PART III

Synthesis of bis-hydroxyquinoline methanes by cyclisation of methylene bis-(cyanacet-arylamides) using polyphosphoric acid as a cyclising agent.

PART III

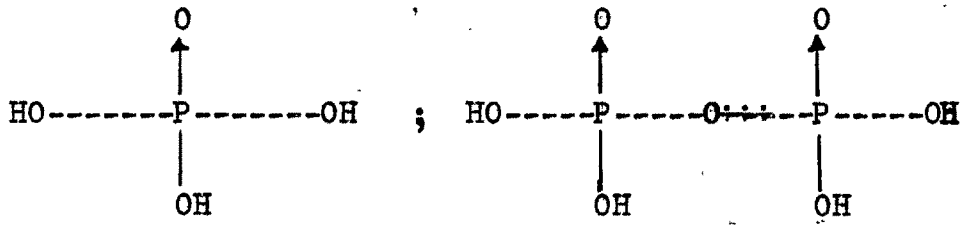
THEORETICAL

Snyder and Werber (1) reported for the first time the application of polyphosphoric acid as a reagent in organic chemistry. In recent years polyphosphoric acid (PPA) has achieved prominence in synthetic organic chemistry as is seen from the review made by Frank D. Popp and William E.McEwen (2). Polyphosphoric acid is a mixture of phosphorus pentoxide and syrupy phosphoric acid. It is used as a condensing agent as well as a general acid catalyst ; and in the present investigation it is described as a hydrolytic agent as well as a cyclising agent.

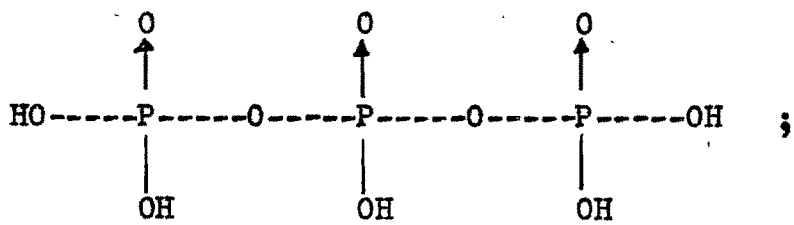
Bell R.N. (3), while determining the composition of strong phosphoric acids, found four acids between $H_2O.P_2O_5$ and $3H_2O.P_2O_5$ and an unidentified acid, all of which occured as mixtures down to $3H_2O.P_2O_5$. He showed that at all phosphorus pentoxide levels, orthophosphoric acid, pyro-phosphoric acid between 72 and 85 % P_2O_5 and a highly polymerized metaphosphoric acid above 83 % P_2O_5 were present.

The unidentified acid, occuring at a slightly lower phosphorus pentoxide content than the highly polymerized meta acid, is believed to be a lower polymer of meta-phosphoric acid. No difference in composition was found between strong phosphoric acids prepared by heat and those prepared by addition of phosphorus pentoxide.

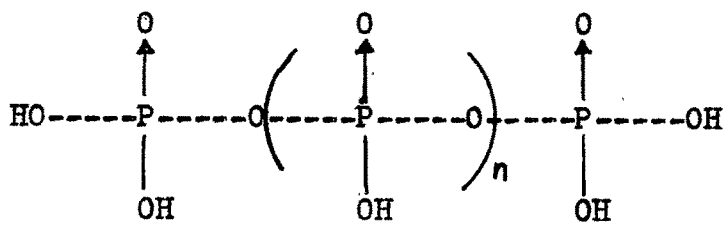
The structures of some of the individual phosphoric acids found in polyphosphoric acid are shown by Thilo and Sauer (4), as follows :



Orthophosphoric acid. Pyrophosphoric acid.



Tripolyphosphoric acid.



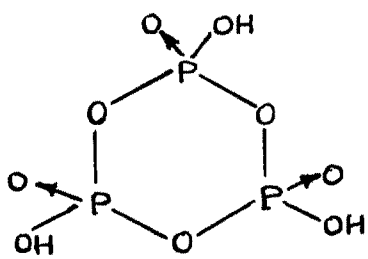
n = 2, Tetrapolyphosphoric acid.

n = 3, Pentapolyphosphoric acid.

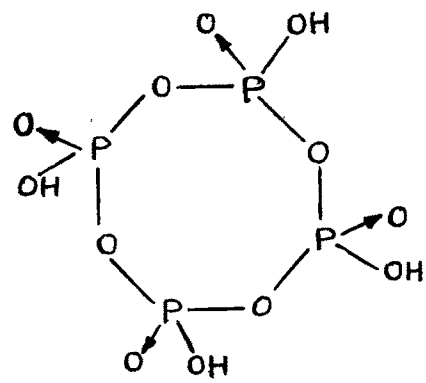
The contents of the commercial phosphoric acid by filter paper chromatographic method were found to be ortho-phosphoric acid, pyrophosphoric acid and linear polyphosphoric acids, having a theoretical P_2O_5 content of 81-85 %. Although commercial polyphosphoric acid (82-84 % P_2O_5) does not contain any detectable quantity of cyclic phosphoric acids, small amount of these acids have been found in mixtures having a theoretical P_2O_5 content greater than 85 %. Polyphosphoric acid, having content of 90 % P_2O_5, contained

three percent trimetaphosphoric acid and also a trace of tetrametaphosphoric acid.

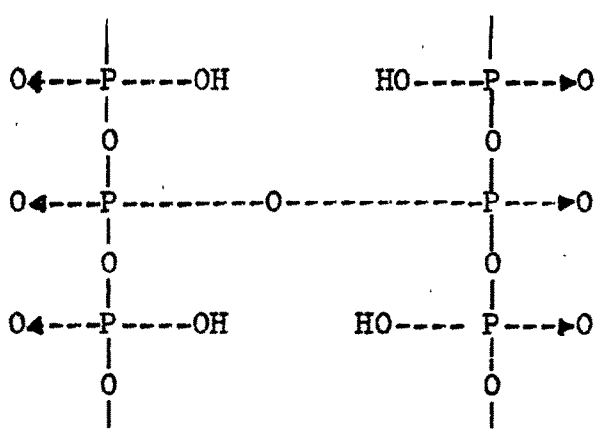
It has been shown that condensed polyphosphoric acids ; having P_2O_5 content greater than 85 %, contained some cross-linked (branched) polyphosphoric acids. Since, the evidence for the presence of the cyclic acids appears only when cross-linked polyphosphoric acids are also present, there is some possibility that the cyclic acids arise only upon hydrolysis of the cross-linked acids. although this problem has not been resolved the cyclic and cross-linked structures are as follows :



Trimetaphosphoric acid.



Tetrametaphosphoric acid.



A cross-linked polyphosphoric acid.

Polyphosphoric acid is a clear, colourless, extremely viscous, hygroscopic liquid, having a specific gravity of 2.060 at 20°C, when theoretical content of P_2O_5 equals 83 % and it is conveniently fluid at 60°C. Another point of interest with regard to condensed polyphosphoric acid is that, for any given content of phosphorus pentoxide, the same ratio of component acid results, no matter what the method of preparation of the acid, provided that a homogenous melt is obtained during the preparation. The versatility and general utility of polyphosphoric acid arise from the fact that it is a mild reagent even though a strong dehydrating agent. Generally, it does not bring about charring of organic compounds and it does not undergo violent reaction with hydroxylic compounds. It does not bring about the phosphonation of aromatic compounds. For these reasons it is a better reagent than the other reagents, such as sulphuric acid, hydrogen flouride, phosphoric anhydride or aluminium chloride (5).

Various workers have prepared and used different concentrations of polyphosphoric acid to bring about the reactions. Fritz Uhlig (6) prepared polyphosphoric acid by slowly adding 150-210 g. P_2O_5 with stirring and cooling to 100 ml. phosphoric acid (d. 1.709) and subsequently heating in a boiling water bath for several hours. This mixture contained 80-84 % P_2O_5 content and was found to be highly active polyphosphoric acid.

Hauser and Murray (7) used commercial polyphosphoric acid (15.0 g.) to cyclise crotonates (3.0 g.) into their

quinoline derivatives. Stephenson (Miss) (8) prepared polyphosphoric acid by adding phosphorus pentoxide (63.0 g.) in phosphoric acid (36.0 ml.) at 105°C till the mixture became clear and this amount was used for 0.01 mole of the reactant.

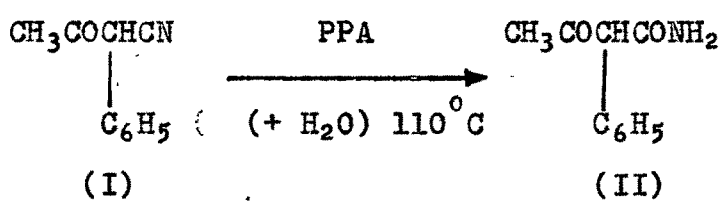
Sukh Dev (9) prepared this reagent by dissolving phosphorus pentoxide (140 g.) with syrupy orthophosphoric acid (60 ml. ; 85 %) in a flask, which was immediately stirred with a glass rod till homogenous ; the heat of the reaction sufficed for the almost complete dissolution of the anhydride, and in case any particles remained undissolved, the flask was heated on a steam-bath at 60°C till clear, and this quantity was applied to cyclise 0.02 mole of the reactant. Further, Krishna Rao and Sukh Dev (10) prepared this reagent from P_2O_5 (270 g.) and syrupy phosphoric acid (d. 1.75 ; 116 ml.). Moreover, Fritz Uhlig (6) observed that for determining optimum operating conditions, the amount of organic substance was mixed with 10-30 times the amount of polyphosphoric acid. If the mixture darkens immediately, ice-cooling is required ; if the colour changes slowly, room temperature is preferable, if any little colour change occurs, heating is necessary.

Polyphosphoric acid as a hydrolyting agent :

In the hydrolysis of nitriles to acids, the use of 100 % phosphoric acid has been known for some long time (11). The effectiveness of polyphosphoric acid in the Beckmann rearrangement (12) indicated the rather exceptional stability of amides in polyphosphoric acid reagent. Again ,

Snyder and Elston (13) found polyphosphoric acid to be effective in the reactions of carboxylic acids with weakly basic amines to yield the corresponding amides, i.e. acetic acid and 2,4-dinitroaniline gave 92 % yield of 2,4-dinitroacetanilide. Further, these authors also observed that the simple aromatic and aliphatic nitriles were hydrolysed to the corresponding amides in high yields by reaction with polyphosphoric acid for approximately one hour at 110°C. Benzonitrile for example, was converted to benzamide in a 96 % yield. Ethyl malonate was isolated in 65 % yield from the hydrolysis of ethyl cyanoacetate. But, this method was not found to be suitable for the hydrolysis of sterically hindered nitriles. Thus, 2,4,6-triisopropyl-benzonitrile and 1-hydroxy-2-cyano-3-methylnaphthalene were inert even at 160°C, while at this temperature, cyano-mesitylene underwent both hydrolysis and decarboxylation to give mesitylene.

Hauser and Murray (7) prepared 4-hydroxyquinoline from anil, which was obtained from aniline and β-ketonitrile; and they observed that polyphosphoric acid was effective in order to bring about both the steps, viz., partial hydrolysis and cyclisation in a single process to form a quinoline derivative. Thus, α-acetyl-α-tolunitrile I (β-ketonitrile) with polyphosphoric acid at 110°C is partially hydrolysed to β-ketoamide (II) as under :



(I) (II)

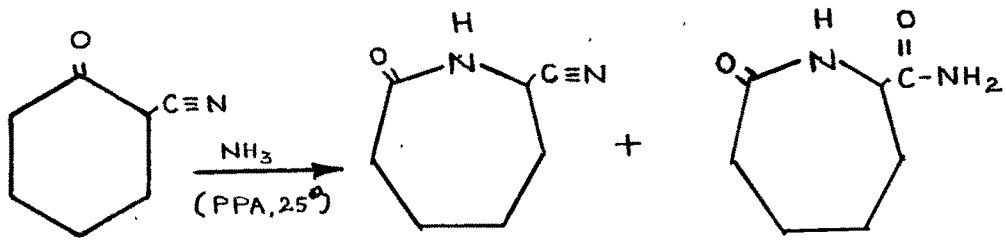
Again, Hauser and Eby (14) hydrolysed some β-ketonitriles into their corresponding β-ketoamides by the method of Hauser and Hoffenberg (15) with boron fluoride in aqueous acetic acid as well as by the method of Snyder and Elston (13) with polyphosphoric acid, and the conclusion was drawn that both the boron fluoride and polyphosphoric acid methods generally gave yield of β-ketoamides. Also these methods were considered superior to other known methods, one of which involved the ammonolysis of the respective β-ketoesters (16). Moreover, most other β-ketoesters that would be required for the preparation of β-ketoamides (III), which are not readily available have been obtained from β-ketonitriles as under :

$$CH_3CN \xrightarrow[(2)\ RCOOCH_3]{(1)\ NaNH_2} RCOCH_2CN \xrightarrow[(+\ H_2O)]{BF_3\text{-}HAc \text{ or } PPA} RCOCH_2CONH_2 \quad (III)$$

(R = $-C_6H_5$ or $-Cl.C_6H_4$-m).

The boron fluoride method involved the rapid saturation of a mixture of β-ketonitrile and aqueous acetic acid with the reagent, under which condition the temperature rose spontaneously to 120-140°C. The reaction was complete within a short time of about 10-20 minutes. The phosphoric acid method consisted generally in heating the β-ketonitriles with the reagent at the steam bath temperature for 30 minutes. It should be pointed out that the reaction of β-ketonitriles with boron trifluoride in aqueous acetic acid produced a boron difluoride complex of the β-ketoamides from which the β-ketoamides were subsequently liberated by means of hot sodium acetate solution.

Robert Conley (17) described the method for effecting the Schmidt transformation of ketones employing polyphosphoric acid both as the solvent and the catalyst. For example 2-cyanocyclohexanone (IV), on rearrangement and ring expansion, gave two products of 7-member ring, viz., 7-cyano-2-keto-hexamethylenimine (V) and 7-carboxamide-2-ketohexamethyenimine (VI) as under :



(IV) (V) (VI)

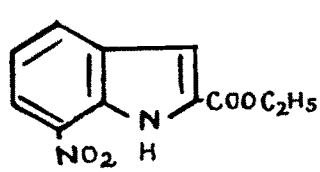
The above amido-lactam (VI) was found to be formed from product (V) by hydration of cyano group using polyphosphoric acid at 60°C. It was also found that the cyano-lactam (V) could be quantitatively converted to the amido-lactam (VI).

Polyphosphoric acid as a condensing agent :

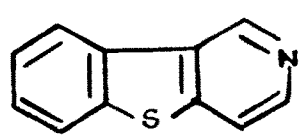
Polyphosphoric acid has been widely used as a condensing agent in the synthesis of numerous hetrocyclic compounds, e.g., in the Fischer indole synthesis and Pomeranz-Fritsch reaction ; in the preparation of cyclic ketones by intra molecular acylation reactions ; in the cyclodehydration reactions of aldehydes,ketones and alcohols ; in the Beckmann, Lossen, Wagner-Meerwein and Schmidt-rearrangement, in the intra molecular acylation and alkylation and in some other miscellaneous uses, viz., nitration, bromination, dehydration, hydrolysis, polymerization and

phosphorylation reactions.

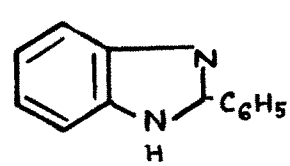
Witkop et al. (18) used polyphosphoric acid and obtained 2-phenylindole in good yield, not only from acetophenone phenylhydrazone but also from a mixture of phenylhydrazine and acetophenone by the method of Fischer indole synthesis. Singer H. and Shive W. (19) carried out similar Fischer cyclisation of ethyl pyruvate-o-nitro-phenylhydrazone with polyphosphoric acid and obtained ethyl-7-nitro-2-indole carboxylate (VII). Herz and Tsai (20) carried out the Pomeranz-Fritsch reaction on thiophene-carboxaldehyde and aminoacetal using polyphosphoric acid and obtained thianaphtheno (2,3-c)pyridine (VIII) 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. (21) carried out the Phillips benzimidazole synthesis using polyphosphoric acid with o-phenylenediamine and benzoic acid to give 2-phenylbenzimidazole (IX). (Miss) E.F.M. Stephenson (22) obtained 3-methyl-3-phenyl-oxindole by cyclisation of (±) -atrolacetanilide with polyphosphoric acid. Hill R.K. (23) cyclised nitrocycloalkanes into spirolactams using polyphosphoric acid.



(VII)

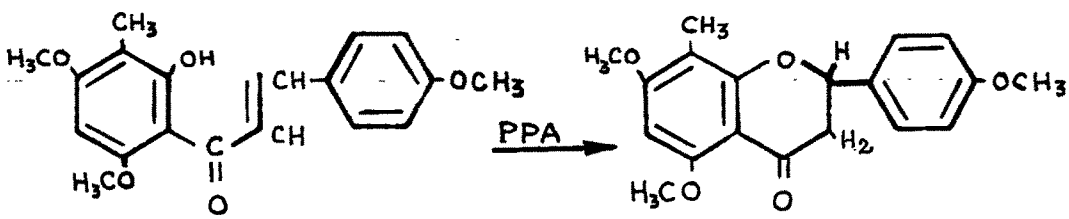


(VIII)



(IX)

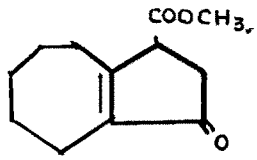
Koo, J. (24).condensed resorcinol with each of β-ketoesters, ethyl acetoacetate, ethyl α-methylacetoacetate and ethyl benzoylacetate in polyphosphoric acid and obtained respectively 4-methyl-7-hydroxycoumarin, 3,4-dimethyl-7-hydroxycoumarin and 4-phenyl-7-hydroxycoumarin in 80-95 % yield. The chalcone (X) has been converted by Nakazawa and Matsuura (25) into the flavanone derivative (XI) in 80 % yield by the action of polyphosphoric acid.



(X) (XI)

Elston (26) 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 (9) converted βγ or γδ unsaturated acids to cyclonones with the aid of polyphosphoric acid, viz., cycloheptylidenesuccinic acid was cyclised to cyclohepteno-cyclopentanone (XII) by treatment with polyphosphoric acid. Cope and Smith (27) carried out the cyclisation of o-(B-phenethyl)phenylacetic acid to 1,2,5,6-dibenz-1,5-cyclooctadiene-3-one (XIII) in 93 % yield using polyphosphoric acid.



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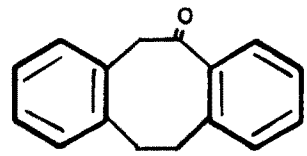
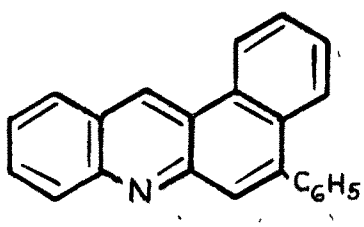


(XII) (XIII)

Phillips (28) prepared 4,7-dimethyl-1-tetralone from γ-p-tolylvaleric acid by polyphosphoric acid catalyzed cyclization. Hauser and Murray (29) synthesised 5-phenyl-benz-acridine (XIV) in 87 % yield from 2-phenacyl-3-phenyl-quinoline using polyphosphoric acid. Poller et al. (30) carried out several conversions of diarylarsinic acids into 9-arsafluorene oxides (XV) by the use of polyphosphoric acid at 160°C for 3 hours.



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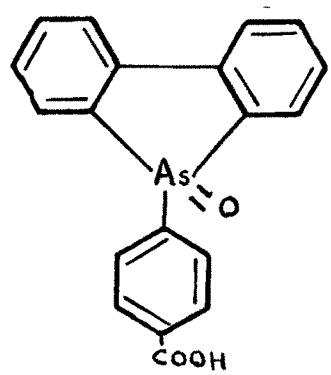
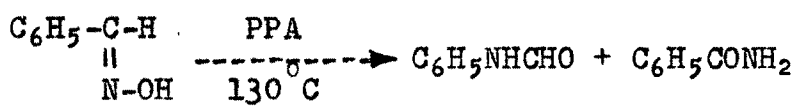


(XIV) (XV)

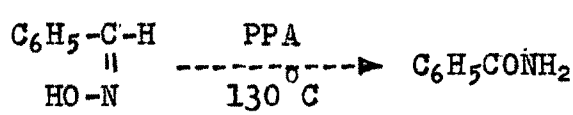
Pratt, Rice and Luckenbaugh (31) prepared 3,4-dihydroisoquinoline from N-formylphenethylamine by Bischler-Napieralski synthesis with polyphosphoric acid. Further, Proctor and Thomson (32) carried out the synthesis of 2-tosyl-1,2,3,4-tetrahydroisoquinoline. Snyder and Werber (1) subjected the Bischler-Napieralski reaction to N-acetyl-phenylalanine with a mixture of polyphosphoric acid and phosphorus oxychloride and obtained 1-methylisoquinoline.

Ghosh,Bhattacharya and Dutta (33) 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-dimethylisoquinoline. Popp and McEwen (34) also used a mixture of polyphosphoric acid and phosphorus oxychloride for preparing 6,7-dimethoxyisoquinoline from veratrylidene-aminoacetal.

Horning et al. (12) studied the Beckmann rearrangement of oximes with polyphosphoric acid e.g. syn benzaldoxime treated with polyphosphoric acid at 130°C gave formanilide and benzamide, while anti form at the same temperature gave only benzamide.



(syn)

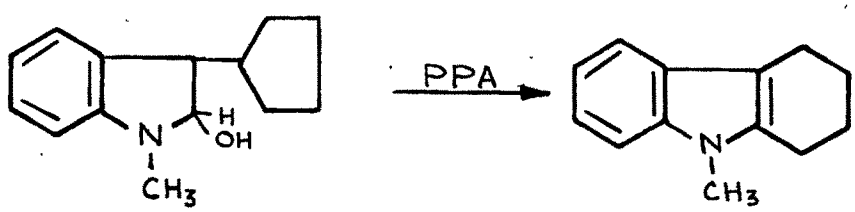


(anti)

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 Lossen 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) (XVI) is treated with the above reagent gave 9-methyl tetrahydrocarbazole (XVII)



(XVI) (XVII)

Klager et al. (35) 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.

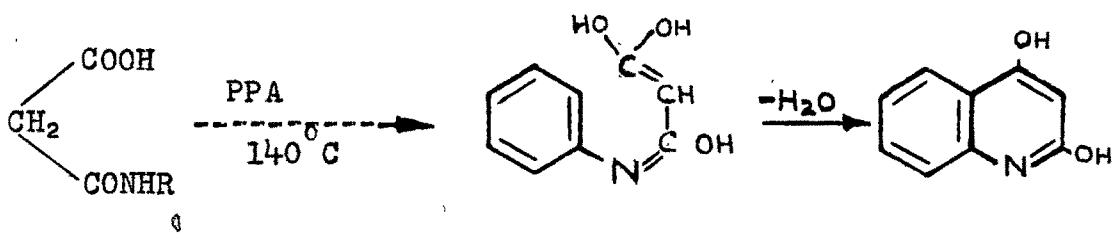
Cherbuliez and Weniger (36) carried out the phosphorylation of alcohols, e.g. methyl phosphate, benzyl phosphate and cetyl phosphate have been prepared by the reaction of the respective alcohols with polyphosphoric acid. Schaad (37) prepared alkylazides by the acid-catalyzed addition of hydrogen azide to alkenes.

Breuer and Hofferth (38) observed that coumarone-indene resins,having low softening points may be upgraded by the 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.

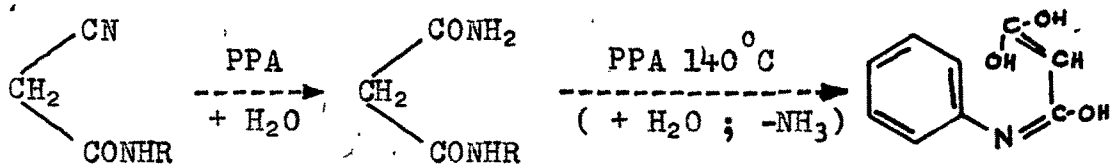
4-Hydroxyquinolines have been obtained on thermal cyclisation of several ethyl β-arylamino-α-unsaturated esters obtained from ethylacetoacetate and primary arylamines (39) (40) (41). Ewins and King (42) synthesised 2-hydroxyquinolines by a modified method of Knorr (43) using concentrated sulphuric acid as a cyclising agent. Bangdiwala and Desai (44) obtained 4-hydroxyquinolines on cyclisation of crotonates and acrylates using a mixture of acetic anhydride and concentrated sulphuric acid as a cyclising agent.

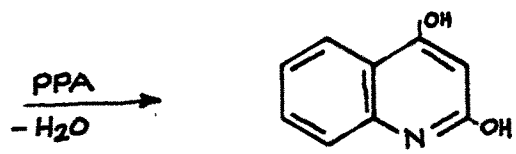
2,4-Dihydroxyquinolines (XVIII) which are found to be important intermediates, have been synthesised from malon arylacids and malonmonoarylamides respectively by Mehta and Patel (45), using polyphosphoric acid as a cyclising agent. The course of the reaction is as under :



(Where, R is phenyl,tolyl,xylyl,naphthyl,etc.groups). Further, they obtained 2,4-dihydroxyquinolines 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, are hydrolysed to malon arylacids with the elimination of

ammonia and then these acids simultaneously underwent cyclisation to give 2,4-dihydroxyquinolines (XVIII) eliminating water as under :-



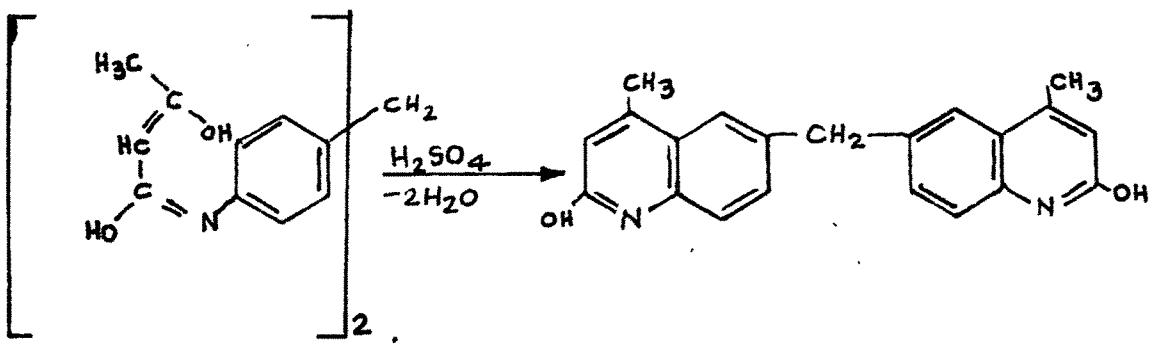


(XVIII)

Kaslow and Reck (46) have stated that very few diquinolylmethanes have been recorded in the literature. Schuller (47) prepared 5,5'-methylene bis-8-hydroxyquinoline by treatment of 8-hydroxyquinoline with formaldehyde in concentrated sulphuric acid. Borsche and Kienitz (48) obtained 6,6'-methylene-bis-quinoline by a Skraup reaction on 4,4'-diaminodiphenyl methane ; while Borsche and Meyer (49) synthesised 6,6'-methylene bis-2-methylquinoline by the action of alcoholic alkali and acetone on 5,5'-diisatyl-methane and decarboxylation of 6,6'-methylene-bis-2-methyl-cinconinic acid which was obtained from this reaction. Monti and Verona (50) have reported the preparation of methylene bis-6-hydroxyquinoline.

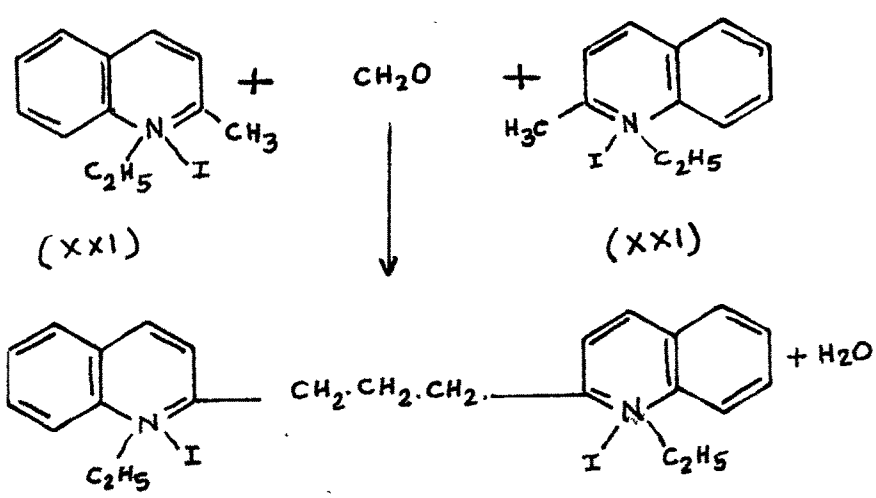
Further, Kaslow et al. (46) reported on the synthesis of several 6,6'-methylene bis-lepidine derivatives from corresponding 6,6'-methylene bis-acetoacetanilides through the carbostyrils and chlorolepidine derivatives. 4,4'-Methylene bis-acetoacetanilide was prepared from

4,4'-diaminodiphenylmethane in acetone with diketone. 6,6'-methylene bis-4-methylcarbostyril (XX) was obtained by cyclising 4,4'-methylene bis-acetoacetanilide (XIX) with concentrated sulphuric acid. This reaction is expressed as :-



(XIX) (XX)

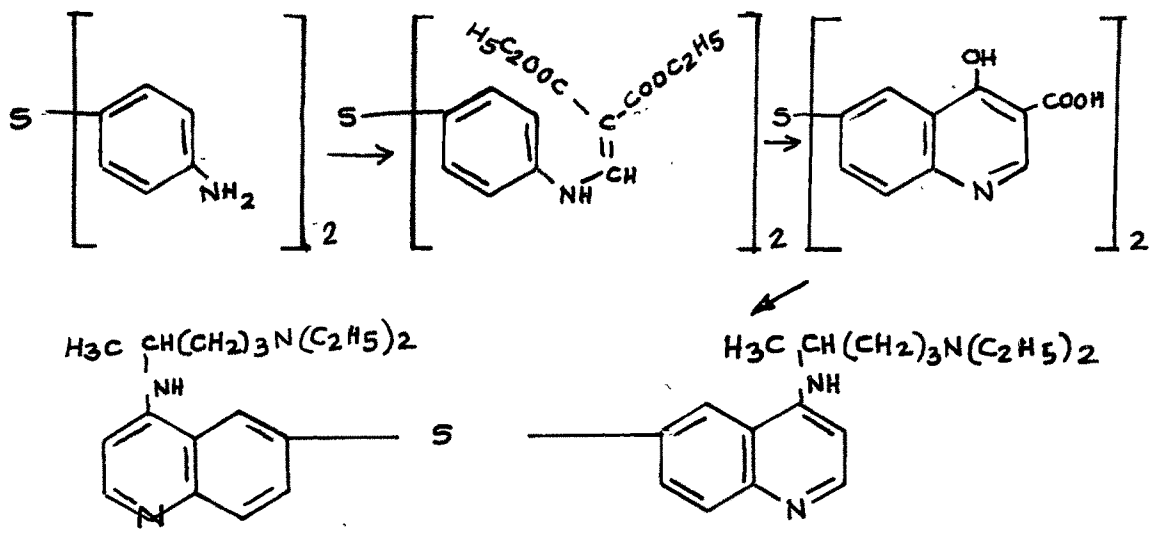
Mills and Hamer (51) condensed quinaldine ethiodide (XXI) with formaldehyde and obtained methylene diquinaldine. They concluded that the above reaction is a strict parallel to the condensation of acetoacetic ester and related compounds with formaldehyde, which gives methylene bis-acetoacetic ester and the compound diethiodide of methylene-diquinaldine (XXII) has actually been isolated as under :-



(XXI) (XXI)

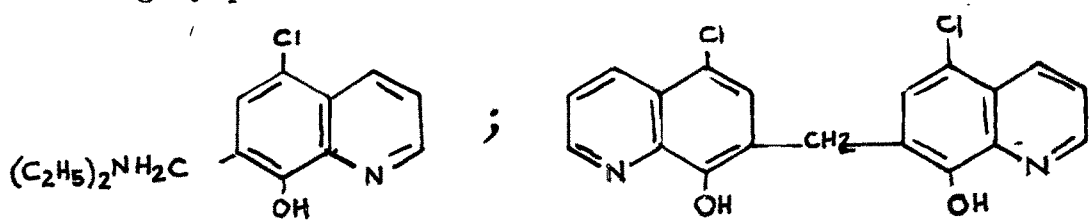
(XXII)

Price, Leonard and Stacy (52) prepared 4-hydroxy-quinolines with sulphur containing substituents using boiling diphenyl ether as cyclising agent. For this they have applied the ethoxymethylmalonic ester synthesis to p-aminophenyl sulphide proceeded successfully to produce 6,6'-bis 4-(4-diethylamino-1-methyl butylamine)-quinolyl sulphide (XXIII) as under :-



(XXIII)

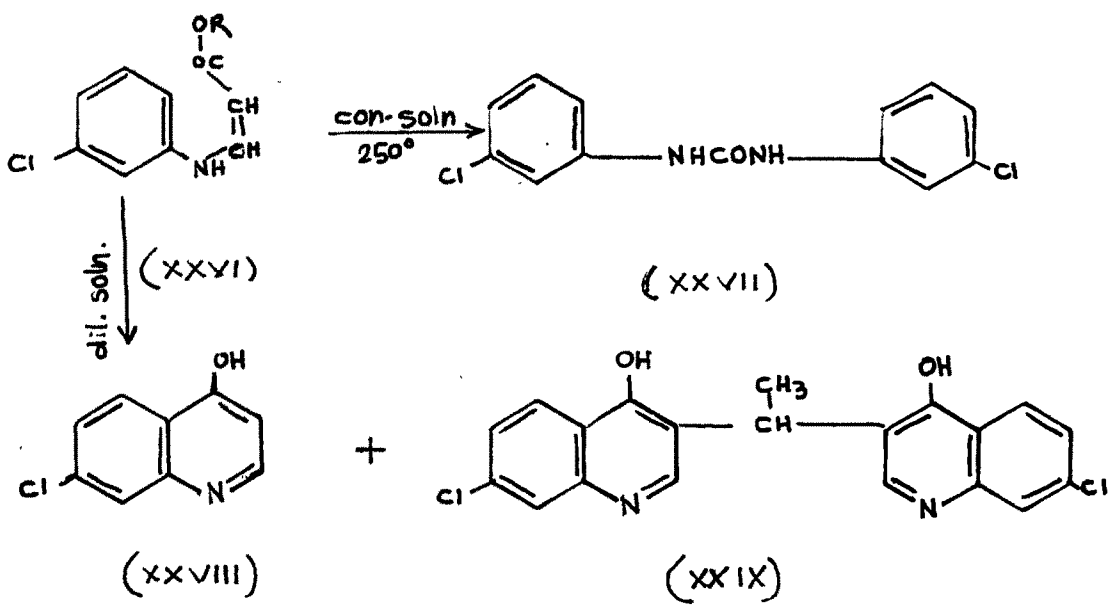
Edgerton et al. (53) prepared some antiamebic agents which while preparing they obtained 5-chloro-7-diethylaminomethyl-8-quinolinol (XXIV) and 7,7'-methylene bis (5-chloro-8-quinolinol) (XXV) as an insoluble high melting by-product.



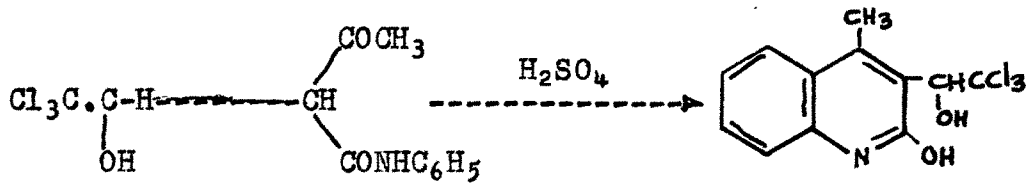
(XXIV) (XXV)

During the period of reflux, the insoluble 5,5'-methylene bis-(7-chloro-8-quinolinol) an isomer of (XXV) gradually formed in appreciable amounts. It was found that methylene bis-compounds were inactive towards amebicidal activity.

Price, Leonard and Reitsema (54) treated β-m-chloroanilinoacrylates (XXVI) in concentrated diphenyl ether and obtained bis-(m-chlorophenyl) urea (XXVII). But at high dilution 7-chloro-4-hydroxyquinoline (XXVIII) was obtained along with 1-1-bis-(7-chloro-4-hydroxy-3-quinolyl) ethane (XXIX), which could also be formed by condensation of 7-chloro-4-hydroxyquinoline with acetaldehyde.



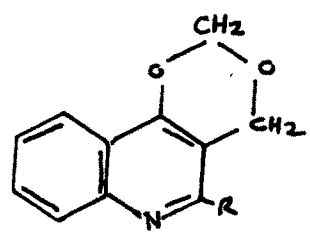
Jean D'ecombe (55) used sodium acetate as a catalyst in the condensation of aldehydes with compounds containing active hydrogen. Acetoacetanilide in aqueous alcohol with trichloroacetaldehyde in the presence of sodium acetate yielded trichlorohydroxymethyl acetoacet-anilide (XXX) which on cyclisation with sulphuric acid gave 2-hydroxy-3-(1-hydroxy-2,2,2-trichloroethyl)-4-methylquinoline (XXXI).



(XXX)

(XXXI)

Lydia Monti, Valeria Girelli and Berenica Romano (56) carried out the reaction of formaldehyde on γ-hydroxyquinolines in presence of sulphuric acid giving the cyclic methylenic ethers of the general structure (XXXII) as under.: (R = CH_3 or C_6H_5)



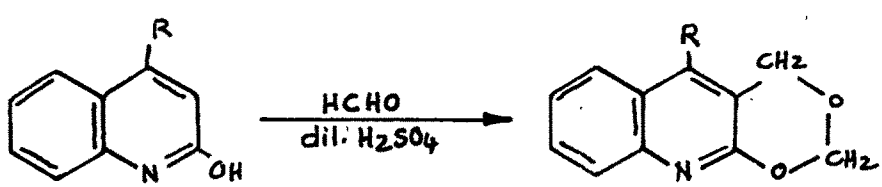
(XXXII)

This reaction is analogous to the reactions with 6-hydroxyquinoline and p-nitrocresols or p-nitrophenols. The identity in behaviour of 6-hydroxyquinoline and γ-hydroxyquinoline is attributable to the positions of the OH with respect to the N - atoms in the two compounds. In 6-hydroxyquinoline, the OH may be regarded as in p-position to the N, as in p-nitrophenol, the OH and NO_2 are in p-position, whereas in γ-hydroxyquinoline, the OH is in the p-position to the N in the same ring. The relatively greater activity of γ-hydroxyquinolines is explainable by the Bonino theory of consitution of aromatic nuclei,i.e. the presence of OH and N in the p-position to each other disturbs the system of negative atoms and increases the

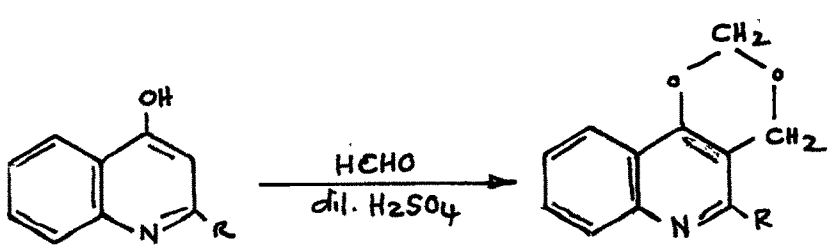
activity of the β-N-atom. In α-hydroxy-γ-alkylquinolines, the OH in the o-position, forms an active system, which makes the former react with formaldehyde as do γ-hydroxy-α-alkyl quinolines.

The γ-hydroxyquinolines were prepared by Lydia et al. (56) based on the method of Limpach (40). Thus, they prepared cyclic methylene ether of 2-methyl-γ-hydroxy-3-quinoline alcohol ; and cyclic methylene ether of 2,8-dimethyl- and 2,6-dimethyl-,4-hydroxy-3-quinoline alcohols. Methylene-quinoline alcohols are insoluble in aqueous alkalies but soluble in concentrated sulphuric acid and they do not give acetyl derivatives with acetic anhydride.

In the Borsche-Berkout modification of Lederer-Manasse reaction (56) (57), both 2- and 4-hydroxyquinolines give cyclic ethers (XXXIII) (XXXIV).

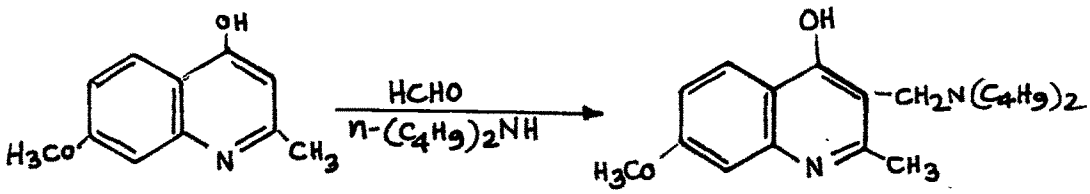


(XXXIII)



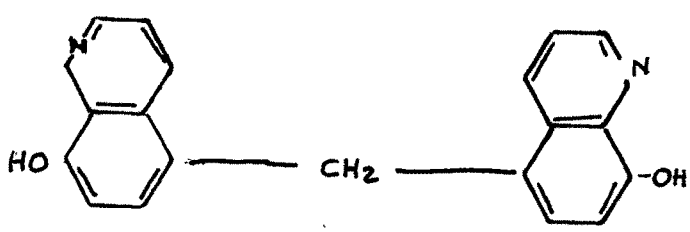
(XXXIV)

Price and Jackson (58) carried out the Mennich reaction of 4-hydroxyquinoline with formaldehyde and n-dibutylamine, giving 3-n-dibutyl aminomethyl derivative (XXXV) as under :-



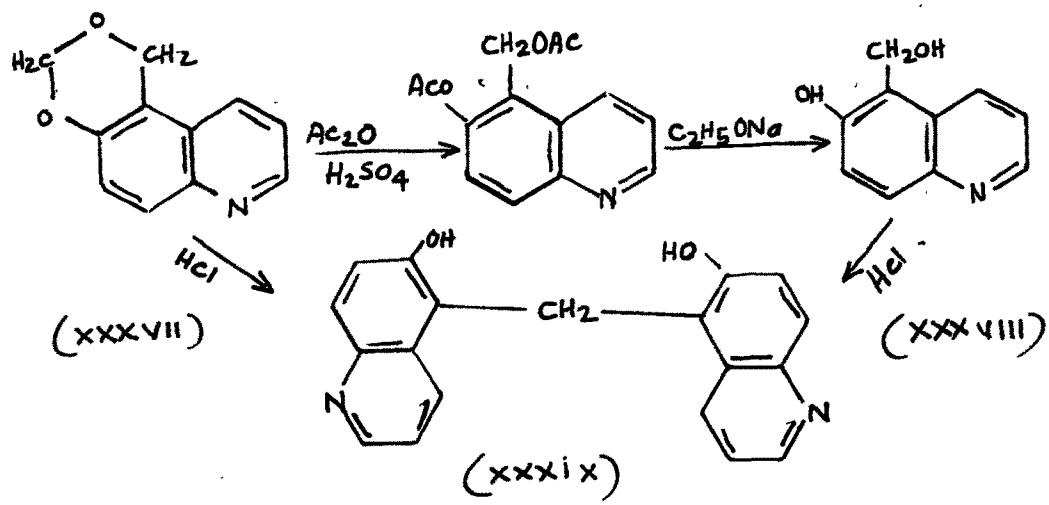
(XXXV)

The Lederer-Manasse reaction with (6-or 8-)hydroxy quinoline, formaldehyde and alkali gives carbinols or methylenebis-diquinolyl derivatives (59) (60). The typical reaction with 8-hydroxyquinoline, formaldehyde and sulphuric acid gave 5,5'-methylene bis-(8-hydroxyquinoline) (XXXVI) (47).



(XXXVI)

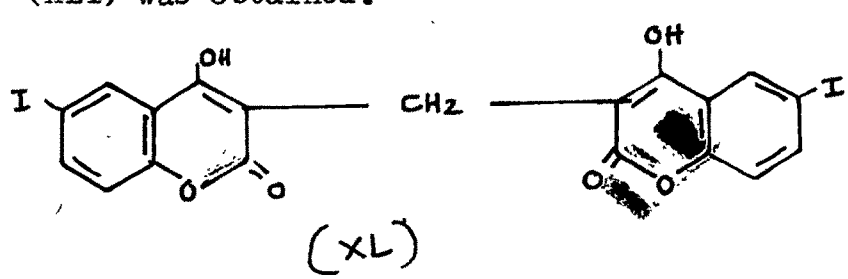
Kaslow and Raymond (61) obtained 6-hydroxy-5-quinolinemethanol (XXXVIII) by careful cleavage of dioxino (5,4-f)quinoline (XXXVII). The carbinol and dioxino compounds can be transformed by hydrochloric acid to 5,5'-methylene bis-(6-hydroxyquinoline) (XXXIX).



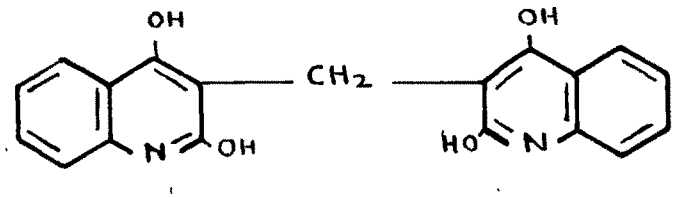
Piscopo et al., (62) condensed 4-hydroxy-6-iodo-coumarin with formaldehyde and obtained 3,3'-methylene bis-(4-hydroxy-6-iodocoumarin (XL). Further, Mentzer et al.(63) observed that the two hydroxy groups are essential for the antivitamin K activity of 3,3'-methylene bis-(4-hydroxycoumarin) and methylation or esterfication of both groups destroys the physiological activity.

Bis(4-hydroxy-3-coumarinyl) acetic acid-(Pelentan-) has been prepared by Fucik, Prochazka and Cechova (64) by condensation of 4-hydroxycoumarin with a solution of glyoxilic acid. Hais (65) used a paper chromatography for the detection and identification of pelentan and dicoumarol and some of their degradation products in blood and urine.

In order to prepare anticoagulants, Fucik, Prochazka, Hach and Strof (66) condensed 4-hydroxycarbostyrils with formaldehyde and 3,3'-methylene bis-(4-hydroxycarbostyril) (XLI) was obtained.

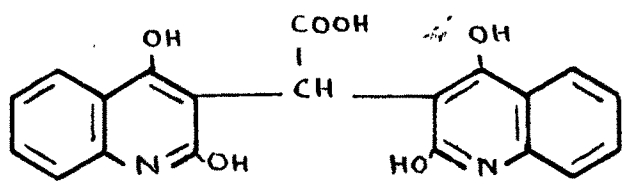


(XL)

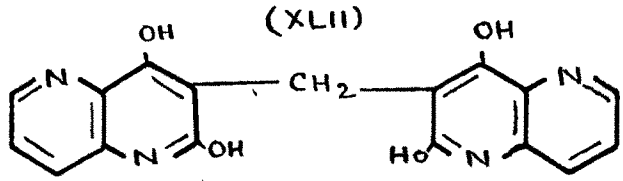


(XLI)

Further, these authors condensed 2,4-dihydroxy-quinoline and glyoxilic acid and obtained 3,3'-bis-(4-hydroxy-3-carbostyril) acetic acid (XLII) ; whereas 2-4-dihydroxy-naphthyridine with glyoxalic acid yielded 3,3'-methylenebis-(2,4-dihydroxynaphthyridine) (XLIII)

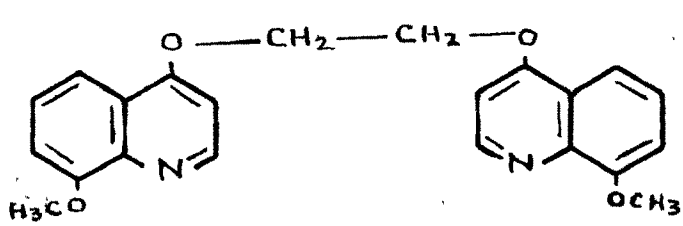


(XLII)



(XLIII)

Rastogi, Khanna and Dhar (67) prepared 1,2-bis(8-methoxy-4-quinolyl oxy) ethane (XLIV) from 4-chloro-8-methoxyquinoline and the di-sodium salt of ethylene glycol.

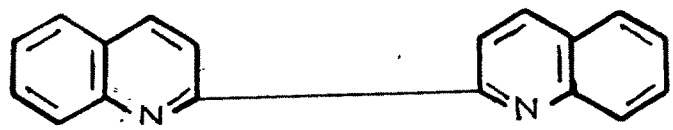


(XLIV)

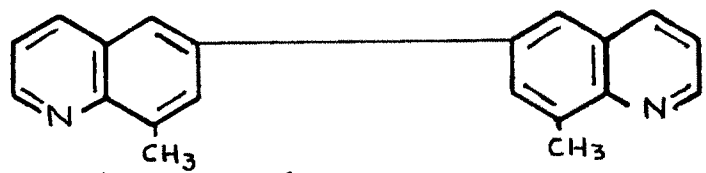
Max Boetius et al. (68) treated 1-substituted carbostyrils with carbonyl compounds at raised temperatures or with unsaturated ketones to give 3,3'-methylene bis-(4-hydroxy carbostyril). Rice et al. (69) from 4-carbethoxy-6-hydroxyquinoline with formaldehyde and appropriate secondary amines synthesised compounds of low toxicity, characterised by physiological activity, as antihistamine, bronchial dilators, medicaments of respiratory disorders and arthritis.

Over and above the diquinolylmethane derivatives a number of biquinolines are also available. Biquinolines are generally obtained either by application of standard quinoline synthesis to bifunctional molecules, by pyrolysis of various quinoline derivatives, or by application of the Ullmann's synthesis. Thus, Nieuwenhuis, Wibaut and Willink (70) obtained 2,2'-biquinoline (XLV), when quinoline was heated in a sealed tube at 325°C with nickel or alumina.

Weidel (71) prepared 2,6'-biquinoline from aniline and quinoline hydrochloride which were heated at 180°C with platinised asbestos in the presence of oxygen. Reich and Serpek (72) reported the formation of 3,3'-biquinoline when quinoline was heated with calcium hydride at 220°C. Ueda (73) obtained 2,2'-and 5,5'-biquinolines by the application of Ullmanns' reaction on catalytic reduction of 2-bromo and 5-bromoquinoline respectively. Ruttan (74) obtained 8,8'-dimethyl-6,6'-biquinoline (XLVI) by Skraup reaction applied to o-toluidine.



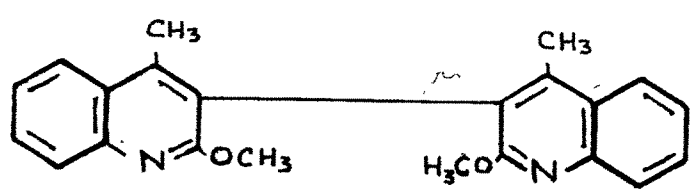
(XLV)



(XLVI)

Ward and Waring (75) obtained 5,5',7,7'-tetramethyl-8,8'-biquinoline by coupling two molecules of 5-nitro-4- iodo-1,3-dimethyl benzene with copper powder and the resulting dinitrotetramethyldiphenyl was reduced and converted by Skraup synthesis.

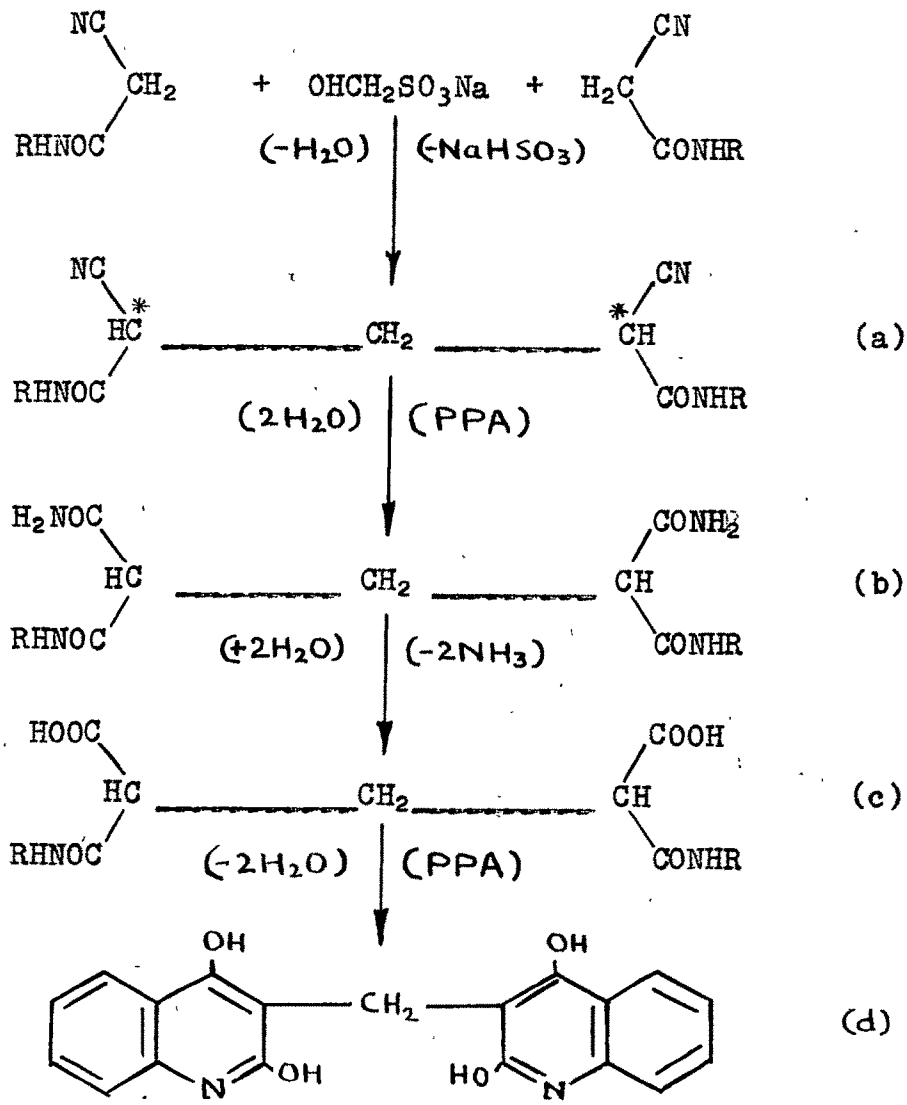
3,3'-(2-methoxy-4-methyl)quinolines of the type (XLVII) have been prepared by Mehta and Mehta (76) by the application of Ullmann's reaction on 3-bromo-2-methoxy-4-methylquinolines with copper bronze in boiling diphenyl ether.



(XLVII)

In the present investigation, methylene bis-(cyanacet arylamides) (a) have been cyclised using polyphosphoric acid as a cyclising agent, to give the

corresponding 3,3'-methylene bis-(2,4-dihydroxyquinolines) (d). The methylene bis-(cyanacet arylamides) have been prepared on condensation of cyanacet arylamide with sodium hydroxy methane sulphonate as described in part II. Here, polyphosphoric acid acts both as hydrolytic and condensing agent. These reactions are given below :



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

Here, the hydrogen atoms of the reactive methylene group marked in asterisks (*), situated between two negative groups (-CO.CH_2.CN) in the methylene bis-(cyanacet arylamides) are enolizable. Under the influence of polyphosphoric acid acting as hydrolytic agent, the methylene bis-(-cyanacet arylamides) (a) are partially hydrolysed by addition of two molecules of water, giving the corresponding methylene bis-(-malon mono arylamides) (b), which are not isolated but remain as intermediates. These intermediary amides (b) undergo further hydrolysis with the elimination of two molecules of ammonia to yield the corresponding methylene bis-(-malon arylacids) (c), which, simultaneously, under the influence of polyphosphoric acid,acting as a condensing agent with elimination of two molecules of water, undergo cyclisation, giving the corresponding 3,3'-methylene bis-(-2,4-dihydroxyquinoline) derivatives (d).

(a) Methylene bis-(cyanacet arylamides)

Two moles of cyanacet arylamide and one mole of sodium hydroxy methane sulphonate were refluxed in 90 % methanol for three hours. The crude product, obtained on dilution with water, was filtered and crystallised from acetic acid (Part II.)

(d) 3,3'-Methylene bis-(2,4-dihydroxyquinolines)

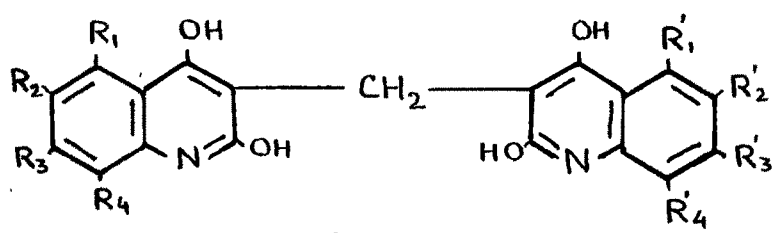
Methylene bis-(cyanacet arylamide) (0.01 M) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was heated in an oil-bath at 140°C for 3 hours, with a calcium chloride gaurd-tube. After cooling,

hydrochloric acid (60 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 and crystallised from glacial acetic acid.

The following methylene bis-(cyanacet arylamides) have accordingly been prepared. :

Methylene bis-(cyanacetanilide) ; Methylene bis-(cyanacet-o-chloroanilide) ; Methylene bis-(cyanacet-p-chloroanilide) ; Methylene bis-(cyanacet-m-toluidide) ; Methylene bis-(cyanacet-p-toluidide) ; Methylene bis-(cyanacet-1:2:4-xylidide) ; Methylene bis-(cyanacet-1:3:4-xylidide) ; Methylene bis-(cyanacet-α-naphthylamide) and Methylene bis-(cyanacet-β-naphthylamide).

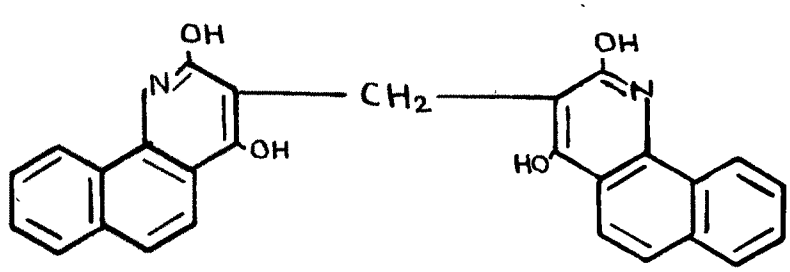
The following 2,2',4,4'-tetrahydroxy-3,3'-diquinolyl methane derivatives have,further, been synthesised on cyclisation of the above mentioned methylene bis-(cyanacet arylamides). Thus,



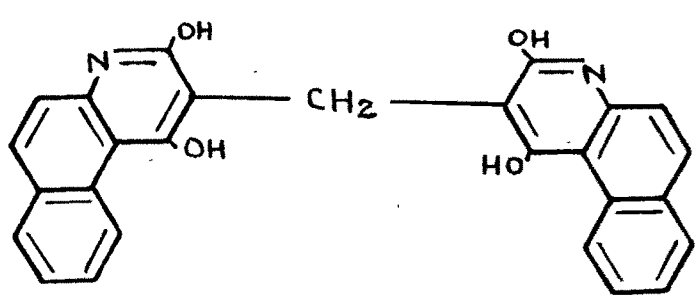
(A)

1. 2,2',4,4'-Tetrahydroxy-3,3'-diquinolylmethane.
   (A, $R_1=R'_1=R_2=R'_2=R_3=R'_3=R_4=R'_4=H$)
2. 2,2',4,4'-Tetrahydroxy-8,8'-dichloro-3,3'-diquinolylmethane.
   (A, $R_1=R'_1=R_2=R'_2=R_3=R'_3=H$; $R_4=R'_4=Cl$)

3. 2,2',4,4'-Tetrahydroxy-6,6'-dichloro-3,3'-diquinolylmethane.
   (A, $R_1=R'_1=R_3=R'_3=R_4=R'_4=H$; $R_2=R'_2=Cl$)
4. 2,2',4,4'-Tetrahydroxy-7,7'-dimethyl-3,3'-diquinolylmethane.
   (A, $R_1=R'_1=R_2=R'_2=R_4=R'_4=H$; $R_3=R'_3=CH_3$)
5. 2,2',4,4'-Tetrahydroxy-6,6'-dimethyl-3,3'-diquinolylmethane.
   (A, $R_1=R'_1=R_3=R'_3=R_4=R'_4=H$; $R_2=R'_2=CH_3$)
6. 2,2',4,4'-Tetrahydroxy-6,6',8,8'-tetramethyl-3,3'-diquinolylmethane.
   (A, $R_1=R'_1=R_3=R'_3=H$; $R_2=R'_2=R_4=R'_4=CH_3$)
7. 2,2',4,4'-Tetrahydroxy-6,6',7,7'-tetramethyl-3,3'-diquinolylmethane.
   (A, $R_1=R'_1=R_4=R'_4=H$; $R_2=R'_2=R_3=R'_3=CH_3$)
8. 2,2',4,4'-Tetrahydroxy-3,3'-dibenzoquinolyl-(7:8)-methane.



9. 2,2',4,4'-Tetrahydroxy-3,3'-dibenzoquinolyl-(5:6)-methane.



EXPERIMENTAL

2,2',4,4'-Tetrahydroxy-3,3'-diquinolyl methane

Methylene bis-(cyanacetanilide) (3.32 g. ; 0.1 mole) was dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml., d. 1.75), and the reaction mixture was heated in an oil-bath at 140°C for three hours with a clacium chloride guard-tube. After cooling, hydrochloric acid (60.0 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 and crystallised from glacial acetic acid. M.P. > 400°C. Yield 1.4 g.

Analysis :

4.324 mg. of the substance gave 10.780 mg. of carbon dioxide and 1.668 mg. of water.

7.256 mg. of the same substance gave 0.574 c.c. of nitrogen at 35°C and 745 mm. pressure.

Found : C = 68.03 % ; H = 4.316 % ; N = 8.595 %.

$C_{19}H_{14}O_4N_2$ requires : C = 68.25 % ; H = 4.22 % ; N = 8.38 %.

2,2',4,4'-Tetrahydroxy-8,8'-dichloro-3,3'-diquinolylmethane

Methylene bis-(cyanacet-o-chloroanilide) (4.01 g.) dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was refluxed and treated as above. The product, on precipitation, was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 1.95 g.

Analysis :

7.036 mg. of the substance gave 0.450 c.c. of nitrogen at 36°C and 745 mm. pressure.

Found : N = 6.926 %.

$C_{19}H_{12}O_4N_2Cl2$ requires: N = 6.948 %.

2,2',4,4'-Tetrahydroxy-6,6'-dichloro-3,3'-diquinolylmethanes

Methylene bis-(cyanacet-p-chloroanilide) (4.01 g.) dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was refluxed and treated as above. The product on precipitation was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 2.1 g.

Analysis :

4.792 mg. of the substance gave 10.380 mg. of carbon dioxide and 1.138 mg. of water.

5.220 mg. of the same substance gave 0.306 c.c. of nitrogen at 32°C and 746 mm. pressure.

Found : C=59.11 % ; H=2.66 % ; N=6.44 %.

$C_{19}H_{12}O_4N_2Cl_2$ requires: C=59.55 % ; H=2.97 % ; N=6.94 %.

2,2',4,4'-Tetrahydroxy-7,7'-dimethyl-3,3'-diquinolylmethane

Methylene bis-(cyanacet-m-toluidide) (3.6 g.) dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was refluxed and treated as above. The crude product,

on precipitation, was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 1.3 g.

Analysis :

4.814 mg. of the substance gave 12.216 mg. of carbon dioxide and 2.332 mg. of water.

8.036 mg. of the same substance gave 0.573 c.c. of nitrogen at 33°C and 746 mm. pressure.

Found : C = 69.25 % ; H = 5.42 % ; N = 7.80 %.

$C_{21}H_{18}O_4N_2$ requires : C = 69.60 % ; H = 5.00 % ; N = 7.73 %.

2,2',4,4'-Tetrahydroxy-6,6'-dimethyl-3,3'-diquinolylmethane

Methylene bis-(cyanacet-p-toluidide) (3.6 g.) dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was refluxed and treated as above. The crude product, on precipitation, was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 1.5 g.

Analysis :

8.672 mg. of the substance gave 0.643 c.c. of nitrogen at 34°C and 746 mm. pressure.

Found : N = 8.09 %.

$C_{21}H_{18}O_4N_2$ requires : N = 7.73 %.

2,2',4,4'-Tetrahydroxy-6,6',8,8'-tetramethyl-3,3'-diquinolylmethane

Methylene bis(cyanacet-1:2:4-xylidide) (3.88 g.) dissolved in a clear solution of polyphosphoric acid prepared

by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was reffluxed and treated as above. The product, on precipitation was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 1.9 g.

Analysis :

7.328 mg. of the substance gave 0.509 c.c. of nitrogen at 35°C and 744 mm. pressure.

Found : N = 7.54 %.

$C_{23}H_{22}O_4N_2$ requires : N = 7.18 %.

2,2',4,4'-Tetrahydroxy-6,6',7,7'-tetramethyl-3,3'-diquinolylmethane

Methylene bis-(cyanacet-1:3:4-xylidide) (3.88 g.) dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was refluxed and treated as above. The product,on precipitation, was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 2.3 g.

Analysis :

4.722 mg. of the substance gave 12.160 mg. of carbon dioxide and 2.373 mg. of water.

7.146 mg. of the same substance gave 0.484 c.c. of nitrogen at 36°C and 745 mm. pressure.

Found : C = 70.28 % ; H = 5.62 % ; N = 7.33 %.

$C_{23}H_{22}O_4N_2$ requires : C = 70.75 % ; H = 5.68 % ; N = 7.18 %.

2,2',4,4'-Tetrahydroxy-3,3'-dibenzoquinolyl-(7:8) methane

Methylene bis-(cyanacet-α-naphthylamide) (4.32 g.) dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (12.0 ml. ; d. 1.75) and the reaction mixture was refluxed and treated as above. The product, on precipitation, was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 2.1 g.

Analysis :

7.664 mg. of the substance gave 0.445 c.c. of nitrogen at 35°C and 745 mm. pressure.

Found : N = 6.30 %.

$C_{27}H_{18}O_4N_2$ requires : N = 6.45 %.

2,2',4,4'-Tetrahydroxy-3,3'-dibenzoquinolyl-(5:6) methane

Methylene bis-(cyanacet-β-naphthylamide) (4.32 g.) dissolved in a clear solution of polyphosphoric acid prepared by dissolving phosphorus pentoxide (20.0 g.) in phosphoric acid (20.0 ml. ; d. 1.75) and the reaction mixture was refluxed and treated as above. The product, on precipitation, was filtered and crystallised from glacial acetic acid. M.P. > 400°C. Yield 2.0 g.

Analysis :

7.624 mg. of the substance gave 0.430 c.c. of nitrogen at 36°C and 745 mm. pressure.

Found : N = 6.11 %.

$C_{27}H_{18}O_4N_2$ requires : N = 6.45 %.

Table 3

Methylene bis-(hydroxyquinolines)

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Nitrogen Found %	Nitrogen reqd. %	Carbon Found %	Carbon reqd. %	Hydrogen Found %	Hydrogen reqd. %
1.	2,2',4,4'-Tetrahydroxy-3,3'-diquinolylmethane	$C_{19}H_{14}O_4N_2$	>400	41.6	8.59	8.38	68.03	68.25	4.32	4.22
2.	2,2',4,4'-Tetrahydroxy-8,8'-dichloro-3,3'-diquinolylmethane	$C_{19}H_{12}O_4N_2Cl_2$	>400	48.7	6.93	6.95	-	-	-	-
3.	2,2',4,4'-Tetrahydroxy-6,6'-dichloro-3,3'-diquinolylmethane	$C_{19}H_{12}O_4N_2Cl_2$	>400	52.5	6.44	6.95	59.11	59.55	2.66	2.97
4.	2,2',4,4'-Tetrahydroxy-7,7'-dimethyl-3,3'-diquinolylmethane	$C_{21}H_{18}O_4N_2$	>400	36.1	7.81	7.73	69.25	69.60	5.42	5.00
5.	2,2',4,4'-Tetrahydroxy-6,6'-dimethyl-3,3'-diquinolylmethane	$C_{21}H_{18}O_4N_2$	>400	41.7	8.10	7.73	-	-	-	-

Table 3 (Contd.)

S.No.	Compound	Molecular formula	M.P. °C	Yield %	Nitrogen Found %	Nitrogen reqd. %	Carbon Found %	Carbon reqd. %	Hydrogen Found %	Hydrogen reqd. %
6.	2,2',4,4'-Tetrahydroxy-6,6',8,8'-tetramethyl-3,3'-diquinolylmethane	$C_{23}H_{22}O_4N_2$	>400	48.0	7.54	7.18	-	-	-	-
7.	2,2',4,4'-Tetrahydroxy-6,6',7,7'-tetramethyl-3,3'-diquinolylmethane	$C_{23}H_{22}O_4N_2$	>400	50.9	7.33	7.18	70.28	70.75	5.62	5.68
8.	2,2',4,4'-Tetrahydroxy-3,3'-dibenzo-quinolyl-(7:8)methane	$C_{27}H_{18}O_7N_2$	>400	48.6	6.31	6.45	-	-	-	-
9.	2,2',4,4'-Tetrahydroxy-3,3'-dibenzo-quinolyl-(5:6)methane	$C_{27}H_{18}O_4N_2$	>400	46.3	6.11	6.45	-	-	-	-

REFERENCES

1. Snyder and Werber, J.Amer.Chem.Soc., 72, 2962 (1950).
2. Bopp and McEwen, Chem.Rev., 58, 321 (1958).
3. Bell R.N., Ind.Eng.Chem., 40, 1464 (1948).
4. Thilo and Sauer, J.Prakt.Chem., [4], 4, 324 (1957).
5. Kennard K.C., Org.Chem. Bull., Eastman Kodak Co., No.1, 29 (1957).
6. Fritz Uhlig, Angew.Chem., 66, 435 (1954). Chem.Abst., 49, 10159 (1955).
7. Hauser and Murray, J.Amer.Chem.Soc., 77, 2851 (1955).
8. Stephenson, J.Chem. Soc., 2557 (1956).
9. Sukh Dev, J.Ind.Chem.Soc., 32, 255 (1955).
10. Krishna Rao and Sukh Dev, J.Ind.Chem.Soc., 34, 255 (1957).
11. Berger and Oliver, Rec.trav.Chim., 46, 600 (1927).
12. Horning et al., J.Amer.Chem.Soc., 74, 5153 (1952).
13. Snyder and Elston, J.Amer.Chem.Soc., 76, 3039 (1954).
14. Hauser and Eby, J.Amer.Chem.Soc., 79, 725 (1957).
15. Hauser and Hoffenberg, J.Org.Chem., 20, 1448 ; 1482 (1955).
16. Abrams and Kipping, J.Chem.Soc., 1988 (1934).
17. Robert Conley, J.Org.Chem., 23, 1330 (1958).
18. Witkop et al., J.Amer.Chem.Soc., 74, 3948 (1952).
19. Siner H. and Shive W., J.Org.Chem., 22, 84 (1957).
20. Herz and Tsai., J.Amer.Chem.Soc., 75, 5122 (1953).
21. Leavitt et al., J.Amer.Chem.Soc., 79, 427 (1957).
22. (Miss) E.F.M.Stephenson, J.Chem.Soc., 1928 (1957).
23. Hill R.K., J.Org.Chem., 22, 830 (1957).
24. Koo J., Chem.and Ind., 445 (1955).
25. Nakazawa and Matsuura., J.Pharm.Soc., Japan, 75, 469 (1955).

26. Elston, Doctoral Dissertation, University of Illinois (1954).

27. Cope and Smith, J.Amer.Chem.Soc., 77, 4596 (1955).

28. Phillips, J.Amer.Chem.Soc., 77, 3658 (1955).

29. Hauser and Murray, J.Amer.Chem.Soc., 77, 3858 (1955).

30. Poller et al., J.Chem.Soc., 1195 (1956).

31. Pratt,Rice and Luckenbaugh, J.Amer.Chem.Soc., 79, 1212 (1957).

32. Proctor and Thomson, J.Chem.Soc., 2302 (1957).

33. Ghosh et al., J.Ind.Chem.Soc., 35, 758 (1958).

34. Popp and McEwen, J.Amer.Chem.Soc., 79, 3773 (1957).

35. Klager et al., J.Amer.Chem.Soc., 77, 5433 (1955).

36. Cherbuliez and Weniger, Helv.Chim.Acta., 29, 2006 (1946).

37. Schaad, U.S.Patent 2557924 (1951).

38. Breuer and Hofferth, U.S.Patent 2740767 (1956).

39. Conrad and Limpach, Ber., 20, 944 (1887) ; ibid., 21, 521 (1888).

40. Limpach, Ber., 64, 969 (1931).

41. Price and Roberts, J.Amer.Chem.Soc., 68, 1204 (1946).

42. Ewins and King, J.Chem.Soc., 103, 104 (1913).

43. Knorr, Ber., 17, 540 (1884).

44. Bangadiwala and Desai., J.Ind.Chem.Soc., 30, 655 (1953).

45. Mehta and Patel, J.Sci.and Ind.Res., 18B, 391 (1959); ibid., 19B, 436 (1960).

46. Kaslow and Reck., J.Amer.Chem.Soc., 69, 864 (1947).

47. Schuller, J.Pract.Chem., [2], 88, 180 (1913).

48. Borsche and Kienitz, Ber., 43, 2334 (1910).

49. Borsche and Meyer, Ber., 54, 2841 (1921).

50. Monti and Verona, Gazz.Chim.ital., 62, 878 (1932).

51. Mills and Hamer., J.Chem.Soc., 117, 1550 (1920).

52. Price,Leonard and Stacy, J.Amer.Chem.Soc., 69, 855 (1947).

53. Edgerton et al., J.Amer.Chem.Soc., 76, 4902 (1954).

54. Price, Leonard and Reitsema, J.Amer.Chem.Soc., 68, 1256(1946).

55. Jean D'ecombe, Compt.rend., 237, 336-7 (1953) ;
Chem.Abst., 48, 10042 (1954).

56. Lydia Monti et al., Gazz.Chim.ital., 66, 42-8 (1936).

57. Ewing and Stesk, J.Amer.Chem.Soc., 68, 2181 (1946).

58. Price and Jackson., J.Amer.Chem.Soc., 68, 1282 (1946).

59. Manasse., Ber., 27, 2409 (1894).

60. Cohn, J.Pract.Chem., [2] ,83, 498 (1911).

61. Kaslow and Raymond, J.Amer.Chem.Soc., 70, 3912 (1948).

62. Piscope et al., Gazz.Chim.ital., 88, 101 (1958) ;
Chem.Abst., 53, 2216 (1959).

63. Mentzer et al., Bull.Soc.Chim., 12, 430 (1945) ;
Chem.Abst., 41, 424 (1947).

64. Fucik et al., Bull.Soc.Chim., France., 99-103 (1949).

65. Hais., Chem.Listy., 45, 76-81 (1951).

66. Fucik et al., United Pharm.Works,Prague. Czech.Chem.Listy.,
45, 23 (1951) ; Chem.Abst., 45, 10245 (1951).

67. Rastogi, Khanna and Dhar., J.Sci.industr.Res., 15C, 177 (1956).

68. Max Boetius et al., German, 13870 (1957) ;
Chem.Abst., 53, 11415 (1959).

69. Rice et al., U.S. 2,803,627 (1957) ; Chem.Abst.,52, 2091(1958).

70. Nieuwenhuis et al., Rec.trav.Chim., 54, 804 (1935).

71. Weidel, Monatsh., 8, 120 (1887).

72. Reich and Serpek., Helv.Chim.Acta., 3, 138 (1920).

73. Ueda, J.Pharm.Soc., Japan, 57, 180 (1937).

74. Ruttan, Trans.Roy.Soc. Canada, III, 35 (1892) ;
Chem. Zentr., 64, II, 52 (1893).

75. Ward and Waring, J.Amer.Chem.Soc., 54, 1697 (1932).

76. Mehta and Mehta, Indian J.Chem., I, No.4, 188 (1963).