was crystallized from aqueous alcohol and was found to be the corresponding malon monoarylamide.

Hydrolysis with sulphuric acid — Cyanacetarylamide (0·01*M*) was dissolved in 10 ml. ice-cold 75 per cent sulphuric acid and the reaction mixture was left overnight at room temperature. It was then poured in ice-cold water and the white product obtained was crystallized as above.

The identity of malon monoarylamides prepared was established by comparing their melting points and mixed melting points with those of authentic samples prepared by hydrolysing malon diarylamides by means of liquor ammonia (*d*, 0·88) according to Whiteley's method[7,8] as modified by Naik *et al.*[9,10]. The yields obtained in both these methods were almost quantitative, but the products obtained by the use of sulphuric acid were purer and the method was also relatively simple.

One of the authors (G.H.P.) is thankful to the M.S. University of Baroda for a research assistantship.

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Formation of Malon Monoarylamides on Partial Hydrolysis of Cyanacetarylamides using Polyphosphoric Acid & Sulphuric Acid

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Manuscript received 6 *July* 1961

A number of cyanacetarylamides have been partially hydrolysed to corresponding malon monoarylamides by means of polyphosphoric acid or 75 per cent sulphuric acid; the yields of the amides are quantitative.

IN the hydrolysis of nitriles to acids, the use of 100 per cent phosphoric acid has been known for some time. Recently, it has been observed that the amides obtained by Beckmann's rearrangement and acylation of amines are stable in polyphosphoric acid and do not undergo hydrolysis[1,2]. The reaction of polyphosphoric acid has, therefore, been investigated with various cyanacetarylamides with a view to preparing with ease malon monoarylamides, which are used as intermediates in the synthesis of 2,4-dihydroxyquinolines[3].

It has been found that simple nitriles can be hydrolysed to amides by polyphosphoric acid[4]. However, the method was not found to be suitable for the hydrolysis of sterically hindered nitriles. Sperber *et al.*[5] carried out the conversion of tributyl acetonitrile to tributyl acetamide on a steam bath using 80 per cent sulphuric acid. These workers tried different concentrations of sulphuric acid and also other reagents, viz. polyphosphoric acid, concentrated hydrochloric acid, etc., and found that the expected tributyl acetic acid from the corresponding amide was not

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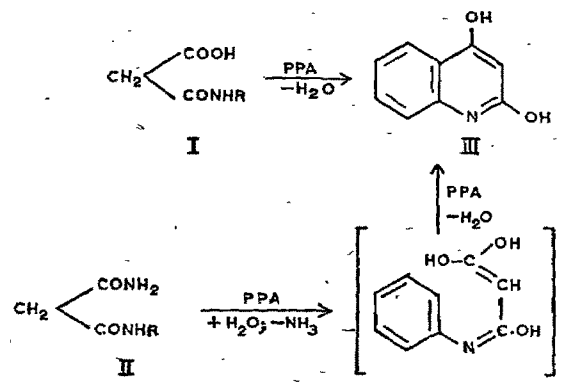
SYNTHESIS OF 2,4-DIHYDROXYQUINOLINE DERIVATIVES BY CYCLIZATION OF MALON MONOARYL ACIDS & MALON MONOARYL AMIDES

BAUMGARTEN AND KÄRGEL[1] CYCLIZED HALF ANILIDES of malonic ester in vacuum at 250°C. to 2,4-dihydroxyquinoline derivatives. Baker *et al.*[2] obtained 3-alkyl-2,4-quinolinediols on refluxing 0·1*M* each of cyclohexylmalonic ester and arylamine in diphenyl ether. Similarly, malon monoaryl acids (I) have been cyclized to give 2,4-dihydroxyquinoline derivatives (III) by means of polyphosphoric acid; but in diphenyl ether instead of the products of cyclization of (I), corresponding N-acetyl arylamines, (CH_3CONHR), are formed on decarboxylation. Further, Hauser and Murray[3] obtained 4-hydroxyquinoline derivatives on cyclization of anil-nitriles, prepared from aniline and β-ketonitrile using polyphosphoric acid. This method involves the conversion of anil-nitrile to corresponding anilamide, which undergoes cyclization eliminating ammonia. In the same way, malon monoaryl amides (II), have been cyclized to yield 2,4-dihydroxyquinoline derivatives (III) with elimination of ammonia by means of polyphosphoric acid (PPA). These reactions are expressed as follows:



where R is phenyl, tolyl, etc., groups.

The compounds of type I have been prepared by the method of Chattaway modified by Ahluwalla *et al.*[4].

Type II compounds have been prepared by the partial hydrolysis of the substituted amides[5] of cyanacetic acid, ($CN\text{-}CH_2\text{-}CONHR$), using 75 per cent sulphuric acid at 0°C. as well as by the method of Whitley modified by Naik and co-workers[6,7]. The experimental procedure is described below.

Malon monoaryl acids (I; 0·01*M*) and malon monoaryl amides (II; 0·01*M*) were dissolved in a clear solution of PPA prepared by dissolving P_2O_5 (10 g.) in phosphoric acid (d 1·75; 6 ml.) and the reaction mixture heated in an oil bath at 140°C. for 3 hr with a calcium chloride guard tube. Hydrochloric acid (1*N*, 30 ml.) was then added in the cold and the reaction mixture neutralized with sodium hydroxide solution (*p*H 4), when the crude product was precipitated. It was then crystallized from dilute acetic acid as a white product. The yield in the case of compound of type I is quantitative, whereas the yield in the case of compound of type II is poor. Further work is in progress and the details will be published elsewhere.

One of the authors (G.H.P.) thanks the M.S. University of Baroda for a Research Assistantship to carry out this work.

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Synthesis of 2,4-Dihydroxyquinolines Using Polyphosphoric Acid as the Cyclizing Agent

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A number of 2,4-dihydroxyquinolines have been synthesized by the cyclization of malon monoaryl acids and malon monoarylamides with polyphosphoric acid as the cyclizing agent. The yields of quinolinediols from the acids are quantitative while those from the amides are poor.

IN a previous communication[1] the synthesis of 2,4-dihydroxyquinolines from malon monoaryl acids and malon monoarylamides, using polyphosphoric acid, was described. Ziegler and Gelfert[2] have reported a new and simple method for the synthesis of 2,4-dihydroxyquinoline derivatives using phosphorus oxychloride as the condensing agent. Shah *et al.*[3] have prepared quinolinediols using a mixture of anhydrous zinc chloride and phosphorus oxychloride. Baumgarten and Kargel[4] and Baker *et al.*[5] have also developed methods which have been found suitable for the preparation of 3-substituted quinolinediols.

A number of 2,4-dihydroxyquinoline derivatives have now been prepared by the cyclization of malon monoaryl acids using polyphosphoric acid as the cyclizing agent. Malon monoaryl acids, required for the synthesis of quinolinediols, have been prepared by the method of Chattaway as modified by Ahluwalia *et al.*[6]. It may, however, be mentioned that on refluxing the malon monoaryl acids in diphenyl ether, we have obtained the corresponding N-acetyl arylamines, instead of the expected quinolinediols due to decarboxylation taking place in the course of reaction.

Further, Hauser and Murray[7], using polyphosphoric acid, synthesized 4-hydroxyquinolines, on cyclization of anilnitriles, through the conversion of anilnitrile to corresponding anilamide. In the same way 2,4-dihydroxyquinolines have now been prepared by the cyclization of malon monoarylamides, using polyphosphoric acid as the cyclizing agent. The required malon monoarylamides have been prepared by the partial hydrolysis[8] of cyanacetarylamides. Cyclization of cyanacetarylamides ($CNCH_2CONHR$), using PPA, however, gave malon monoarylamides instead of the expected 2,4-quinolinediols.

Experimental procedure

Malon monoaryl acids listed in Table 1 have been prepared by the following general method.

Primary arylamine (1 mole) and ethyl malonate (1·75 moles) were heated for 40 min. in a flask fitted with an air condenser. The solid product was mixed with ethanol (100 ml.) and allowed to cool, when

TABLE 1 — MALON MONOARYL ACIDS AND AMIDES

Sl No.	Compound	M.P.* °C.	Mol. formula	Nitrogen Found %	Nitrogen Reqd %
1	Malon anilic acid	136	—	—	—
2	Malon-*p*-toluidic acid	154	—	—	—
3†	Malon-*p*-chloroanilic acid	145	$C_9H_8O_3NCl$	6·100	6·550
4†	Malon-*p*-anisidic acid	157	$C_{10}H_{11}O_4N$	6·574	6·698
5	Malon-*m*-toluidic acid	106	—	—	—
6†	Malon-*m*-chloroanilic acid	131	$C_9H_8O_3NCl$	6·151	6·550
7†	Malon-*o*-toluidic acid	144	$C_{10}H_{11}O_3N$	7·220	7·250
8†	Malon-*o*-anisidic acid	148	$C_{10}H_{11}O_4N$	6·302	6·698
9	Malon-1,3,4-xylidic acid	156	—	—	—
10†	Malon-α-naphthylanilic acid	155	$C_{13}H_{11}O_3N$	5·862	6·113
11†	Malon-β-naphthylanilic acid	176	$C_{13}H_{11}O_3N$	5·958	6·113
12	Malon-monophenylamide	133	—	—	—
13	Malon-mono-*p*-tolylamide	144	—	—	—
14	Malon-mono-1,3,4-xylidide	166	—	—	—

*All melting points uncorrected.
†Compounds prepared for the first time.

TABLE 2 — 2,4-QUINOLINEDIOLS

Sl No.	Compound	M.P.* °C.	Mol. formula	Nitrogen Found %	Nitrogen Reqd %
1	2,4-Dihydroxyquinoline	360	$C_9H_7O_2N$	8·410	8·70
2†	6-Methyl-2,4-dihydroxyquinoline	342	$C_{10}H_9O_2N$	8·329	8·00
3†	6-Chloro-2,4-dihydroxyquinoline	370	$C_9H_6O_2NCl$	7·677	7·20
4	6-Methoxy-2,4-dihydroxyquinoline	308	$C_{10}H_9O_3N$	7·305	7·30
5†	7-Methyl-2,4-dihydroxyquinoline	388	$C_{10}H_9O_2N$	7·730	8·00
6	7-Chloro-2,4-dihydroxyquinoline	340	$C_9H_6O_2NCl$	6·784	7·20
7†	8-Methyl-2,4-dihydroxyquinoline	360	$C_{10}H_9O_2N$	7·720	8·00
8	8-Methoxy-2,4-dihydroxyquinoline	248	$C_{10}H_9O_3N$	7·421	7·30
9†	6,7-Dimethyl-2,4-dihydroxyquinoline	345	$C_{11}H_{11}O_2N$	7·232	7·40
10	2,4-Dihydroxy-7,8-benzoquinoline	338 (decomp.)	$C_{13}H_9O_2N$	6·340	6·63
11†	2,4-Dihydroxy-5,6-benzoquinoline	381 (decomp.)	$C_{13}H_9O_2N$	6·200	6·63
12	2,4-Dichloroquinoline	65	—	—	—
13	8-Methoxy-2,4-dichloroquinoline	92	—	—	—
14	2,4,7-Trichloroquinoline	105	—	—	—

*All melting points uncorrected.
†Compounds prepared for the first time.

malon diamide crystallized out. This was filtered and the filtrate contained malon arylamate, which, after addition of sodium carbonate solution (8 g. in 70 ml. water), was steam distilled for 1 hr until the first separated oily ester had disappeared. On cooling, a small amount of the diamide separated out which was filtered. The filtrate, on acidification with hydrochloric acid, gave a white product which was filtered and crystallized from water.

Malon monoarylamides[8] listed in Table 1 have been prepared as follows.

Cyanacetarylamide (0·01 mole) was dissolved in ice-cold sulphuric acid (10 ml.; 75 per cent) and the reaction mixture was kept overnight at room temperature. It was then poured into cold water (25 ml.) when a white product was obtained which was filtered and crystallized from dilute ethanol. The amides obtained by this method were found to be identical with those prepared by the method of Whiteley modified by Naik *et al.*[9,10].

2,4-Dihydroxyquinolines listed in Table 2 were prepared by the following general method.

Malon monoaryl acid (0·01 mole) and malon monoarylamide (0·01 mole) were separately dissolved to a clear solution in polyphosphoric acid [prepared by dissolving 10 g. of phosphorus pentoxide in 6 ml. of phosphoric acid (d. 1·75)]. The reaction mixture was then heated in an oil bath at 140°C. for 3 hr with a calcium chloride guard tube. After cooling, hydrochloric acid (30 ml.; 1*N*) was added and the mixture neutralized with sodium hydroxide solution (*p*H 4), when the crude product was precipitated. It was then filtered and crystallized from acetic acid.

Malon monoarylamides 12, 13 and 14 (Table 1) have been cyclized with PPA to give 2,4-dihydroxyquinolines which are found to be identical with 1-, 2- and 9-quinolinediols respectively (Table 2) by their melting points and mixed melting points.

The di- and trichloroquinolines 12, 13 and 14 (Table 2) have been respectively prepared from quinolinediols 1, 8 and 6 (Table 2). The melting points of these di- and trichloro derivatives were found to be identical with those of the respective authentic samples by their melting points and mixed melting points.

The yield in the case of quinolinediols from malon monoaryl acids is quantitative, while those prepared from malon monoarylamides are poor.

Acknowledgement

One of the authors (G.H.P.) is thankful to the M.S. University of Baroda for a research assistantship.

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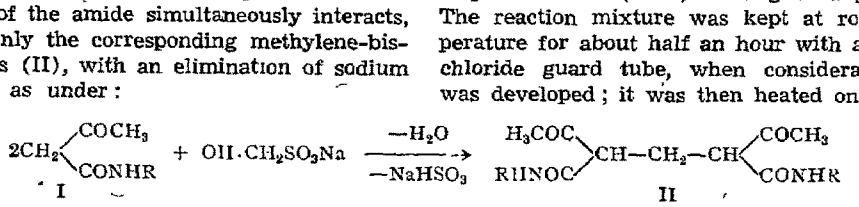
FORMATION OF METHYLENE-BIS-DERIVATIVES

1. Acetoacetarylamides by Means of Sodium Hydroxy Methane Sulphonate

SUTER, BAIR AND BORDWELL[1] carried on sulphomethylation reactions with phenols and compounds containing carbonyl groups, wherein from ethyl malonate they obtained its dimethane sulphonate, using the mixture of 40% formaldehyde with a solution of sodium sulphite; they also believed acetoacetic ester to have reacted in a similar manner. Shearing and Smiles[2] from 2-naphthol, by means of the mixture of solutions of formaldehyde and of sodium sulphite, prepared sodium 2-hydroxy-1-naphthylmethane sulphonate in part by a cleavage of bis-(2-hydroxy-1-naphthyl) methane with sodium sulphite; they further observed that 6-bromo-2-naphthol gave its sulphonate together with bis-(6-bromo-2-hydroxy naphthyl)-1-methane. The process is shown to be reversible when sulphonate and naphthoxide interact to give the bis-derivative with an elimination of sodium sulphite.

In the present work, sodium hydroxy methane sulphonate[3,4] ($OHCH_2SO_3Na$) is allowed to react with methylene-CH_2-group of the substituted amides of acetoacetic acid (I); and the products isolated from the reaction mixture are found to be methylene-bis-derivatives (II) of the corresponding acetoacetarylamides (I). The course of reaction is believed to have taken place through the intermediate formation of sulphonates of (I), with which hydrogen atom of the reactive methylene group of unreacted molecule of the amide simultaneously interacts, yielding only the corresponding methylene-bis-derivatives (II), with an elimination of sodium bisulphite as under:

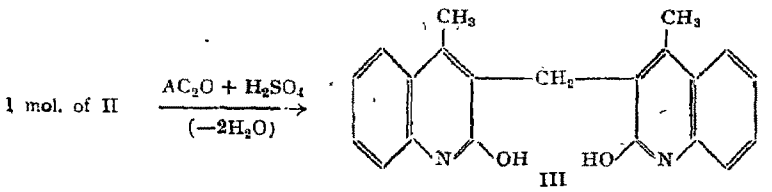


where, R is phenyl, tolyl, xylyl and naphthyl radicals. The reaction mixture is refluxed in 90% methanol and the product crystallised from acetic acid in 55-60% yield.

2. Quinoline Derivatives on Cyclisation of Methylene-Bis-Acetoacetarylamides

Ewins and King[5] cyclised acetoacetarylamides to give 2-hydroxy-4-methyl quinoline derivatives in presence of concentrated sulphuric acid. Jean De' combe[6] cyclised the condensed product of acetoacetanilide and chloral in presence of sodium acetate giving 2-hydroxy-3 (1-hydroxy-2, 2, 2-trichloroethyl)-4-methyl quinoline. Bangdiwala and Desai[7] obtained 4-hydroxy quinoline derivatives on cyclisation of crotonates using acetic anhydride and conc. H_2SO_4; they observed that the presence of anhydride prevents the tendency of decomposition of intermediate product undergoing cyclisation.

In the studies of 4-hydroxy quinoline derivatives formed through ethoxy methylene malonic ester, Price *et al.*,[8,9] prepared a number of 6 : 6'-bis-(4-hydroxy quinolyl) sulphide derivatives. Here in this work 3 : 3'-methylene-bis-(2-hydroxy-4-methyl quinoline) derivatives (III) have been synthesised on cyclisation of the corresponding methylene-bis-derivatives of acetoacetarylamides (II) using acetic anhydride and conc. H_2SO_4 as under:



where R, is phenyl, tolyl, xylyl and naphthyl radicals: Acetoacetarylamides (I) have been prepared by the method of Ewins[5] modified by Naik.[10]

To a mixture of methylene-bis-derivative (M : 0·01 M) and acetic anhydride (3 c.c.), conc. sulphuric acid (3 c.c.) was gradually added. The reaction mixture was kept at room temperature for about half an hour with a calcium chloride guard tube, when considerable heat was developed; it was then heated on a steam bath for about 5 minutes. The mixture on pouring in excess of ice-water gave brownish-white mass. The filtered mass after charcoaling, was crystallised from acetic acid. The

FORMATION OF METHYLENE-BIS-DERIVATIVES

By

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products are found to be pure but the yields are about 40-45%. Further work on compounds of types II and III is in progress and the details will be published elsewhere.

One of the authors (G. H. P.) thanks the M.S. University of Baroda for a Research Assistantship to carry out this work.

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Bromination of the Substituted Amides of Acetoacetic Acid

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A number of monobromo acetoacetarylamides have been prepared from acetoacetarylamides using bromine in acetic acid in the presence of a trace of iodine as catalyst in 70-75 per cent yields.

BACKES *et al.*[1] prepared monobromo derivatives of the substituted amides of malonic acid by brominating the amides in acetic acid. West[2] further brominated malon diarylamides and found that the hydrogen atom in the *para* position of the phenyl group and one of the hydrogen atoms in the methylene group were equally susceptible to the attack of bromine. Naik and Shah[3] prepared chloro derivatives of the substituted amides of malonic acid using sulphuryl chloride in the presence of dry benzene. Naik *et al.*[4] obtained monochloro derivative of acetoacetarylamides in the cold, using sulphuryl chloride in dry ether. Avasare *et al.*[5] iodinated cyanacetarylamides and acetoacetarylamides by means of iodine and iodic acid, and obtained mono- and di-iodo derivatives in both the cases. Desai[6] prepared monobromo derivatives of cyanacetarylamides using bromine in hot acetic acid.

In the present work monobromo acetoacetarylamides have been prepared in much better yields from acetoacetarylamides using bromine in acetic acid in the presence of a trace of iodine as catalyst:

$$CH_3COCH_2CONHR \xrightarrow[(\text{Trace of } I_2)]{Br_2 \text{ in acetic acid}} CH_3COCHBrCONHR$$

where R is phenyl, tolyl, xylyl or naphthyl group.

The amide (0·01*N*) was dissolved in 10-15 ml. of glacial acetic acid, to which 20 per cent solution of bromine in acetic acid (0·01*M*) was added in the presence of a trace of iodine. The flask was kept overnight at room temperature and the reaction mixture, on pouring into cold water, gave a white product, which was filtered and crystallized from benzene.

One of the authors (G.H.P.) is thankful to the M.S. University of Baroda for a research assistantship.

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BROMINATION OF 2, 4-SUBSTITUTED QUNINOLINE DERIVATIVES

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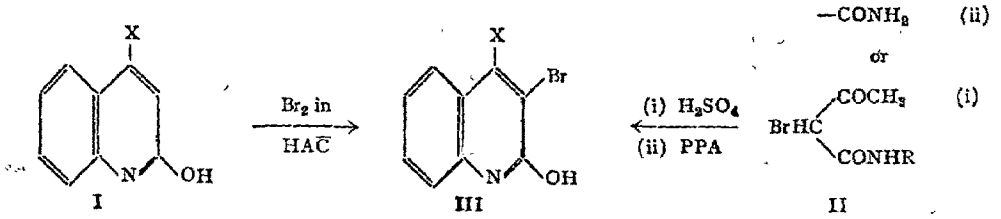
BROMINATION OF 2, 4-SUBSTITUTED QUINOLINE DERIVATIVES

RIEGEL *et al.*[1] have prepared 3-bromo-4-quinolinol on bromination of 4-quinolinol in warm glacial acetic acid with bromine. Surrey and Cutler[2] have reported preparation of 3-halo-2, 4-substituted quinolines by means of sulphuryl chloride, bromine or iodine monochloride in glacial acetic acid. Meyer *et al.*,[3] by brominating 2, 4-substituted quinoline, also obtained its 3-bromo derivative. Chick and Wilsmore,[4] by direct bromination prepared 3-bromo-2-hydroxy-4-methylquinoline, which was shown to be identical with the product obtained by cyclisation of monobromo acetoacetanilide with concentrated sulphuric acid.

A number of 3-bromoquinoline derivatives (III), using bromine in acetic acid in presence of a trace of iodine as catalyst, has been prepared from 2, 4-substituted quinolines (I). These 3-bromoquinolines (III) have also been obtained by cyclisation of monobromo acetoacetarylamides and of monobromo malonmonoarylamides (II).



(X = $-CH_3$ or $-OH$; R = $-C_6H_5$, $-C_7H_7$, $-C_8H_9$ or $-C_{10}H_7$).

Hydroxy-4-methylquinolines have been prepared by the method of Ewins and King,[5] while 2, 4-dihydroxyquinolines by that of Mehta and Patel.[6] These 3-bromo quinoline derivatives are crystallized from alcohol in white needles.

Acetoacetarylamides,[5,7] on bromination, gave corresponding monobromo derivatives, which, on cyclisation with concentrated sulphuric acid, yielded 3-bromo-2-hydroxy-4-methylquinolines; whereas the respective monobromo derivatives from malonmonoarylamides,[8,9] on cyclisation with polyphosphoric acid at 140° C., gave 3-bromo-2, 4-dihydroxyquinolines. These 3-bromoquinolines, obtained both by direct and indirect methods, are found to be identical by determination of their melting points and mixed melting points.

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