INTRODUCTION

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Quonilines or benzo(b)pyridines occur in coal tar. A large number of alkylquinolines has been isolated from California petroleum. The quinoline ring system is the basic nucleus of a large group of alkaloids, chief of which are the cinchona alkaloids. Many quinoline derivatives have been found to possess therapeutic value. Quinine has been the standard drug for the suppression and treatment of malaria for centuries. It has now been superseded by the synthetic drugs such as chloroquine and camoquin. Vioform, chiniofon are valuable amebicidal agents.

The literature on quinoline is enormous. It is not possible to enumerate all the reactions carried out on quinolines in the space of a few pages nor is such a listing of reactions necessary as some of them are quite well known and form the subject matter of text books. Brief reviews of the work done on quinoline derivatives pertaining to the present work are given under the relevant chapters.

On reviewing the literature it seems that the synthesis of furoquinolines and pyranoquinolines is meagre. With a view to synthesise furoquinolines and pyranoquinolines the present work was undertaken. There was also controversy regarding the position of bromine atom in the bromination of acetoacetarylamides and hence in bromoquinolines. In the present work the pattern of substitution of bromine atom is established and has been confirmed by NMR spectrum. It was also thought of interest to utilise these bromoquinoline derivatives to synthesise a variety of new quinoline derivatives.

Chapter I consists of two sections. Section I deals with the synthesis of furo(3,2-c)quinoline and furo (2,3-b)quinoline derivatives. The structures of furo(3,2-c) quinoline derivatives obtained have been established by their synthesis of known pattern from 2-methyl-3-formyl-4-quinolinol and ethylbromomalonate and also by its IR spectra. Section II deals with the synthesis of quinolino-lactones and pyrano(3,2-c)quinoline derivatives by application of Perkin reaction.

Chapter II is divided into two sections. Section I describes the bromination of acetoacetarylamides and their cyclisation to 4-bromomethylcarbostyril derivatives. 4-Methylcarbostyril derivatives are also brominated with bromine in acetic acid and with N-bromosuccinimide. In section II, the bromomethylcarbostyril derivatives described in section I,have been converted into corresponding cinchoninic acid derivatives.

Chapter III deals with the studies on bromomethyl carbostyril derivatives described in section I, chapter II. In section I, the bromomethyl derivatives are reacted with primary and secondary bases to obtain Mannich bases. Section II deals with the synthesis of 1-cyano-1,2-bis(2-chloro-4-quinolyl)ethane derivatives from the bromomethyl derivatives by the action of potassium cyanide followed by treatment with phosphorus oxychloride. The hydrolysis of the cyano derivatives with sulphuric acid was studied in which 1,2-bis(2-chloro-4-quinolyl)ethane derivatives were obtained.

In section III, the condensation of 2-chloro-4-chloromethyl-quinoline with sodio malonic ester is described. The NMR spectrum of 2,2-dicarboethoxy-1,3-bis(2-chloro-4-quinolyl) propane and alkaline hydrolysis were studied.

CHAPTER I

Studies in the synthesis of furoquinolines, quinolino-lactones and pyranoquinolines

CHAPTER - I

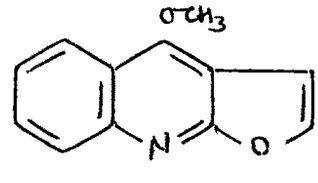
Studies in the synthesis of furoquinolines, quinolino-lactones and pyranoquinolines

Section I

Synthesis of furoquinolines

Theoretical

In recent years furoquinolines have received considerable importance. They not only occur in nature but also possess therapeutic properties. Furoquinoline alkaloids are isolated from plants of the Rutaceae (especially Australian species). Dictamnine (1) is a simple and typical furoquinoline alkaloid[1]. Pyranoquinoline derivatives such as flindersine[2] (2) are also isolated from the same species. The majority of compounds in this group are alkoxylated dictamnines - maculine[3] (3) a methylenedioxy derivative and acronycidine[4] (4) a trimethoxy derivative. Several new furoquinoline alkaloids have recently been discovered such as kokusaginine (5), evolitrine (6), γ-fagarine (7) and skimmianine (8).



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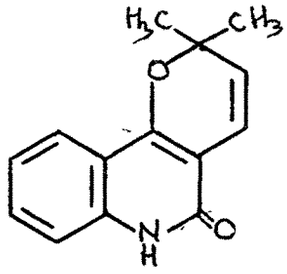

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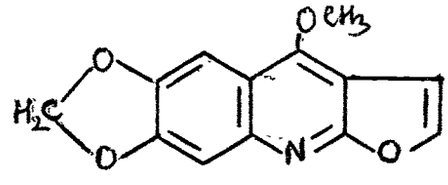

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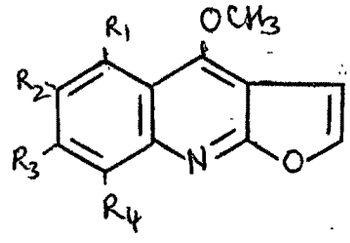
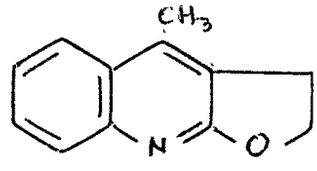


No.	R_1	R_2	R_3	R_4
4	OCH_3	H	OCH_3	OCH_3
5	H	OCH_3	OCH_3	H
6	H	H	OCH_3	H
7	H	H	H	OCH_3
8	H	H	OCH_3	OCH_3

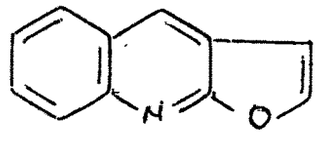
Chemically the members of this group of alkaloids are methoxylated derivatives of furo(2,3-b)quinoline (9). All these compounds are very weak bases, hardly soluble in water and forming unstable salts.

Dictamnine has the ability to increase the tonus of heart muscle and to contract blood vessels. 4-Methyl-2,3-dihydrofuro(2,3-b)quinoline (10) has contracting action on guinea pig uterus[5] about twice that of sparteine sulphate and its derivatives[6].



(10)

The following types of furoquinolines are found in the literature of which furo(3,2-c)quinoline and furo (2,3-b)quinoline derivatives have been synthesised by various methods especially the latter in order to synthesise naturally occurring furoquinoline alkaloids.



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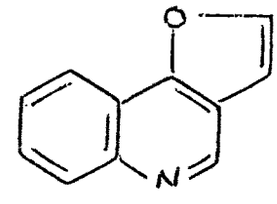

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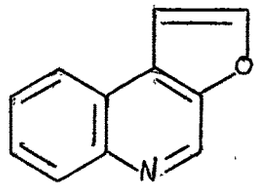

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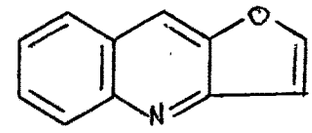

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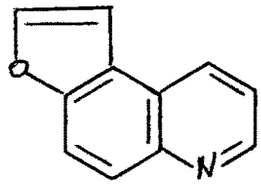

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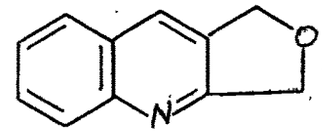

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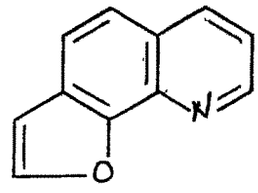
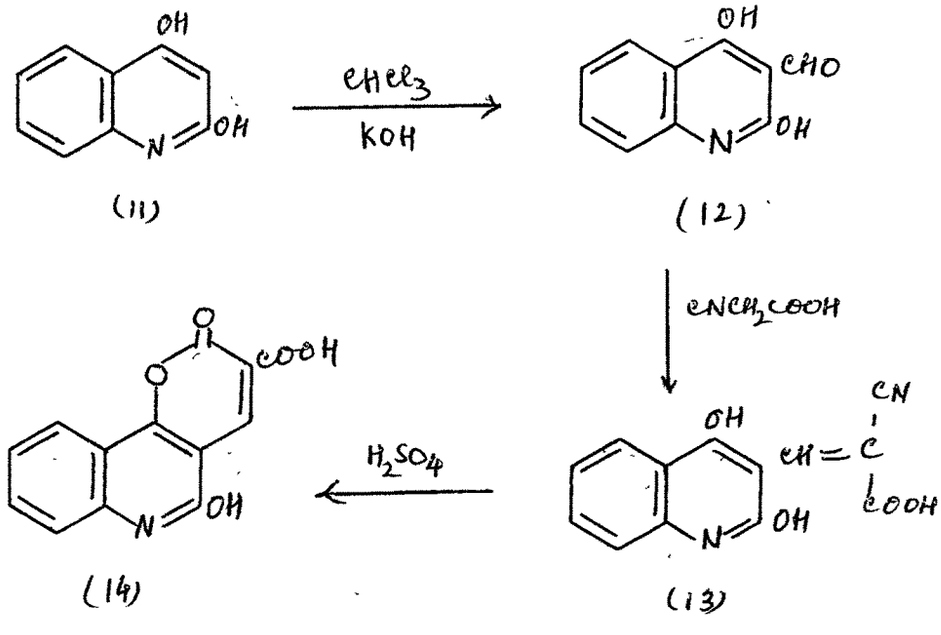


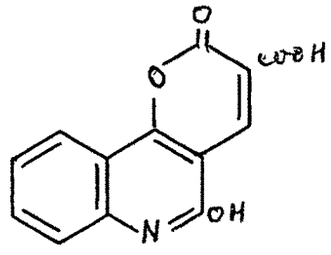
Type VII

Dictamnine was first isolated from white dittany root by Thoms in 1923. Later in 1930 it was isolated from the leaves of Skimmia repens Nakai by Asahina, Ohta and Inubuse[7] who proved its identity with the dictamnus root alkaloid and elucidated its structure as 4-methoxy-furo (2,3-b)quinoline (1). None of the alkaloid of this group was synthesised upto 1952. An attempt by Asahina and Inubuse[8] in 1932 to synthesise dictamnine as described

below led to an isomer of the alkaloid which was named pseudo-dictamnine (18).

2,4-Dihydroxyquinoline (11) was subjected to Reimer-Tiemann reaction in the presence of alkali and chloroform to give 3-formyl derivative (12) which was further condensed with cyanoacetic acid in the presence of alkali to nordictamnal-cyanoacetic acid (13). The product on treatment with conc.sulphuric acid afforded 5-hydroxy-2-oxo-2H-3-carboxypyrano(3,2-c)quinoline (14). This acid was decarboxylated by heating over free flame to 5-hydroxy-2-oxo-2H-pyrano(3,2-c)quinoline (15). This on bromination gave the 3-bromo derivative (16) which on hydrolysis with alcoholic potassium hydroxide gave 4-hydroxyfuro(3,2-c) quinoline-2-carboxylic acid (17). This on successive methylation and dry distillation yielded pseudo-dictamnine (18). Since this was not identical with isodictamnine(19) must be a derivative of furo(3,2-c)quinoline.





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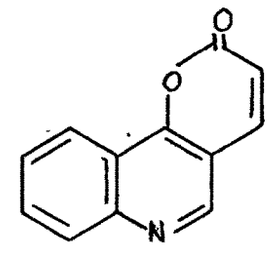

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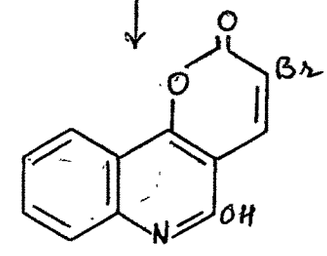

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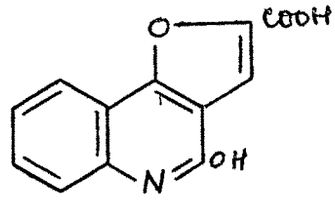

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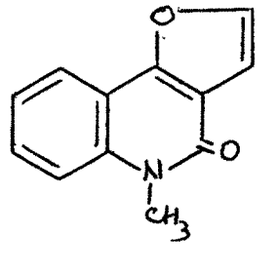

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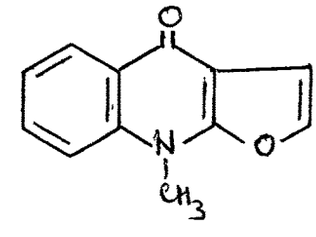
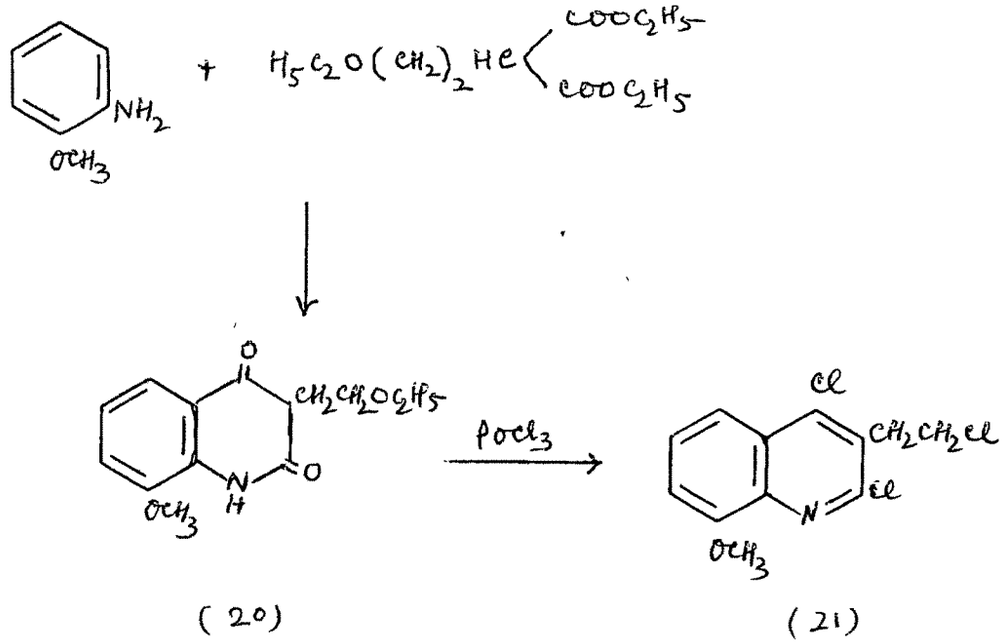


(19)

Grundon and McCorkindale[9] synthesised both dictamnine and γ-fagarine. To prepare the latter o-anisidine was condensed with ethyl-2-ethoxyethyl-malonate giving the dihydroxyquinolone (20) in one step which on treatment with phosphorus oxychloride gave the trihalide (21). Since 2-chloroquinolines are much more labile than 4-chloroquinolines towards acid hydrolysis, such treatment afforded the 2-quinolone (22) which was converted into an analogue (23) of a dihydrobenzofuran and dehydrogenated with N-bromosuccinimide. The resulting chloroquinoline was converted into γ-fagarine (7) by means of sodium methoxide. Dictamnine (1) was prepared similarly from aniline.



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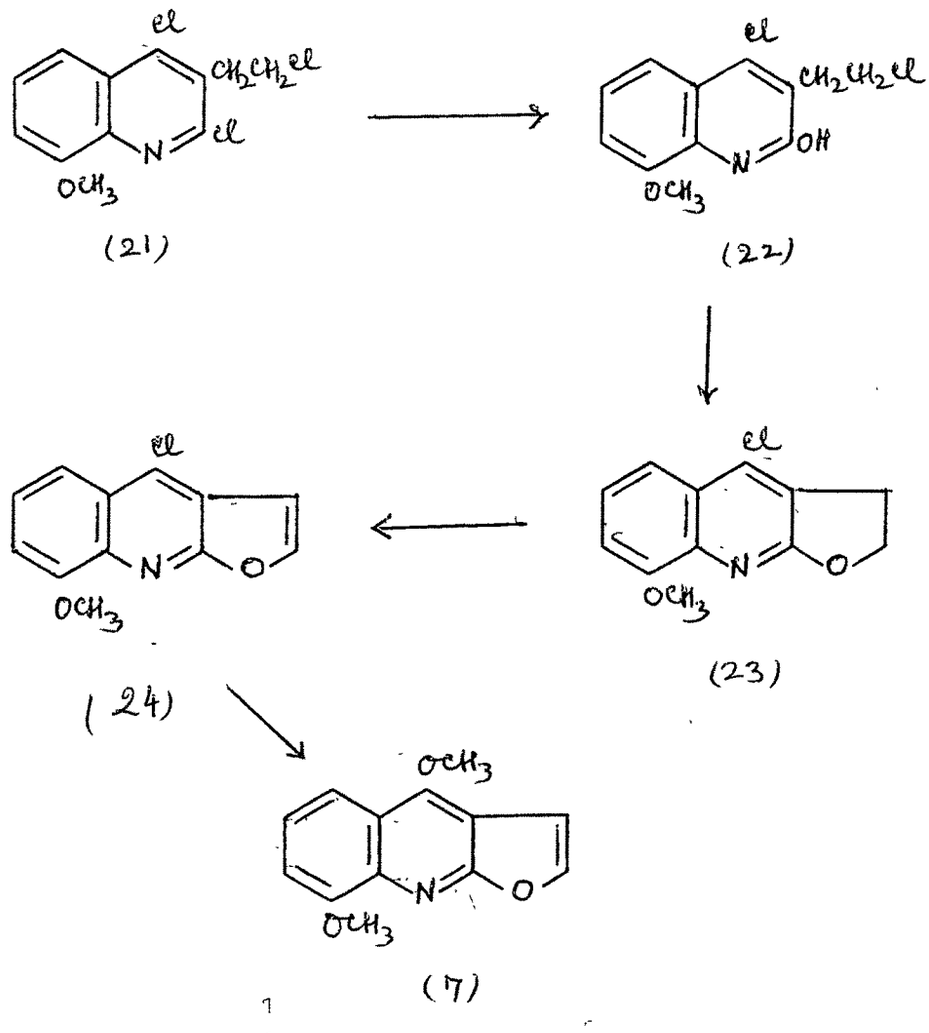
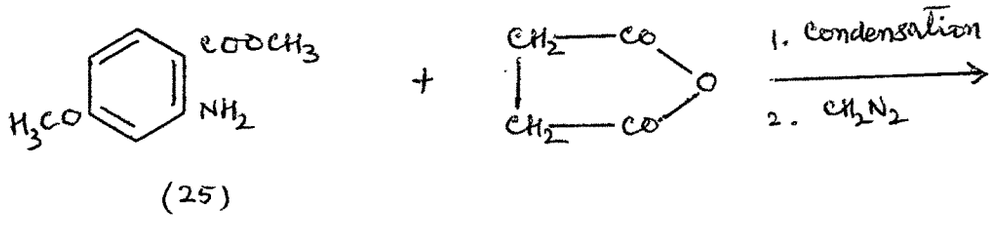


Cooke and Hynes[10] have described another synthesis of dictamnine and of evolitrine. Price[11] also reported the outline of synthesis of dictamnine upto the penultimate stage along with the evidence for the linear structure of the alkaloid. The appropriate anthranilic ester (25) was converted to the succinanilic ester (26) by reaction with succinic anhydride and subsequent esterification with diazomethane. Cyclisation with sodium (Camps synthesis) then gave the hydroxyquinolone ester(27)

and another product believed to be (28). The compound(27) was methylated by diazomethane to give the 4-methoxy-2-quinolone derivative (29) which was then reduced with lithium aluminium hydride to the primary alcohol (30). Cyclisation to the dihydrofuroquinoline (31) by heating with polyphosphoric acid was less efficient than conversion into the halide and treatment with silver oxide. Dehydrogenation of (31) by the bromination-dehydrobromination technique (N-bromosuccinimide and collidine), gave evolitrine (6).



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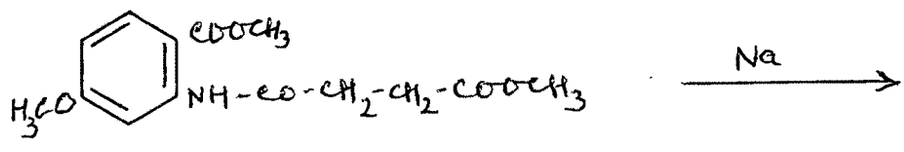

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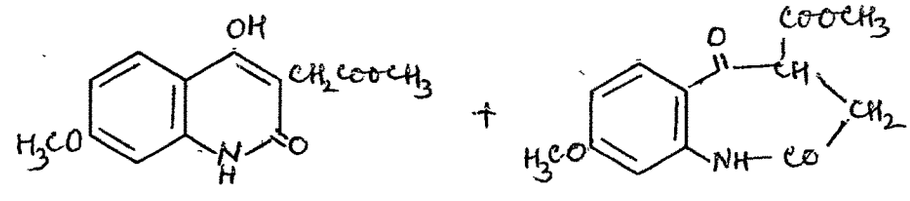

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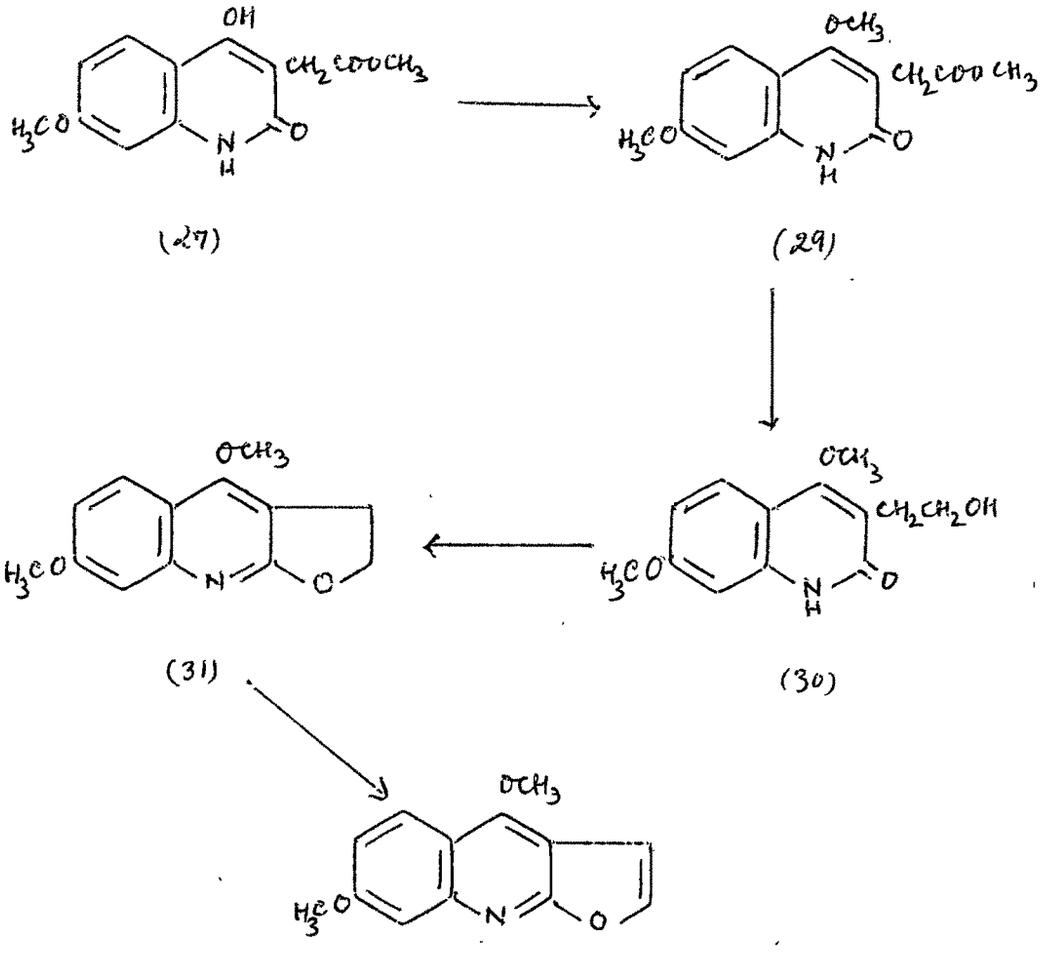
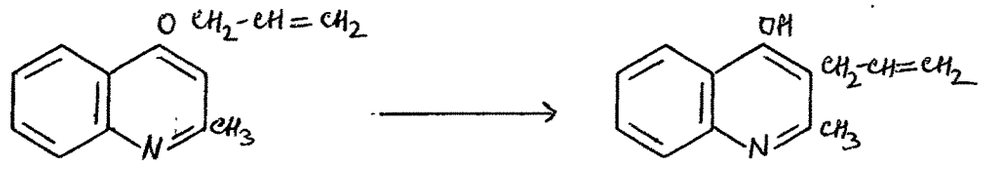


(27) (29) (31) (30) (6)

Various methods were developed to synthesise furo (2,3-b)quinoline and furo(3,2-c)quinoline derivatives. The important methods involve the preparation of o-hydroxyallyl-quinolines. In contrast to the behaviour of the 4-methoxy-quinolines when heated, the 4-allyloxy compounds undergo the normal Claisen rearrangement to the o-hydroxyallyl-quinolines in theoretical yields.[12]

Rearrangement[13] of allyloxyquinolines were carried out as early as in 1924. 2-Allyloxyquinoline was

prepared by reacting 2-chloroquinoline with sodium allyloxide in allylalcohol. The ether was rearranged by heating it to 325-330°. 1-Allyl-2-quinolone was isolated as the product. Some 8 years later Mander-Jones and Trikojus[14] investigated the behaviour of 4-allyloxy - quinoline derivatives. It is well known that α and γ-N-heterocyclic enols show a marked tautomeric mobility of the enolic hydrogen between oxygen and nitrogen with preferential attachment to the nitrogen. The alkoxy ethers on heating usually undergo a rearrangement of the alkyl group, which wanders invariably to the nitrogen atom in preference to a nuclear carbon atom. One might expect that the allyl group would undergo an analogous migration[13]. There are reports in which N-isomeride is obtained instead of C-isomeride in case of o-allyl carbostyril. 4-Allyloxyquinaldine (36) pyrolyses almost quantitatively on heating for a short time at 200° to 3-allyl-4-hydroxyquinaldine (37).

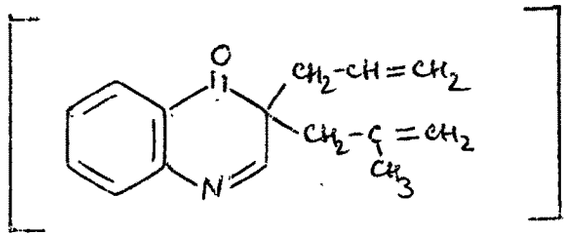


(36) (37)

The constitution of 3-allyl-4-hydroxyquinaldine (37) has been proved by its synthesis from α-allyl-β-phenylamino-crotonic ester. This is interesting since, in the case of 4-methoxyquinaldine[76] migration of the methyl group takes place to the nitrogen atom.

The allyl ethers[16] were also obtained by reacting hydroxyquinoline with allylbromide in acetone in the presence of potassium carbonate. None of the product from such a reaction was examined to varify if they were N-allyl or O-allyl derivative. These were then subjected to rearrangement in alpha methylnaphthalene and the products of rearrangement were assumed to be the corresponding C-allylhydroxyquinolines. Thus 2-methyl-3-allyl-4-quinolone ; 7-methoxy-2-methyl-3-allyl-4-quinolone; 5-methoxy-2-methyl-3-allyl-4-quinolone ; 7-methoxy-2-methyl-3(1-methylallyl)-4-quinolone were prepared. The most thorough and systematic investigation into behaviour of allyloxyquinolines has been carried out by Makisumi[17] in last 5 years. He studied the Claisen rearrangement of allyl,methyllal and crotyl ethers of 2-methyl-4-quinolinols. These investigations have thrown much light into the mechanistic features of the Claisen rearrangement as applicable to nitrogen heterocyclic systems. All the rearrangement in the quinoline series were effected without solvent at 200°. Yields were almost quantitative in almost all instances although more than one product often resulted from a single starting material. The common feature of allylic inversion was clearly established in

these investigations. The intermediacy of the cyclohexadienone type structure (48) was also demonstrated.

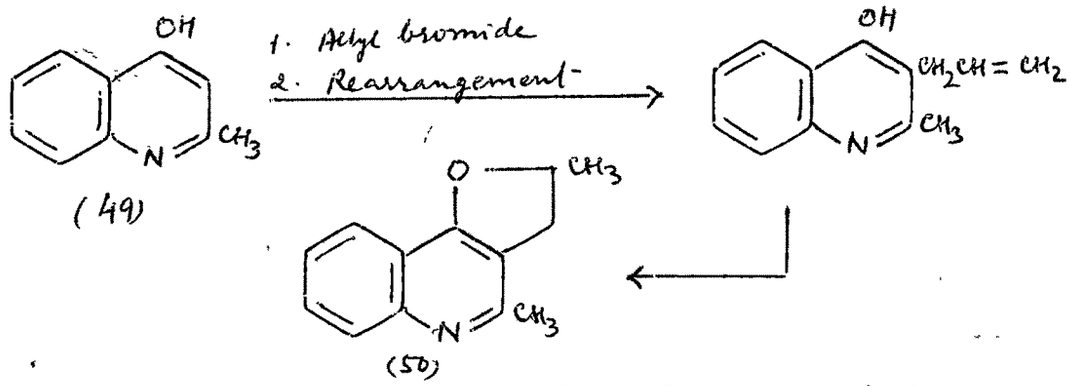


(48)

It was established that 3-substituted-4-allyl ethers of quinoline rearrange to the nitrogen atom rather than to the benzene ring.

Synthesis of furo(3,2-c)quinoline derivatives

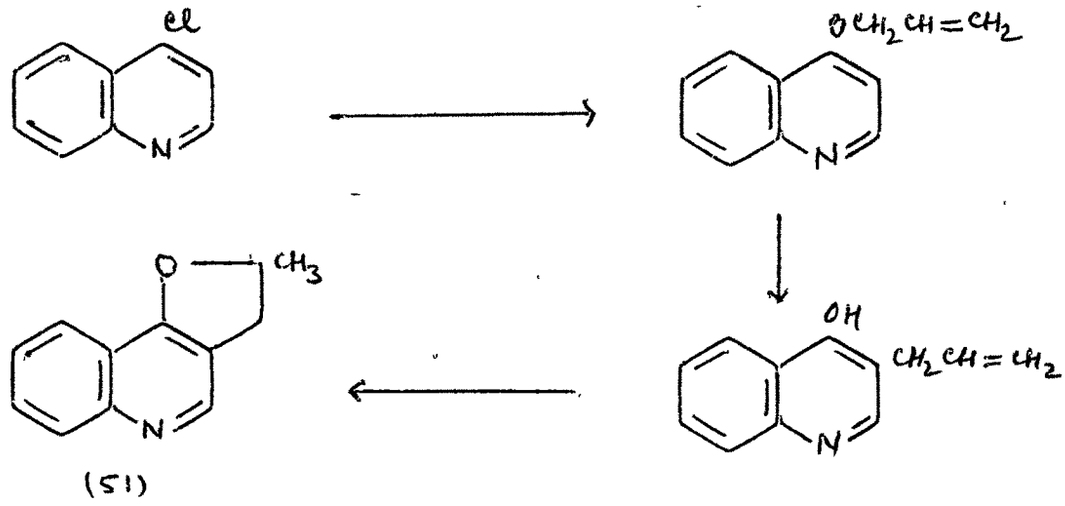
Makisumi[17] synthesised 2,3-dihydro-2,4-dimethyl furo(3,2-c)quinoline (50) by condensing 4-hydroxy-2-methyl-quinoline (49) with allyl bromide followed by Claisen rearrangement and subsequent cyclisation with pyridine hydrochloride.



(49) (50)

2,3-Dihydro-2-methyl furo(3,2-c)quinoline (51) was synthesised by condensing 4-chloroquinoline with sodium allyloxide followed by migration and subsequent cyclisation by the same author. Similarly methyllalchloride was condensed with the silver salt of 4-hydroxy-2-methylquinoline

which rearranged to 3-methyllal derivative (52) and cyclised to 2,2,4-trimethyl-2,3-dihydro furo(3,2-c)quinoline (53).



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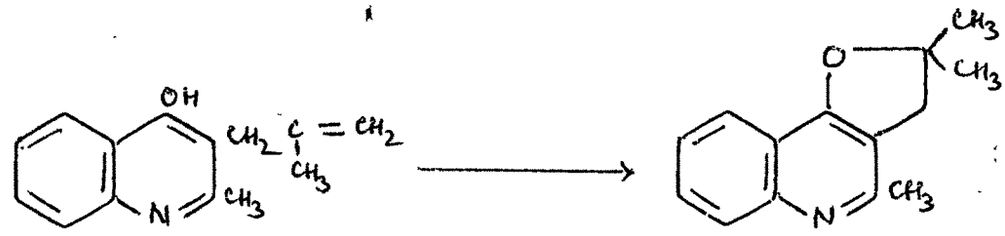
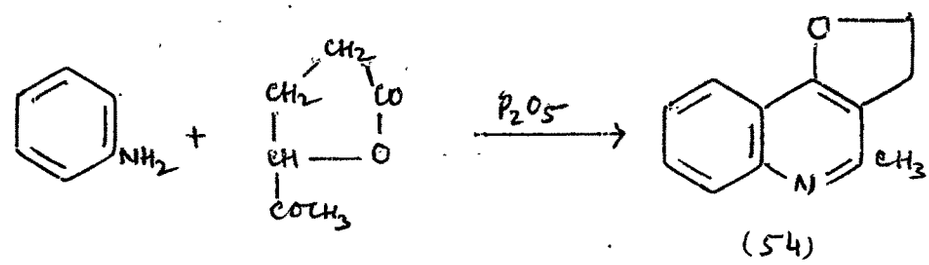


(52) (53)

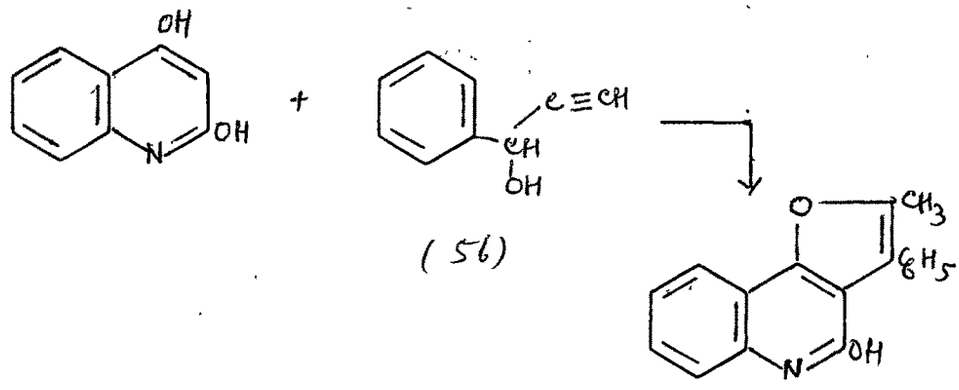
Andersag and Timmler[18] prepared 2,3-dihydro-4-methyl furo(3,2-c)quinoline (54) by boiling aniline with α-acetyl-γ-butyrolactone in tetraline in the presence of phosphorus pentoxide.



(54)

2-Methyl-3-phenyl furo(3,2-c)quinolin-4-one[19] (55) was synthesised by condensing 4-hydroxycarbostyril with (56)

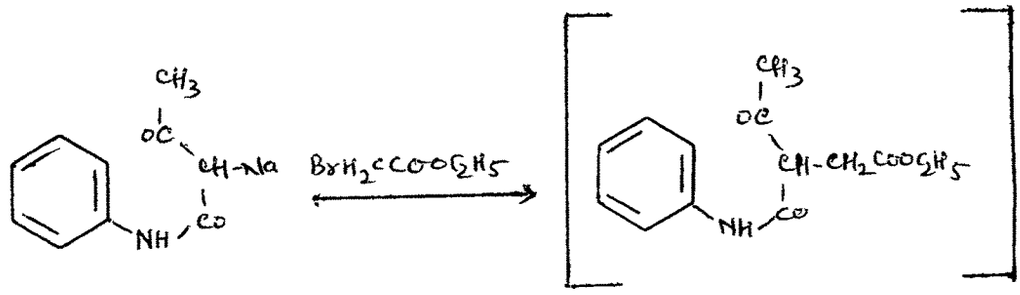
in the presence of conc.sulphuric acid or boron trifluoride etherate in acetic acid.

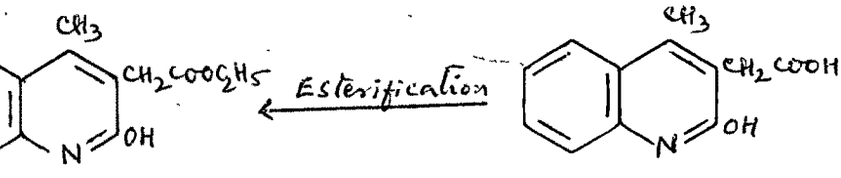


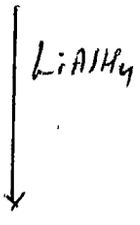
Synthesis of furo(2,3-b)quinoline derivatives :

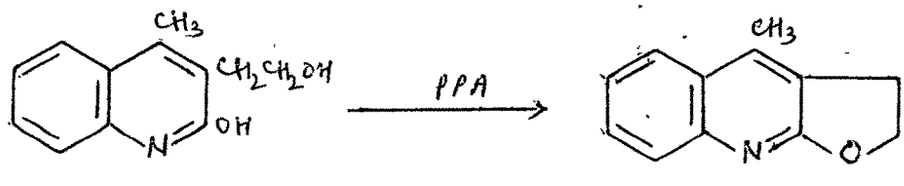
Raman et al.[20] synthesised 2,3-dihydro-4-methyl furo(2,3-b)quinoline (60) and 2,3-dihydro-2,4-dimethyl furo (2,3-b)quinoline (62) as follows :

Sodium derivative of acetoacetanilide was condensed with bromoacetic ester to give an intermediate which on cyclisation with conc.sulphuric acid gave 4-methyl-2-quinolone-3-acetic acid (57). This on esterification with ethanol and sulphuric acid gave ethyl 4-methyl-1,2-dihydro-2-oxo-quinoline-3-acetate (58). This ester with lithium aluminium hydride on reduction yielded 3-(2-hydroxyethyl)-4-methyl-1,2-dihydro-2-oxoquinoline (59). This was then cyclised with carbonyl chloride in chloroform as well as with polyphosphoric acid to dihydro furoquinoline derivative (60). When sodium derivative of acetoacetanilide was condensed with allylbromide it gave α-allyl derivative(61)





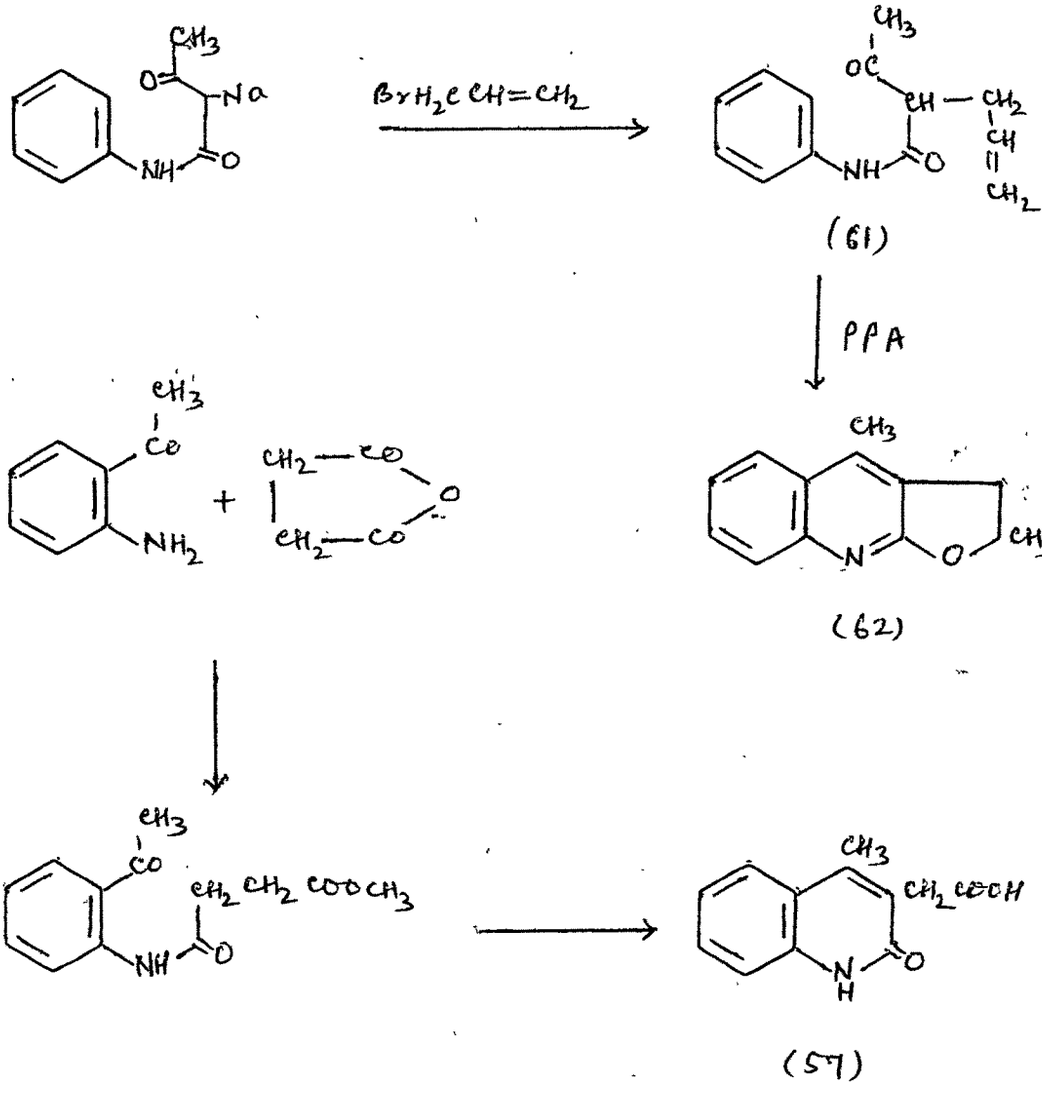




(59) (60)

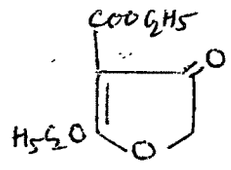
which with polyphosphoric acid gave 2,3-dihydro-2,4-dimethyl furo(2,3-b)quinoline (62). However, attempts to dehydrogenate both the furoquinoline derivatives were unsuccessful.

Shanmugam[21] prepared 4-methyl-2-quinolone-3-acetic acid (57)by refluxing o-aminoacetophenone and succinic anhydride in benzene and hydrolysing the product with 2 % potassium hydroxide. Thus acid obtained was esterified,reduced with lithium aluminium hydride in tetrahydrofuran and cyclised to furoquinoline derivative (60).

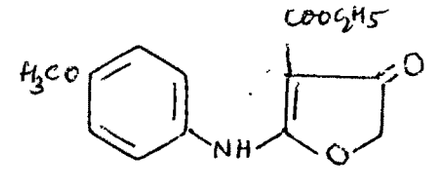


Pai et al.[22] synthesised 6-methoxydictamnine as follows :

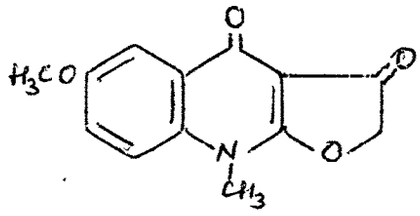
Condensation of p-anisidine with ethyl 2-ethoxy-4,5-dihydro-4-oxofuran-3-carboxylate (64) (prepared in situ from chloroacetyl chloride and sodio malonic ester)[23] yielded ethyl 4,5-dihydro-2-(p-methoxyanilino)-4-oxo furan-3-carboxylate (65). On heating this ester in paraffin 2,3-dihydro-4-hydroxy-6-methoxy-3-oxo furo(2,3-b) quinoline (66) was formed. Methylation with diazomethane yielded a mixture of o-methyl (67) and N-methyl (68) compounds. Sodium borohydride reduction of (67) gave 2,3-dihydro-3-hydroxy-4,6-dimethoxy furo(2,3-b)quinoline (69). Dehydration of (69) with potassium bisulphate yielded 6-methoxy dictamnine (70), identical with natural product isolated[24] from Platydesma Campanulata Mann.



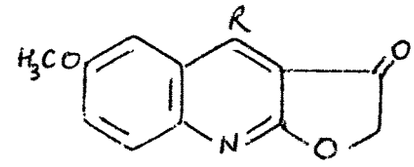
(64)



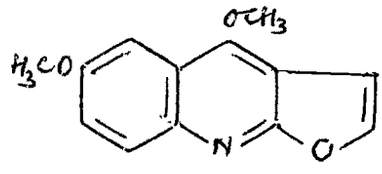
(65)



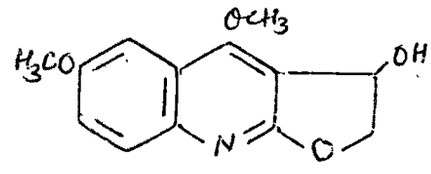
(68)



(66); R = OH
(67); R = OCH_3

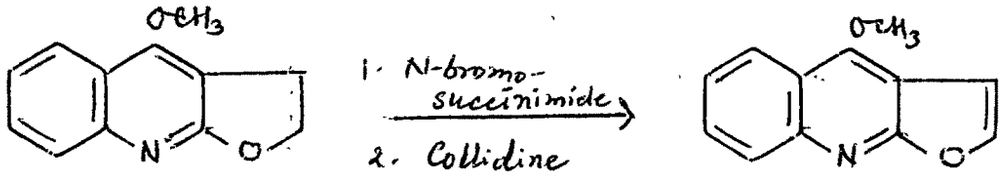


(70)

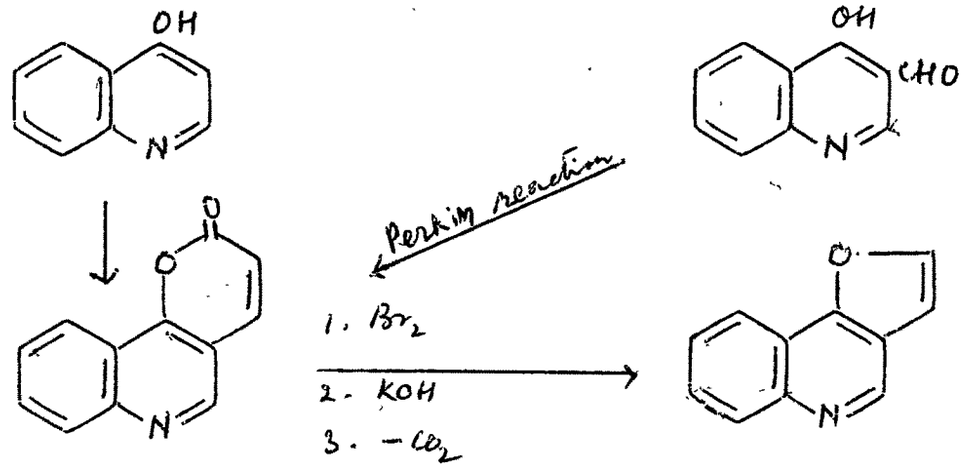


(69)

The present work deals with the synthesis of furo(2,3-b)quinoline and furo(3,2-c)quinoline derivatives. On reviewing the literature, it has been observed that all naturally occurring furoquinoline derivatives have unsubstituted furan ring and this has been built up generally from the dihydrofuroquinolines by making use of the bromination-dehydrobromination technique in very poor yields.

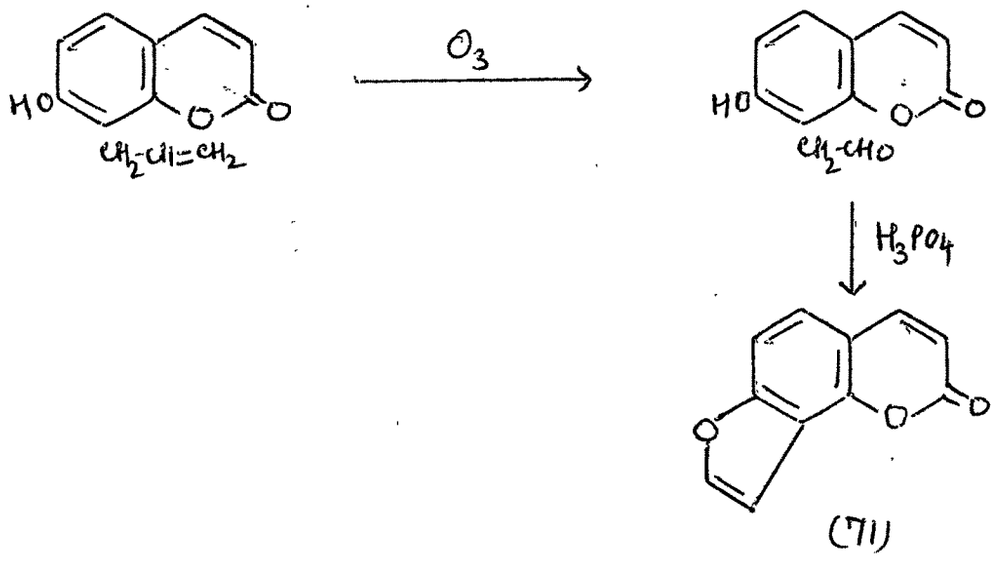


The other method makes the use of building up of the α-pyrone ring on o-hydroxyaldehydes or by Pechmann reaction on 4-hydroxyquinoline derivatives followed by bromination and ring contraction by alcoholic potassium hydroxide solution.



Both these methods suffer from the same disadvantage of very poor yields of the final furoquinoline derivatives.

In 1958, Aneja, Mukherjee and Seshadri[252] developed a good method for the synthesis of naturally occurring unsubstituted furocoumarin angelicin by subjecting 7-hydroxy-8-allylcoumarin to ozonolysis to give 7-hydroxy-8-acetaldehydocoumarin which underwent cyclisation in the presence of o- phosphoric acid to angelicin (71).

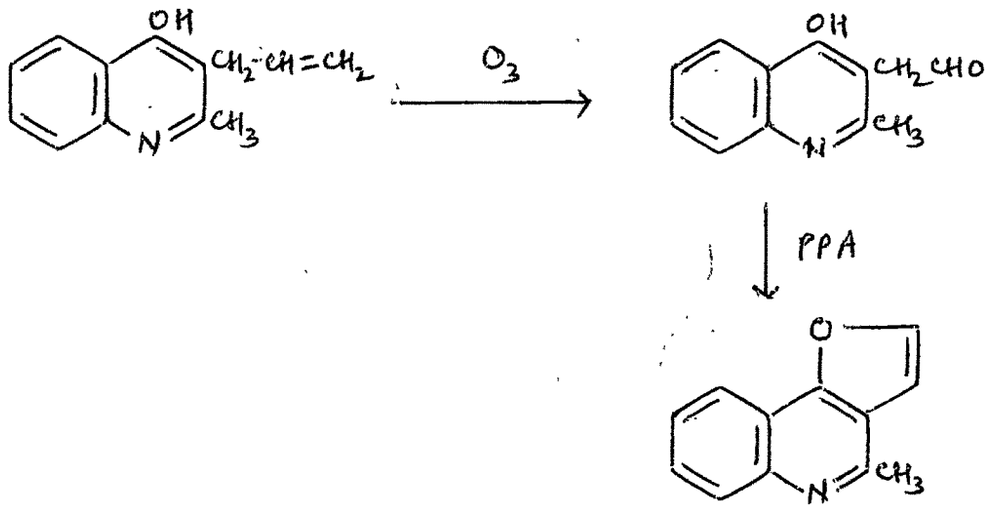


(71)

Using this procedure, Seshadri and coworkers have synthesised several naturally occurring furocoumarins and furochromones. It was, therefore, thought of interest to apply this method of building up of the furan ring from o-hydroxyallylquinoline derivatives as no work has been reported so far using this procedure on quinoline derivatives.

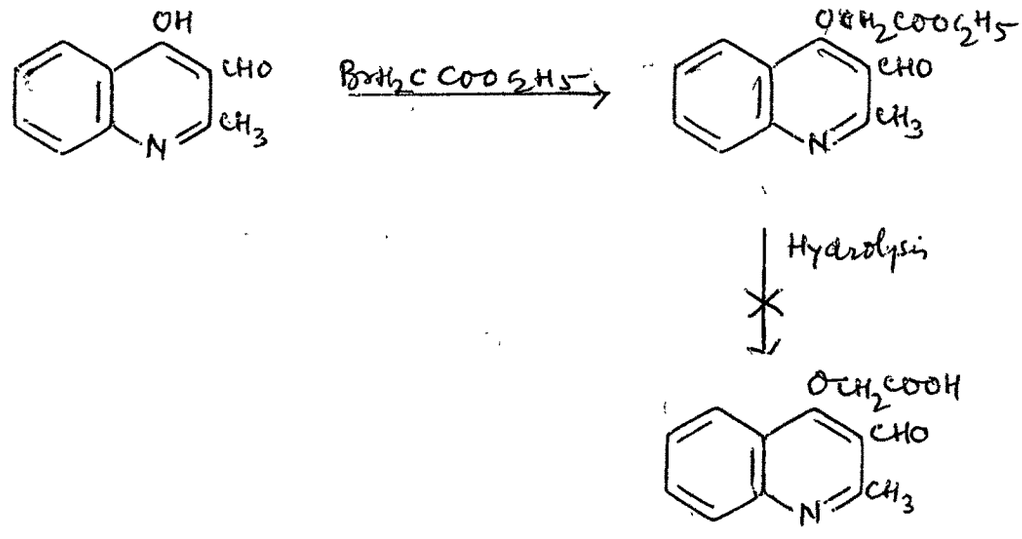
2-Methyl-3-allyl-4-hydroxyquinoline was subjected to ozonolysis according to Seshadri et al.[25] This ozonised

product, on hydrogenation in the presence of palladised charcoal afforded the corresponding 2-methyl-3-acetaldehydo-4-hydroxyquinoline which was cyclised with polyphosphoric acid to 4-methylfuro(3,2-c)quinoline (72) as follows :



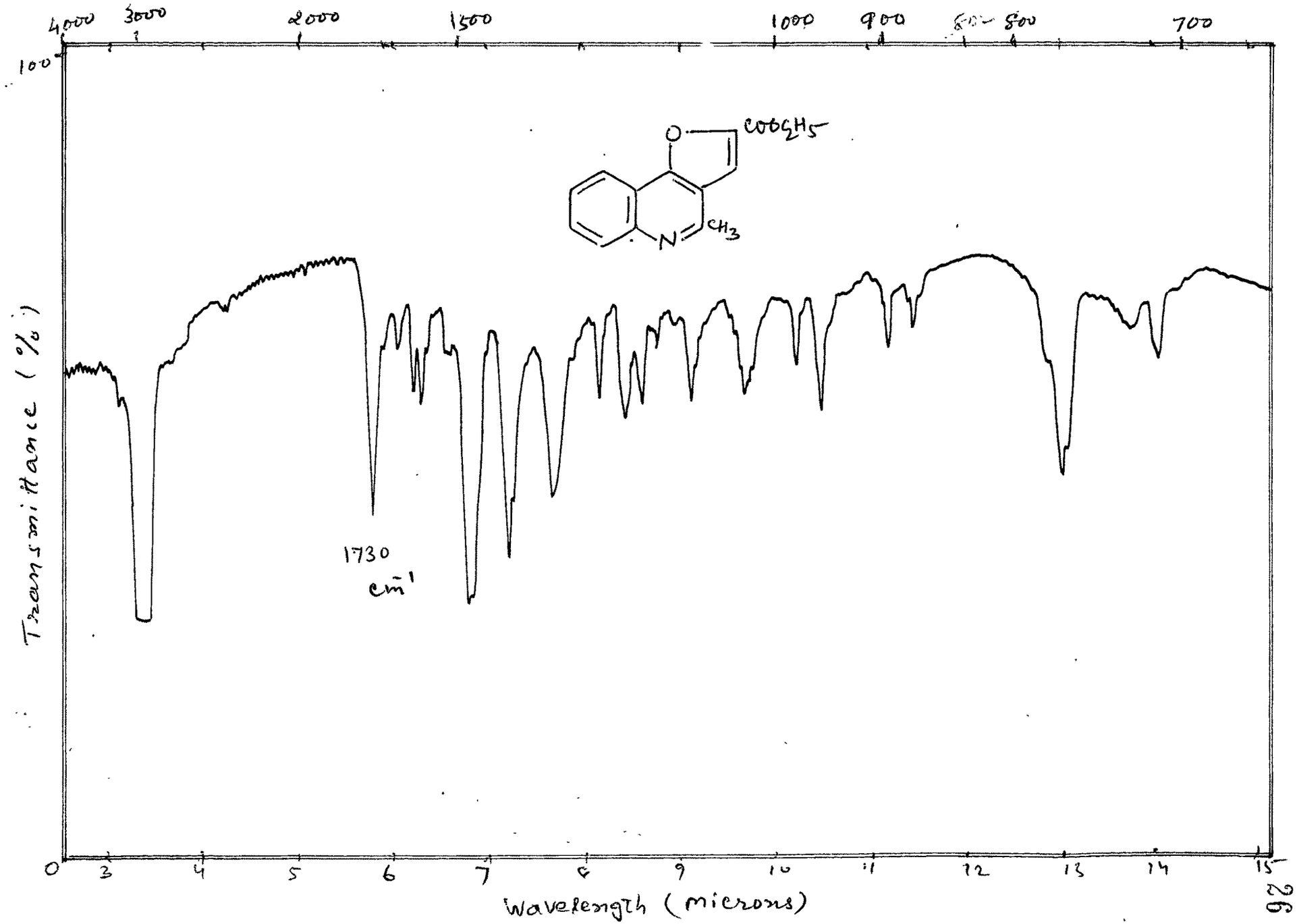
(72)

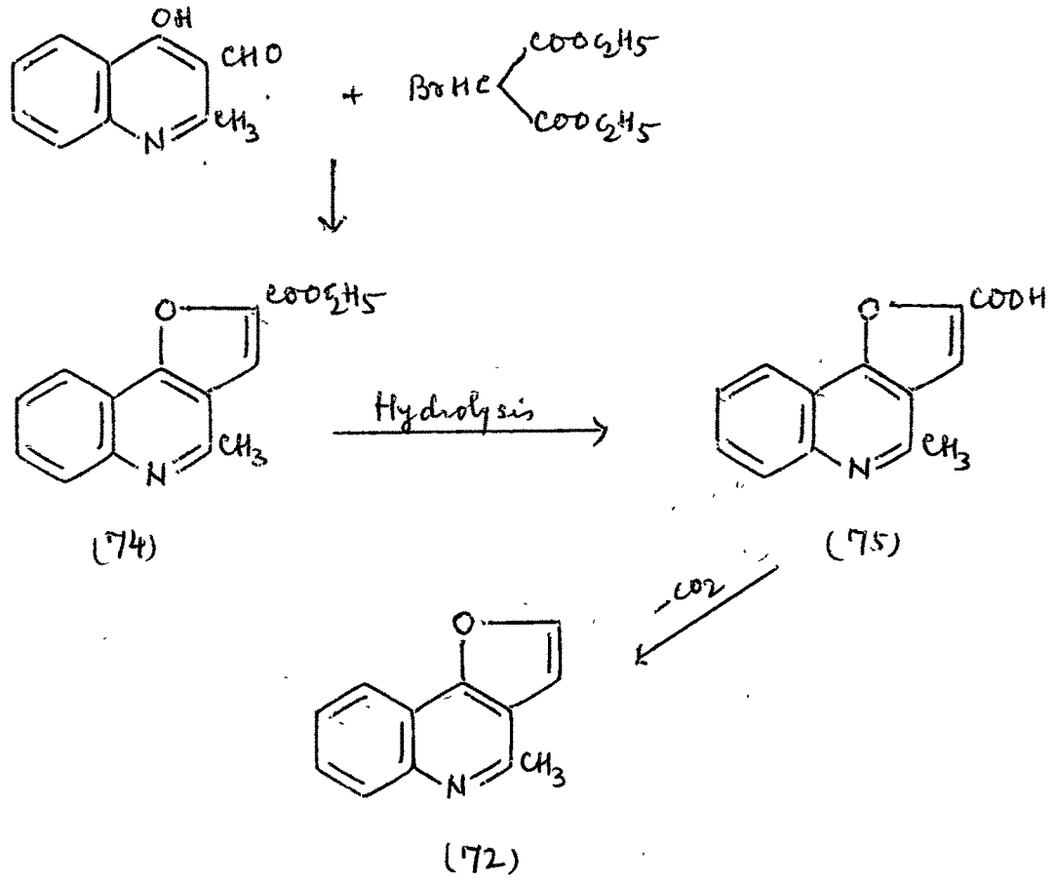
Another method which has been used for building up of the unsubstituted furan ring makes the use of o-hydroxyaldehydes as starting product. This is reacted with ethyl bromoacetate followed by hydrolysis and ring closure to furan ring. No work is so far reported of using this procedure on o-hydroxyaldehydoquinoline derivatives. 2-Methyl-3-formyl-4-hydroxyquinoline was reacted with ethyl bromoacetate in the presence of potassium carbonate in boiling ethyl methyl ketone to give 2-methyl-3-formyl-4-carboethoxymethoxyquinoline. This on hydrolysis did not give the corresponding acid (73) but original 2-methyl-3-formyl-4-hydroxyquinoline was obtained back.



(73)

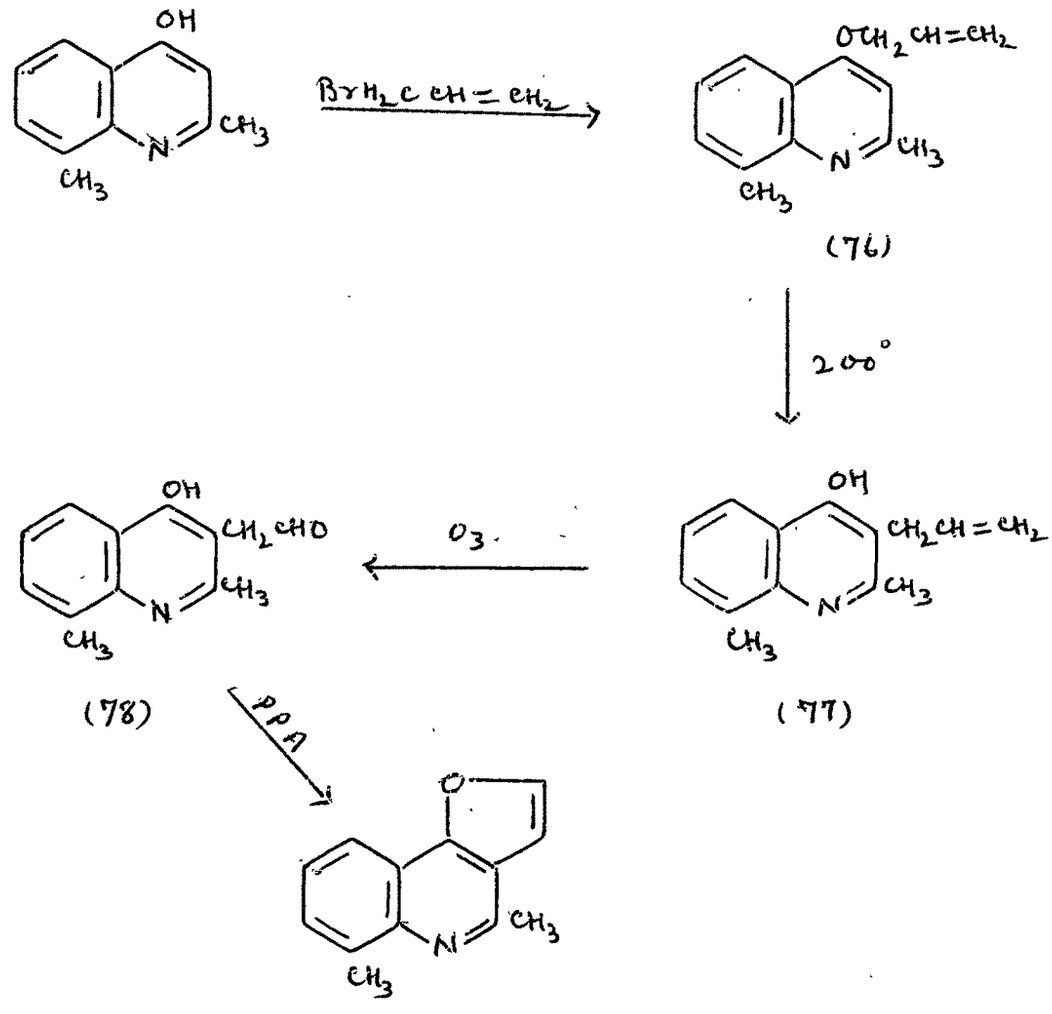
In view of the failure of this method in the quinoline series, the method developed by Tanaka[26] to build up unsubstituted furan ring by making use of ethyl bromomalonate was next tried. When 2-methyl-3-formyl-4-hydroxyquinoline was condensed with ethyl bromomalonate in the presence of potassium carbonate in refluxing ethyl methyl ketone for 35 hr., it gave 4-methyl-2-carboethoxy furo(3,2-c)quinoline (74). IR spectra (nujol) showed a strong ester carbonyl band at 1730 cm^{-1}. This (74) was then hydrolysed to 4-methyl furo(3,2-c)quinoline-2-carboxylic acid (75). This acid (75) underwent decarboxylation to 4-methyl furo(3,2-c)quinoline (72) when heated with copper bronze above its melting point under vacuum. The mixed m.p. of this product with the product obtained by ozonolysis of 2-methyl-3-allyl-4-hydroxy-quinoline followed by ring closure with poly phosphoric acid was not depressed.


4000
3000
2000
1500
1000
900
800
700
100
0
Transmittance (%)
1730
cm⁻¹
O
COOC₂H₅
CH₃
N
3
4
5
6
7
8
9
10
11
12
13
14
15
Wavelength (microns)
92



4,6-Dimethyl furo(3,2-c)quinoline

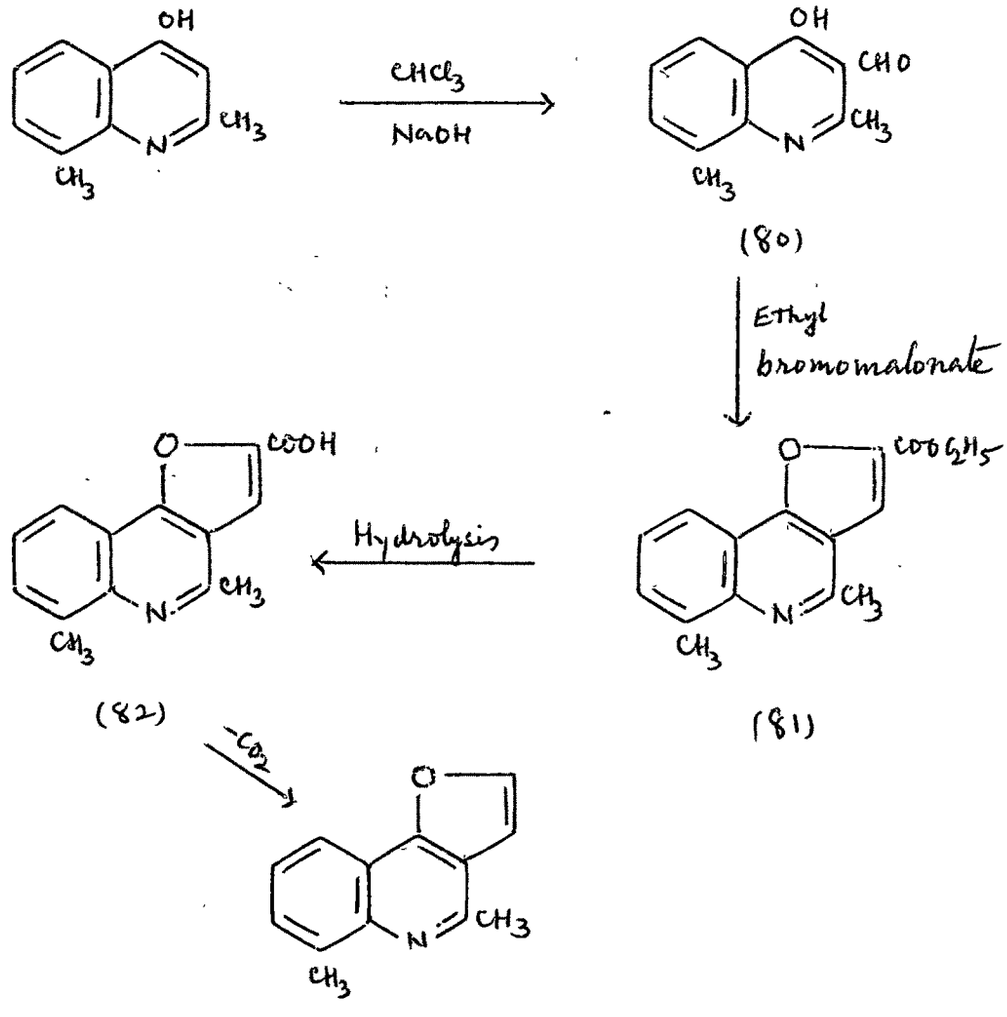
2,8-Dimethyl-4-hydroxyquinoline on allylation with allyl bromide in ethyl methyl ketone in the presence of anhydrous potassium carbonate gave the 4-allyloxy derivatives (76) which on Claisen rearrangement by heating in an oil bath at 200° afforded 2,8-dimethyl-3-allyl-4-hydroxyquinoline (77). This was then subjected to ozonolysis followed by hydrogenation with palladised charcoal in ethyl acetate to give 2,8-dimethyl-3-acetaldehydo-4-hydroxy-quinoline (78) which on cyclisation with polyphosphoric acid gave 4,6-dimethyl furo(3,2-c)quinoline (79).



The same furoquinoline was prepared for comparison by an alternate method as follows :

2,8-Dimethyl-4-hydroxyquinoline was subjected to Reimer-Tiemann reaction with excess of alkali and chloroform. The 3-formyl derivative (80) obtained, on condensation with ethyl bromomalonate in ethyl methyl ketone in the presence of anhydrous potassium carbonate afforded 4,6-dimethyl-2-carboethoxy furo(3,2-c)quinoline (81). The ester(81) on hydrolysis gave 4,6-dimethyl furo(3,2-c)quinoline-2-

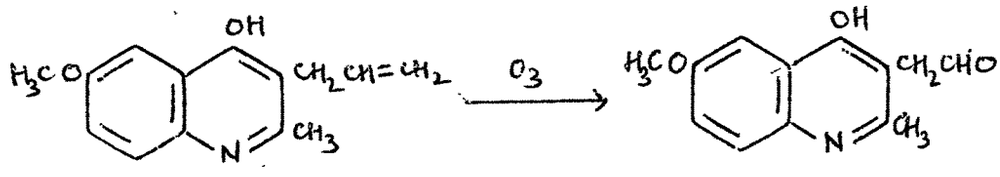
carboxylic acid (82) which on decarboxylation by heating above its m.p. under vacuum with copper bronze yielded 4,6-dimethyl furo(3,2-c)quinoline (79). M.P. and mixed m.p. with the compound described above was not depressed.



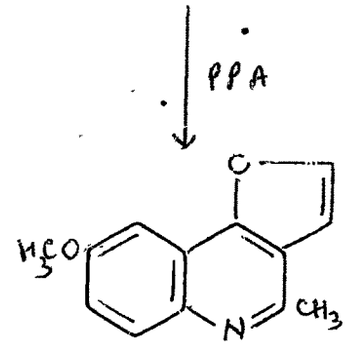
8-Methoxy-4-methyl furo(3,2-c)quinoline

6-Methoxy-2-methyl-3-allyl-4-hydroxyquinoline on ozonolysis followed by hydrogenation in the presence of palladised charcoal afforded 6-methoxy-2-methyl-3-acetaldehydo-4-hydroxyquinoline (83) which with

polyphosphoric acid gave 8-methoxy-4-methyl furo(3,2-c) quinoline (84).



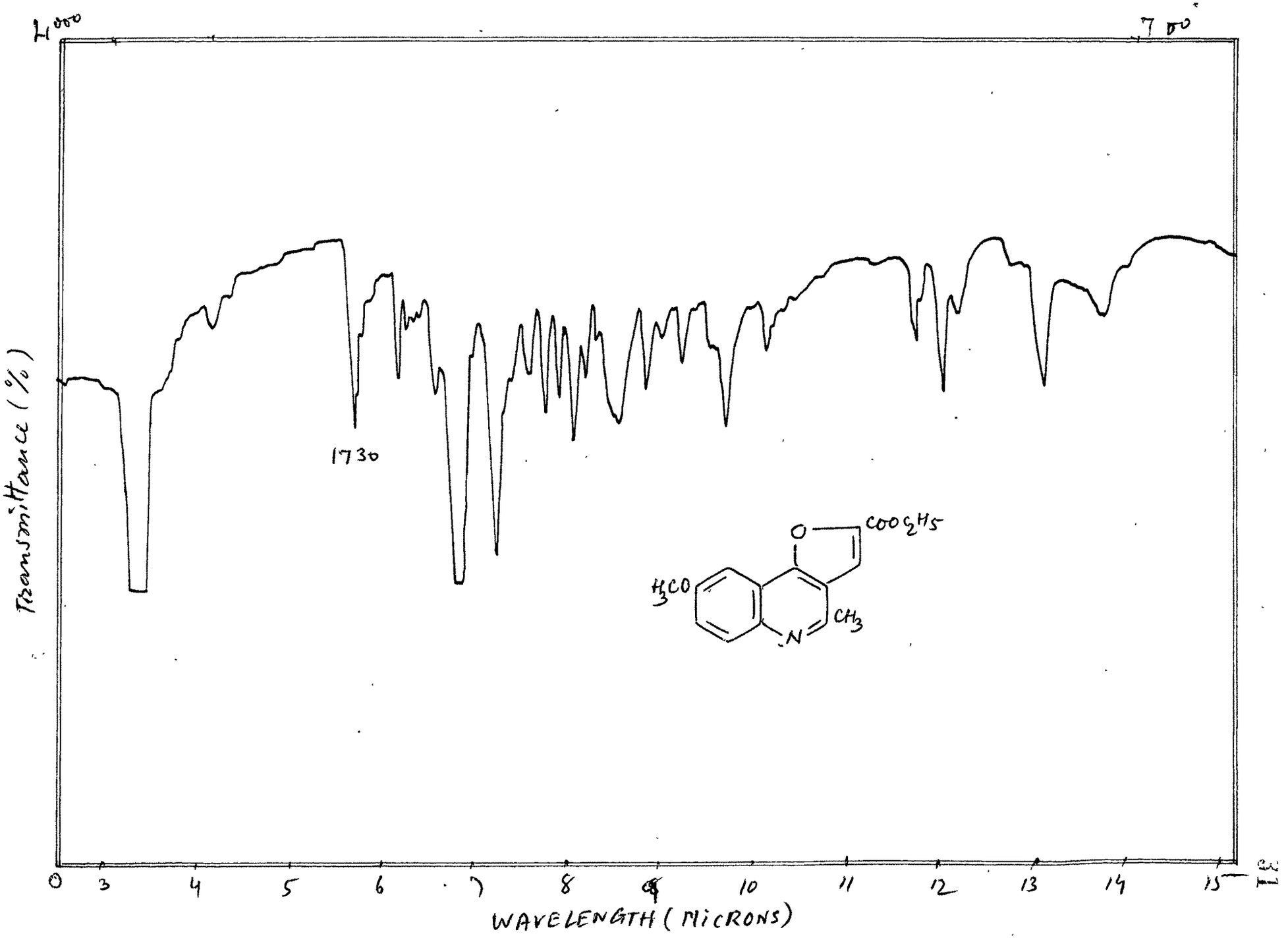
(83)

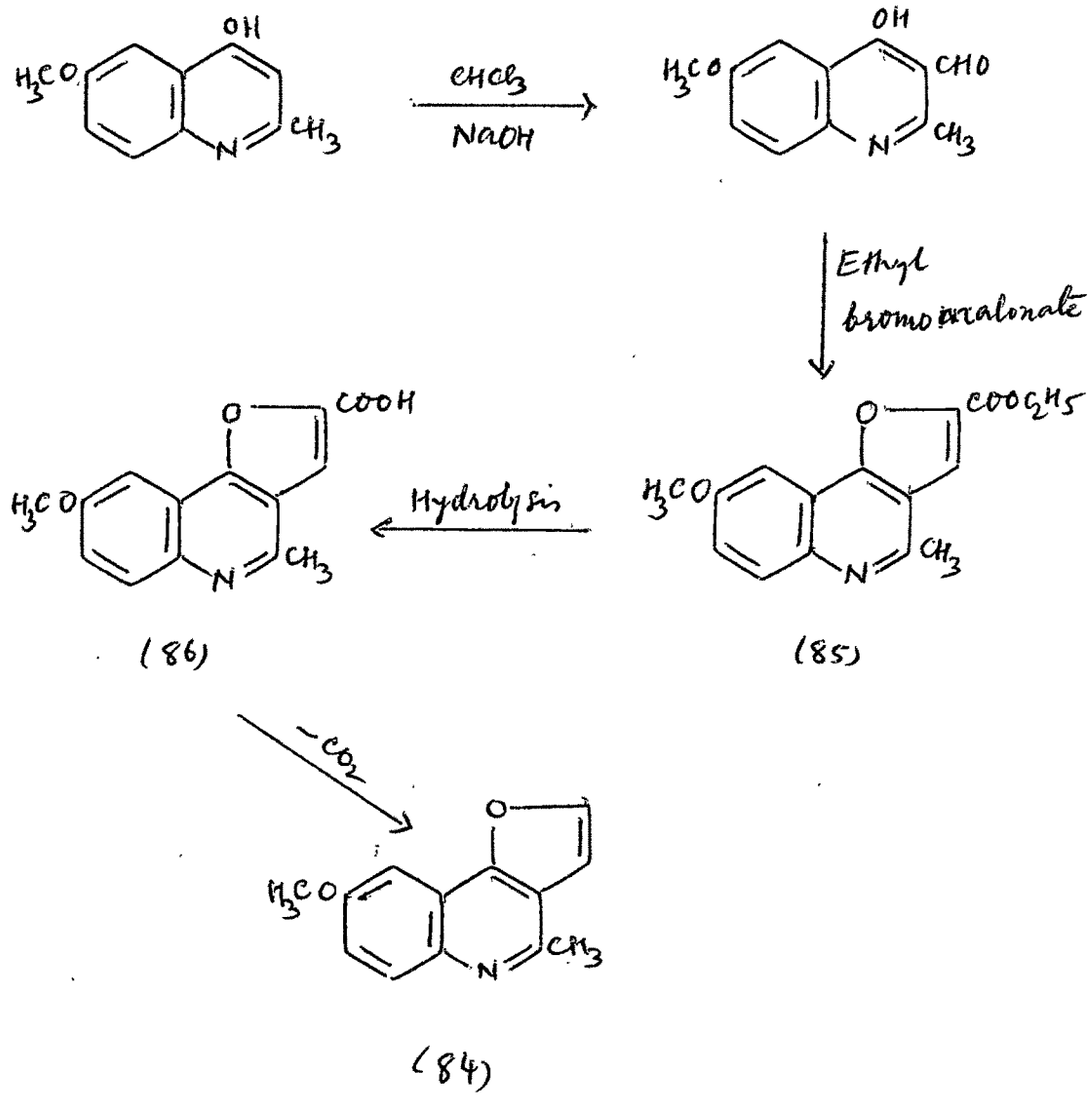


(84)

The same furoquinoline was prepared by an alternate method as follows:

6-Methoxy-2-methyl-3-formyl-4-hydroxyquinoline was prepared by Reimer-Tiemann reaction on 6-methoxy-2-methyl-4-hydroxyquinoline with chloroform and alkali. It was condensed with ethyl bromomalonate to give 8-methoxy-4-methyl-2-carboethoxy furo(3,2-c)quinoline (85). IR spectra (nujol) showed a strong ester carbonyl band at 1730 cm^{-1}. This on hydrolysis gave the corresponding acid (86) which when heated with copper bronze above its melting point gave a product identical with furoquinoline (84) described above.


4000
700
Transmittance (%)
1730
O
COOC2H5
H3CO
CH3
N
0
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVELENGTH (MICRONS)

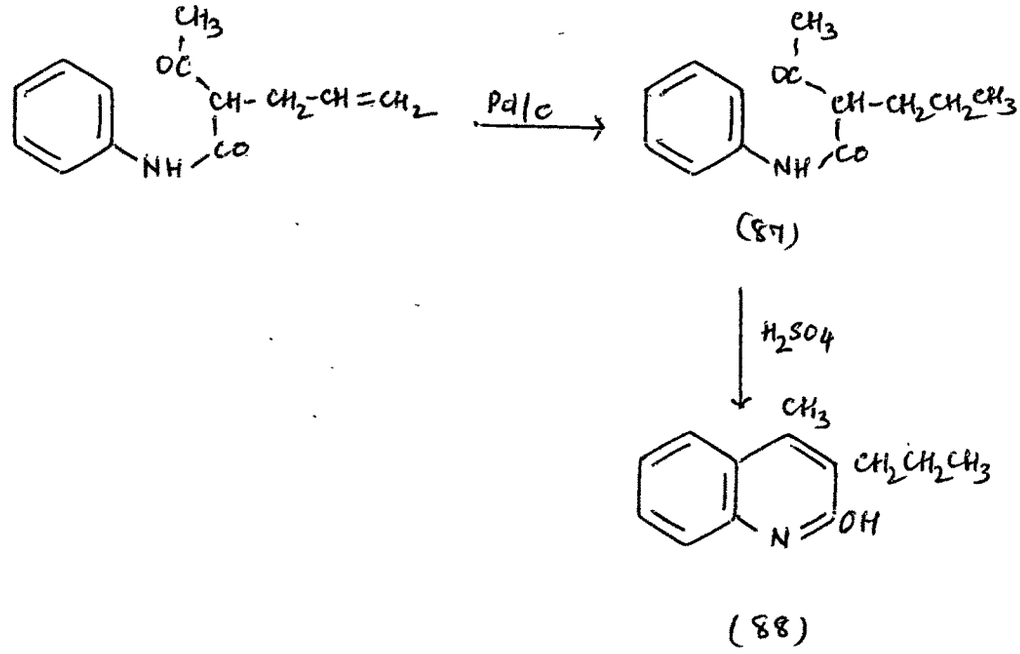


(86) (85)

(84)

As 2-hydroxy-3-allyl-4-methyl quinoline could not be obtained from the corresponding α-allyl acetoacetanilide, an attempt was made to prepare unsubstituted furo(2,3-b) quinoline derivative by subjecting this α-allyl derivative of acetoacetarylamides to ozonolysis followed by ring closure with sulphuric acid. When α-allylacetoacetanilide was subjected to ozonolysis followed by hydrogenation it did not give the corresponding acetaldehydo derivative but instead α-propyl acetoacetanilide (87) was isolated. The

same propyl derivatives was also obtained when α-allyl-acetoacetanilide was subjected to hydrogenation in the presence of palladised charcoal. This product on cyclisation with concentrated sulphuric acid gave 4-methyl-3-propylcarbostyril (88).

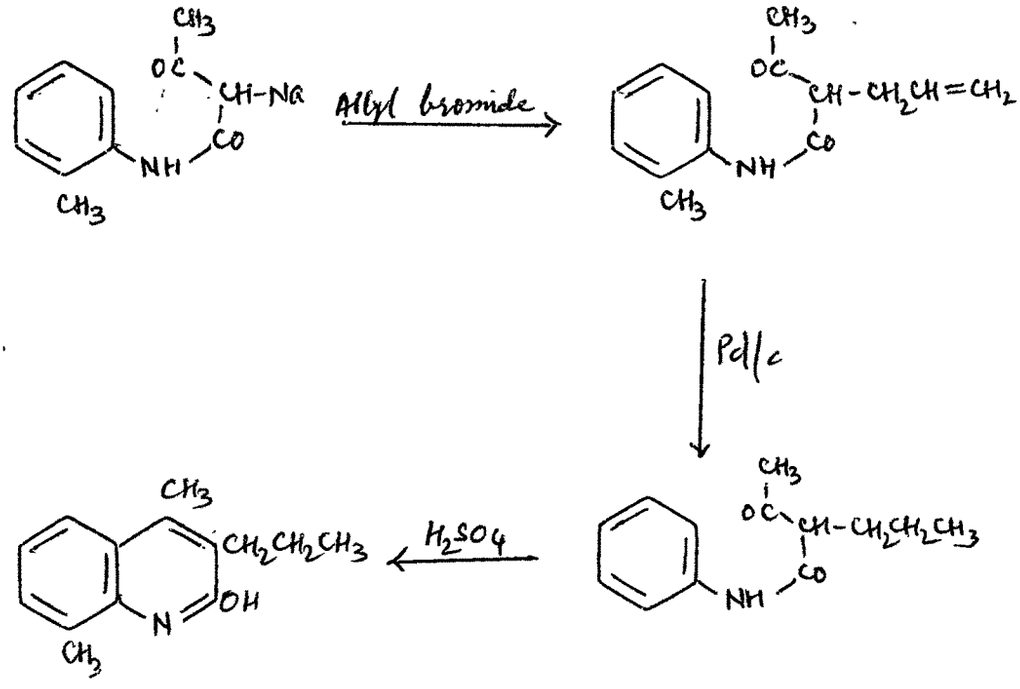


(87)

(88)

4,8-Dimethyl-3-propylcarbostyril

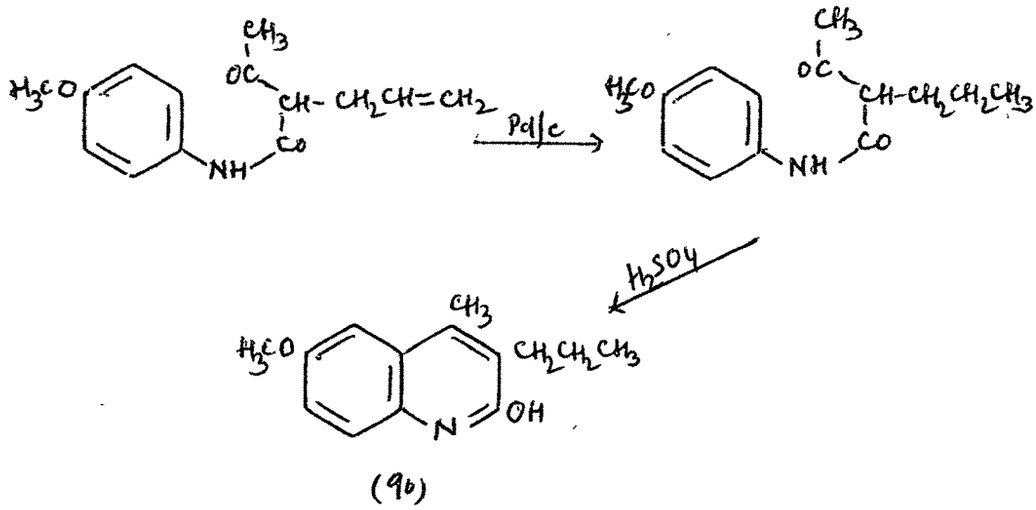
Sodium salt of acetoacet-o- toluidide prepared by reacting sodium with acetoacet-o-toluidide, on condensation with allyl bromide gave α-allylacetoacet-o-toluidide. This on hydrogenation in the presence of palladised charcoal in ethyl acetate gave α-propyl acetoacet-o-toluidide which on cyclisation with concentrated sulphuric acid gave 4,8-dimethyl-3-propylcarbostyril (89).



(89)

6-Methoxy-4-methyl-3-propylcarbostyril

Sodium salt of acetoacet-p-anisidide prepared by reacting sodium with acetoacet-p-anisidide, on condensation with allyl bromide gave α-allyl acetoacet-p-anisidide. This on hydrogenation in the presence of palladised charcoal gave α-propyl acetoacet-p-anisidide which on cyclisation with concentrated sulphuric acid afforded 6-methoxy-4-methyl-3-propylcarbostyril (90).

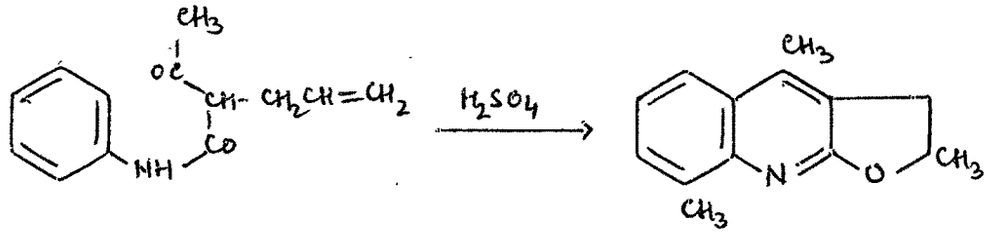


(90)

Raman[20] synthesised 2,3-dihydro-2,4-dimethyl furo(2,3-b)quinoline from α-allylacetoacetanilide. This type of dihydrofuroquinoline derivatives were also prepared in the following cases :

2,3-Dihydro-2,4,8-trimethyl furo(2,3-b)quinoline

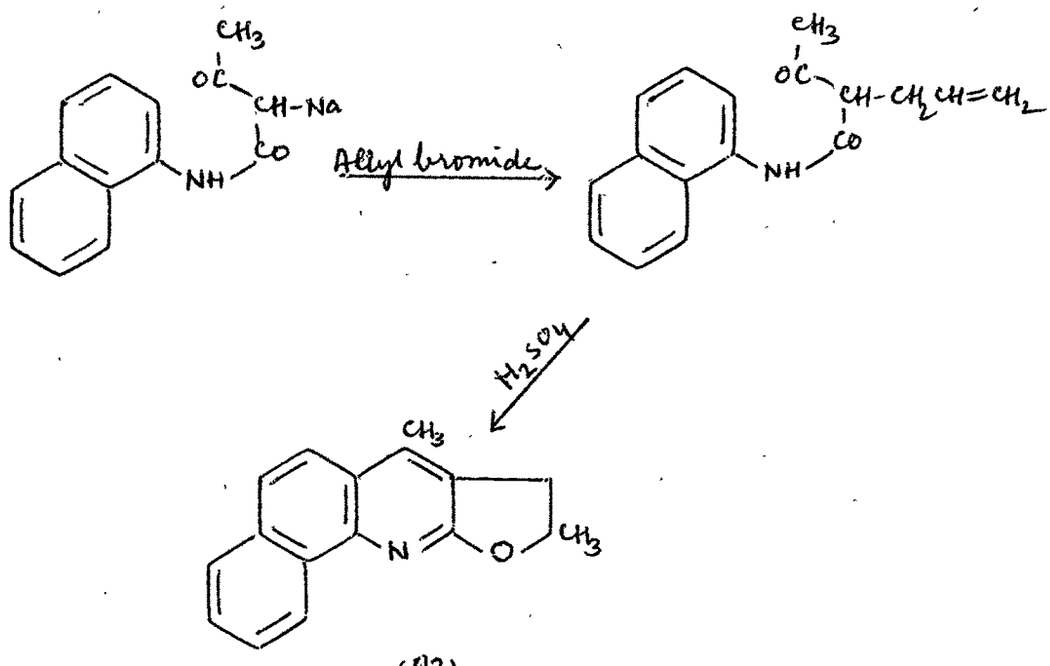
α-Allylacetoacet-o- toluidide described earlier was cyclised with concentrated sulphuric acid to 2,3-dihydro-2,4,8-trimethyl furo(2,3-b)quinoline (91). The structure was assigned on the basis of analytical results. Attempts to dehydrogenate by refluxing with palladised charcoal in diphenyl ether met with failure.



(91)

2,3-Dihydro-2,4-dimethyl-benzo(h) furo [2,3-b] quinoline

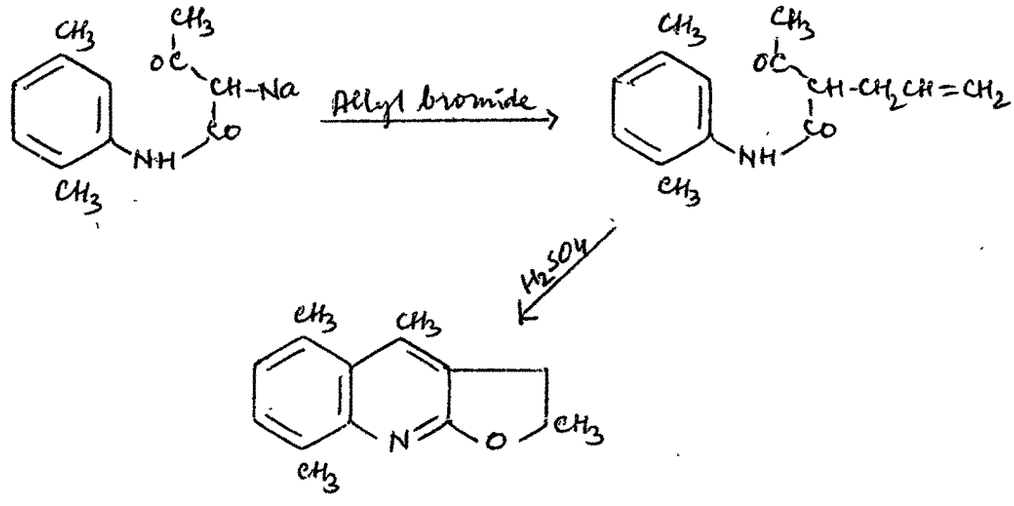
Acetoacet-α-naphthylamide with sodium gave its sodium derivative which on condensation with allyl bromide gave α-allylacetoacet-α-naphthylamide. This with concentrated sulphuric acid afforded 2,3-dihydro-2,4-dimethylbenzo(h) furo[2,3-b] quinoline (92).



(92)

2,3-Dihydro-2,4,5,8-tetramethyl furo(2,3-b) quinoline

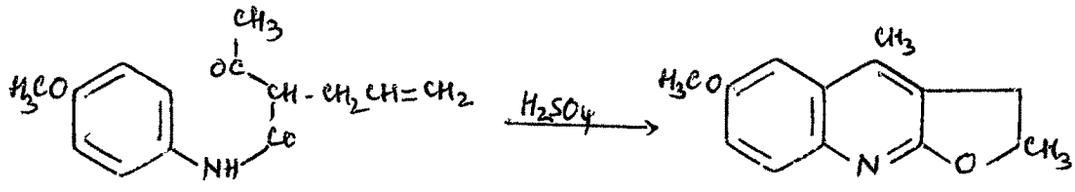
Acetoacet-p-xylidide with sodium gave sodium derivative which on condensation with allyl bromide gave α-allylacetoacet-p-xylidide. This on cyclisation with concentrated sulphuric acid gave 2,3-dihydro-2,4,5,8-tetramethyl furo(2,3-b)quinoline (93).



(93)

6-Methoxy-2,3-dihydro-2,4-dimethyl furo(2,3-b) quinoline

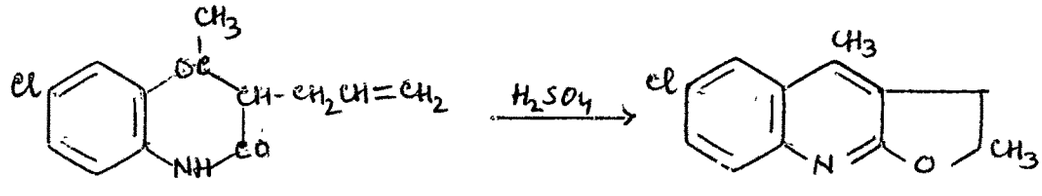
α-Allylacetoacet-p-anisidide described above on cyclisation with concentrated sulphuric acid gave 6-methoxy-2,3-dihydro-2,4-dimethyl furo(2,3-b)quinoline (94).



(94)

6-Chloro-2,3-dihydro-2,4-dimethyl furo(2,3-b) quinoline

α-Allylacetoacet-p-chloroanilide was prepared by reacting sodium with acetoacet-p-chloroanilide followed by condensation with allyl bromide. This on cyclisation with concentrated sulphuric acid gave 6-chloro-2,3-dihydro-2,4-dimethyl furo(2,3-b)quinoline (95).



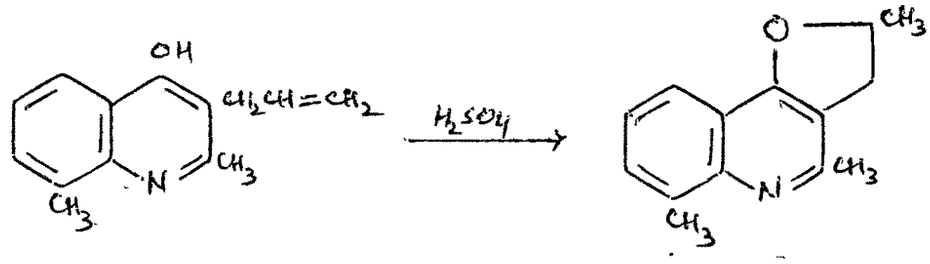
(95)

Having synthesised dihydrofuro(2,3-b)quinoline derivatives, it was thought of interest to synthesise dihydrofuro(3,2-c)quinoline derivatives from 2-methyl-3-allyl-4-hydroxyquinoline derivatives.

The following dihydrofuro(3,2-c)quinoline derivatives were prepared in the present work.

2,3-Dihydro-2,4,6-trimethyl furo(3,2-c)quinoline

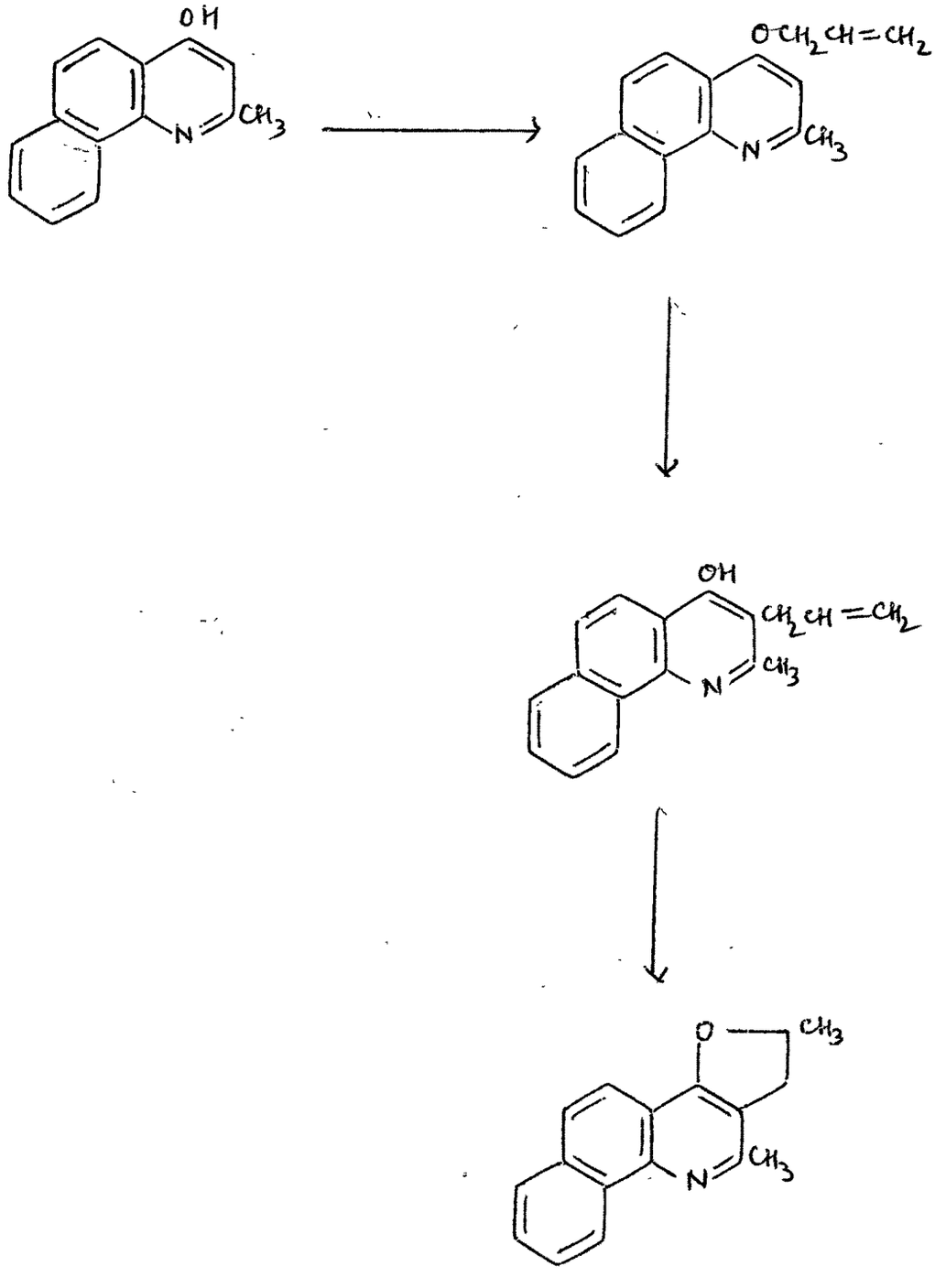
2,8-Dimethyl-3-allyl-4-hydroxyquinoline described earlier on cyclisation with concentrated sulphuric acid gave 2,3-dihydro-2,4,6-trimethylfuro(3,2-c)quinoline (96). Attempts to dehydrogenated this by refluxing with palladised charcoal (5 %) in diphenyl ether met with failure.



(96)

2,3-Dihydro-2,4-dimethyl-benzo(h)furo(3,2-c)quinoline

2-Methyl-7,8-benzo-4-hydroxyquinoline on allylation with allyl bromide in the presence of anhydrous potassium carbonate gave 4-allyloxy derivative which on Claisen rearrangement yielded 2-methyl-3-allyl-7,8-benzo-4-hydroxy-quinoline. This on cyclisation with concentrated sulphuric acid gave 2,3-dihydro-2,4-dimethyl-benzo(h)furo(3,2-c) quinoline (97).



(97)

EXPERIMENTAL

Ozonolysis of 2-methyl-3-allyl-4-hydroxyquinoline : 2-Methyl-3-acetaldehydo-4-hydroxyquinoline

2-Methyl-3-allyl-4-hydroxyquinoline (1 g.) was dissolved in formic acid (30 ml.) and the solution was cooled to 15°. Ozone was passed through this solution for 1 hr.. It was then hydrogenated with room temperature with palladised charcoal (0.5 g.; 5 %) with continuous stirring in the atmosphere of hydrogen for 1.1/2 hr.. The reaction mixture was filtered and neutralised with sodium carbonate. The product which separated crystallised from ethyl acetate, m.p. 230°. Yield 0.3 g..

Analysis : Found : C, 71.80; H, 5.51; N, 6.58 %.

$C_{12}H_{11}O_2N$ requires: C, 71.64; H, 5.47; N, 6.96 %.

4-Methyl furo (3,2-c) quinoline

2-Methyl-3-acetaldehydo-4-hydroxyquinoline (0.5 g.) was treated with polyphosphoric acid (5 g. phosphorous pentoxide and 3 ml. of o-phosphoric acid) and heated on a water bath for 3 hr.. The reaction mixture was diluted with water and neutralised with sodium carbonate. The separated product crystallised from ether petroleum, m.p. 89°. Yield 0.2 g.

Analysis Found : C, 78.87; H, 4.81; N, 7.41 %.

$C_{12}H_9ON$ requires: C, 78.68; H, 4.91; N, 7.64 %.

The same furoquinoline was prepared for comparison by the method given below :

Condensation of 2-methyl-3-formyl-4-hydroxyquinoline with ethyl bromomalonate : 4-Methyl-2-carboethoxy furo(3,2-c) quinoline

2-Methyl-3-formyl-4-hydroxyquinoline (3.7 g.) was dissolved in ethyl methyl ketone (200 ml.) and refluxed with ethyl bromomalonate (4.8 g.) in the presence of anhydrous potassium carbonate (10 g.) for 35 hr. on a steam bath. The ethyl methyl ketone was removed and the reaction mixture was added to water. The product which separated crystallised from benzene petroleum ether mixture (1:1), m.p. 115°. Yield 2.0 g.

Analysis : Found : C, 70.21; H, 4.87; N, 5.31 %.

$C_{15}H_{13}O_3N$ requires: C, 70.60; H, 5.09; N, 5.49 %.

4-Methyl furo(3,2-c)quinoline-2-carboxylic acid :

The above ester (1 g.) was treated with alcoholic potassium hydroxide solution (20 ml.; 10 %) and left overnight. The resulting solution was just acidified with hydrochloric acid (50 %). On cooling in refrigerator the product which separated crystallised from alcohol, m.p. 280°. Yield 0.6 g.

Analysis : Found : C, 68.55; H, 3.55; N, 5.78 %.

$C_{13}H_9O_3N$ requires C, 68.71; H, 3.96; N, 6.16 %.

(Analysed after heating in vacuum at 110° for 4 hr.)

Decarboxylation of 4-methyl furo(3,2-c)quinoline-2-carboxylic acid : 4-Methyl furo(3,2-c)quinoline:

The above acid (0.5 g.) was mixed with copper bronze

(1 g.) and heated in an oil bath above its melting point (280°) with vacuum till the effervescence ceased (10 min.). After cooling the product was extracted with benzene. On evaporation of the solvent the product obtained crystallised from benzene petroleum ether mixture (1:2), m.p. 89°. Mixed m.p. with 4-methyl furo(3,2-c)quinoline described before was not depressed.

2,8-Dimethyl-4-allyloxyquinoline :

2,8-Dimethyl-4-hydroxyquinoline (3.4 g.) was dissolved in ethyl methyl ketone (200 ml.) and refulxed with anhydrous potassium carbonate (7 g.) and allylbromide (2.4 g.) on a water bath for 6 hr., The ethyl methyl ketone was removed and the reaction mixture was added to water. The product which separated crystallised from ether petroleum, m.p. 61°. Yield 1.5 g.

Analysis : Found : C, 78.70; H, 6.67; N, 6.55 %.

$C_{14}H_{15}ON$ requires : C, 78.87; H, 7.04; N, 6.57 %.

Claisen rearrangement of 2,8-dimethyl-4-allyloxyquinoline : 2,8-Dimethyl-3-allyl-4-hydroxyquinoline

2,8-Dimethyl-4-allyloxyquinoline (1 g.) was heated in an oil bath at 200 - 210° for 30 min., The product after washing with benzene crystallised from dilute acetic acid, m.p. 254 - 55°. Yield 0.6 g.

Analysis : Found : C, 78.56; H, 6.88; N, 6.52 %.

$C_{14}H_{15}ON$ requires : C, 78.87; H, 7.04; N, 6.57 %.

Ozonolysis of 2,8-dimethyl-3-allyl-4-hydroxyquinoline: 2,8-Dimethyl-3-acetaldehydo-4-hydroxyquinoline

2,8-Dimethyl-3-allyl-4-hydroxyquinoline (1 g.) was

dissolved in ethylacetate (200 ml.) and the solution was cooled to 15°. Ozone was passed through this solution for 1 hr.. It was then hydrogenated with palladised charcoal (0.5 g.; 5 %) with continuous stirring in the atmosphere of hydrogen for 1.1/2 hr./ After filteration the solution was concentrated to a small volume by distillation and mixed with ether petroleum. The product which separated crystallised from xylene, m.p. 233°. Yield 0.4 g.

Analysis : Found : C, 72.59; H, 6.33; N, 6.44 %.

$C_{13}H_{13}O_2N$ requires : C, 72.56; H, 6.04; N, 6.51 %.

4,6-Dimethyl furo(3,2-c)quinoline :

2,8-Dimethyl-3-acetaldehydo-4-hydroxyquinoline (0.5 g.) was heated in a water bath with polyphosphoric acid (5 g. phosphorus pentoxide and 3 ml. of o-phosphoric acid) for 3 hr./ The reaction mixture was diluted with water and neutralised with sodium carbonate. The product obtained was filtered and crystallised from ether petroleum, m.p. 128°. Yield 0.15 g.

Analysis : Found : C, 79.32; H, 5.76; N, 6.99 %.

$C_{13}H_{11}ON$ requires : C, 79.17; H, 5.58; N, 7.10 %.

The same furoquinoline was prepared for comparison as described below :

2,8-Dimethyl-3-formyl-4-hydroxyquinoline

2,8-Dimethyl-4-hydroxyquinoline (5 g.) was mixed with sodium hydroxide solution (50 ml.; 25 %.) and chloroform (10 ml.). The reaction mixture was refluxed on a water bath for 10 hr./ After removing chloroform it was diluted with water and filtered. The clear filtrate on acidification with

glacial acetic acid gave the product which was filtered and crystallised from alcohol, m.p. 258°. Yield 1.5 g.

Analysis : Found : C, 71.96; H, 5.58; N, 6.95 %.

$C_{12}H_{11}O_2N$ requires : C, 71.64; H, 5.47; N, 6.96 %.

The 2,4-Dinitrophenylhydrazone

2,8-Dimethyl-3-formyl-4-hydroxyquinoline (0.2 g.) was dissolved in acetic acid (10 ml.) and then added to a solution of 2,4-dinitrophenylhydrazine (0.2 g.) in acetic acid (5 ml.) The product separated at once, was filtered and crystallised from glacial acetic acid, m.p. 310°.

Analysis : Found : N, 17.95 %.

$C_{18}H_{15}O_5N_5$ requires : N, 18.37 %.

Condensation of 2,8-dimethyl-3-formyl-4-hydroxyquinoline with ethyl bromomalonate : 4,6-Dimethyl-2-carboethoxy furo(3,2-c)quinoline :

2,8-Dimethyl-3-formyl-4-hydroxyquinoline (3 g.) was dissolved in ethyl methyl ketone (250 ml.) and refluxed with anhydrous potassium carbonate (7 g.) and ethyl bromomalonate (3.6 g.) on a steam bath for 35 hr.. The ethyl methyl ketone was removed and the reaction mixture was added to water. The product which separated crystallised from benzene petroleum ether mixture (1:1), m.p. 128°. Yield 1.5 g.

Analysis : Found : C, 71.33; H, 5.22; N, 5.28 %.

$C_{16}H_{15}O_3N$ requires : C, 71.36; H, 5.57; N, 5.20 %.

4,6-Dimethyl furo(3,2-c)quinoline-2-carboxylic acid :

The above ester (1 g.) was treated with alcoholic potassium hydroxide solution (20 ml.; 10 %) and left overnight. The resulting solution was just acidified with

hydrochloric acid (50 %). On cooling in refrigerator the product which separated crystallised from dilute alcohol, m.p. 248°. Yield 0.5 g.

Analysis : Found : C, 69.58; H, 4.22; N, 5.69 %.

$C_{14}H_{11}O_3N$ requires : C, 69.71; H, 4.56; N, 5.80 %.

(Analysed after heating in vacuum at 110° for 4 hr.)

Decarboxylation of 4,6-dimethyl furo(3,2-c)quinoline-2-carboxylic acid : 4,6-Dimethyl furo(3,2-c)quinoline

The above acid (0.5 g.) was mixed with copper bronze (1 g.) and heated in oil bath above its melting point (248°) with vacuum till the effervescence ceased (10 min.). After cooling the product was extracted with benzene. On evaporation of the solvent the product obtained crystallised from ether petroleum, m.p. 128°. Mixed m.p. with 4,6-dimethyl furo(3,2-c)quinoline described earlier was not depressed.

Ozonolysis of 6-methoxy-2-methyl-3-allyl-4-hydroxy-quinoline : 6-Methoxy-2-methyl-3-acetaldehydo-4-hydroxy-quinoline

6-Methoxy-2-methyl-3-allyl-4-hydroxyquinoline (1 g.) was dissolved in formic acid (30 ml.) and the solution was cooled to 15°. Ozone was passed through this solution for 1 hr.. It was then hydrogenated with palladised charcoal (0.5 g.; 5 %) with continuous stirring in the atmosphere of hydrogen at room temperature for 1.12 hr.. The reaction mixture was filtered and neutralised with sodium carbonate. The product which separated crystallised from ethyl acetate,

m.p. 235°. Yield 0.3 g.

Analysis : Found : C, 67.37; H, 5.56; N, 5.95 %.

$C_{13}H_{13}O_3N$ requires : C, 67.53; H, 5.62; N, 6.06 %.

8-Methoxy-4-methyl furo(3,2-c)quinoline :

6-Methoxy-2-methyl-3-acetaldehydo-4-hydroxyquinoline (0.5 g.) was treated with polyphosphoric acid (5 g. phosphorus pentoxide and 3 ml. of o-phosphoric acid) and heated on a water bath for 3 hr.. The reaction mixture was diluted with water and neutralised with sodium carbonate. The product which separated crystallised from ether petroleum, m.p. 81°. Yield 0.1 g.

Analysis : Found : C, 73.07; H, 4.88; N, 6.43 %.

$C_{13}H_{11}O_2N$ requires : C, 73.23; H, 5.16; N, 6.57 %.

The same furoquinoline was prepared for comparison as described below :

Reimer-Tiemann reaction on 6-methoxy-2-methyl-4-hydroxyquinoline : 6-Methoxy-2-methyl-3-formyl-4-hydroxyquinoline

6-Methoxy-2-methyl-4-hydroxyquinoline (5 g.) was treated with sodium hydroxide solution (50 ml. ; 25 %.) and chloroform (10 ml.). It was refluxed on a water bath for 10 hr. Chloroform was removed and the reaction mixture was diluted with water and filtered. The clear filtrate on acidification with acetic acid gave the product which crystallised from glacial acetic acid, m.p. 290°. Yield 2 g.

Analysis : Found : C, 66.18; H, 5.20; N, 6.71 %.

$C_{12}H_{11}O_3N$ requires : C, 66.35; H, 5.06; N, 6.45 %.

The 2,4-Dinitrophenylhydrazone

6-Methoxy-2-methyl-3-formyl-4-hydroxyquinoline (0.2 g.) was dissolved in glacial acetic acid (10 ml.) and then added to a solution of 2,4-dinitrophenylhydrazine (0.2 g.). in acetic acid (5 ml.). The product separated at once, was filtered and crystallised from glacial acetic acid, m.p. 320°.

Analysis : Found : N, 17.43 %.

$C_{18}H_{15}O_6N_5$ requires : N, 17.63 %.

Condensation of 6-methoxy-2-methyl-3-formyl-4-hydroxyquinoline with ethyl bromomalonate : 8-Methoxy-4-methyl-2-carboethoxy furo(3,2-c)quinoline

6-Methoxy-2-methyl-3-formyl-4-hydroxyquinoline (2.2 g.) was dissolved in ethyl methyl ketone (300 ml.) and refluxed with anhydrous potassium carbonate (5 g.) and ethyl bromomalonate (2.4 g.) for 35 hr. on a steam bath. The ethyl methyl ketone was removed and the reaction mixture was added to water. The separated product crystallised from benzene (charcoal), m.p. 182°. Yield 0.8 g.

Analysis : Found : C, 67.19; H, 5.11; N, 4.85 %.

$C_{16}H_{15}O_4N$ requires : C, 67.37; H, 5.26; N, 4.91 %.

8-Methoxy-4-methyl furo(3,2-c)quinoline-2-carboxylic acid

The above ester (1 g.) was treated with alcoholic potassium hydroxide solution (20 ml.; 10 %.) and left overnight. On working up as before the acid crystallised from alcohol, m.p. 277-8°. Yield 0.5 g.

Analysis : Found : C, 65.22; H, 4.10; N, 5.00 %.

$C_{14}H_{11}O_4N$ requires : C, 65.37; H, 4.28; N, 5.44 %.

(Analysed after heating in vacuum at 110° for 4 hrs.)

Decarboxylation of 8-methoxy-4-methyl furo(3,2-c) quinoline-2-carboxylic acid : 8-Methoxy-4-methyl furo (3,2-c)quinoline

The above acid (0.5 g.) was mixed with copper bronze (1 g.) and heated in an oil bath above its melting point (278°) with vacuum till the effervescence ceased (10 min.). On working up as before the product crystallised from ether petroleum, m.p. 81°. Mixed m.p. with 8-methoxy-4-methyl furo(3,2-c)quinoline described earlier was not depressed.

Condensation of 2-methyl-3-formyl-4-hydroxyquinoline with ethyl bromoacetate : 2-Methyl-3-formyl-4-carboethoxy-methoxyquinoline

2-Methyl-3-formyl-4-hydroxyquinoline (1.8 g.) was dissolved in ethyl methyl ketone (100 ml.) and refluxed with ethyl bromoacetate (1.6 g.) in the presence of anhydrous potassium carbonate (5 g.) for 12 hr. on a steam bath. The ethyl methyl ketone was removed and the reaction mixture was added to water. The product which separated crystallised from benzene, m.p. 189°. Yield 0.8 g.

Analysis : Found : C, 65.80; H, 5.45; N, 5.60 %.

$C_{15}H_{15}O_4N$ requires : C, 65.94; H, 5.49; N, 5.12 %.

Attempted hydrolysis of 2-methyl-3-formyl-4-carboethoxymethoxyquinoline : 2-Methyl-3-formyl-4-hydroxyquinoline

2-Methyl-3-formyl-4-carboethoxymethoxyquinoline (1 g.) was mixed with alcoholic sodium hydroxide solution

(20 ml.; 10 %) and left overnight. The resulting solution was neutralised with dilute hydrochloric acid and the product which separated crystallised from alcohol, m.p. 273°. Mixed m.p. with an authentic specimen of 2-methyl-3-formyl-4-hydroxyquinoline was not depressed.

Condensation of 2,8-dimethyl-3-formyl-4-hydroxyquinoline with ethyl bromoacetate : 2,8-Dimethyl-3-formyl-4-carboethoxymethoxyquinoline

2,8-Dimethyl-3-formyl-4-hydroxyquinoline (2 g.) was dissolved in ethyl methyl ketone (150 ml.) and refluxed with anhydrous potassium carbonate (5 g.) and ethyl bromoacetate (1.67 g.) for 12 hr. on a steam bath. The ethyl methyl ketone was removed and reaction mixture was added to water. The product which separated crystallised from benzene, m.p. 108°. Yield 0.8 g.

Analysis : Found : C, 67.11; H, 5.99; N, 4.83 %.

$C_{16}H_{17}O_4N$ requires : C, 67.38; H, 5.96; N, 4.91 %.

Attempted hydrolysis of 2,8-dimethyl-3-formyl-4-carboethoxymethoxyquinoline : 2,8-Dimethyl-3-formyl-4-hydroxyquinoline

2,8-Dimethyl-3-formyl-4-carboethoxymethoxyquinoline (1 g.) was mixed with alcoholic sodium hydroxide solution (20 ml.; 10 %) and left overnight. The resulting solution was neutralised with dilute hydrochloric acid and the product which separated crystallised from alcohol, m.p. 258°. Mixed m.p. with 2,8-dimethyl-3-formyl-4-hydroxyquinoline described earlier was not depressed.

Attempted ozonolysis of α-allylacetoacetanilide :

α-Propylacetoacetanilide

α-Allylacetoacetanilide (1 g.) was dissolved in ethyl acetate (40 ml.) and the solution was cooled to 15°. Ozone was passed through the solution for 45 minutes. It was then hydrogenated at room temperature with palladised charcoal (0.5 g.; 5 %) with continuous stirring in the atmosphere of hydrogen for 1.1/2 hr. The reaction mixture was filtered and the solvent was evaporated. The product separated as thick oil (0.5 g.)

4-Methyl-3-propylcarbostyril

The above oily product (0.5 g.) was heated with conc.sulphuric acid (2 ml.) on a water bath for 2 hr. The reaction mixture was added to water and neutralised with sodium carbonate. The product which separated crystallised from benzene, m.p. 175°. Yield 0.2 g.

Analysis : Found : C, 77.87; H, 7.20; N, 7.20 %

$C_{13}H_{15}ON$ requires : C, 77.60; H, 7.46; N, 6.96 %.

This was also obtained when α-allylacetoacetanilide (1 g.) was subjected to hydrogenation with palladised charcoal (0.5 g.; 5 %). followed by treatment with con.sulphuric acid (2 ml.).

α-Allylacetoacet-o-toluidide

Acetoacet-o- toluidide (3.8 g.) in dry benzene (50 ml.) was refluxed with pulverised sodium (0.46 g.) on a water bath for 5 hr. To this was added allyl bromide (2.4 g.) and the

reaction mixture was refluxed further for 6 hr. It was poured in water and benzene layer was separated and dried with anhydrous calcium chloride. Removal of the solvent gave the product which crystallised from ether petroleum, m.p. 90°. Yield 2.5 g.

Analysis : Found : : C, 72.63; H, 7.27; N, 6.47 %.

$C_{14}H_{17}O_2N$ requires : C, 72.73; H, 7.35; N, 6.06 %.

α-Propylacetoacet-o- toluidide

α-Allylacetoacet-o-toluidide (1 g.) was dissolved in ethyl acetate (30 ml.) and the solution was stirred with palladised charcoal (0.5 g.; 5 %.) in the atmosphere of hydrogen for 1.1/2 hr. Removal of the solvent after filteration gave the product which crystallised from ether petroleum, m.p. 97°. Yield 0.5 g.

Analysis : Found : C, 71.91; H, 8.14; N, 5.71 %.

$C_{14}H_{19}O_2N$ requires : C, 72.05; H, 8.15; N, 6.00 %.

4,8-Dimethyl-3-propylcarbostyril :

The above α-propyl derivative (0.8 g.) was heated on a water bath with con. sulphuric acid (2 ml.) for 2 hr. It was poured in ice water and neutralised with sodium carbonate. The product which separated crystallised from benzene, m.p. 187°. Yield 0.2 g.

Analysis: Found : C, 78.02; H, 7.70; N, 6.16 %.

$C_{14}H_{17}ON$ requires : C, 78.13; H, 7.90; N, 6.51 %.

α-Allylacetoacet-p-anisidide :

Acetoacet-p-anisidide (4.1 g.) in dry benzene (50 ml.) was refluxed with pulverised sodium (0.46 g.) for 6 hr. on a

water bath. Allyl bromide (2.4 g.) was added and the reaction mixture was refluxed further for 8 hr. On working up as before the product crystallised from benzene petroleum ether mixture (1:2), m.p. 99°. Yield 2.5 g.

Analysis: Found : C, 67.92; H, 6.55; N, 5.70 %.

$C_{14}H_{17}O_3N$ requires : C, 68.01; H, 6.88; N, 5.66 %.

α-Propylacetoacet-p-anisidide

α-Allylacetoacet-p-anisidide (1 g.) was dissolved in ethyl acetate (40 ml.) and was stirred with palladised charcoal (0.5 g.; 5 %.) in the atmosphere of hydrogen for 1 hr. The product obtained on evaporation of the clear filtrate, crystallised from ether petroleum, m.p. 80°. Yield 0.5 g.

Analysis : Found : C, 67.67; H, 7.39; N, 5.98 %.

$C_{14}H_{19}O_3N$ requires : C, 67.46; H, 7.67; N, 5.62 %.

6-Methoxy-4-methyl-3-propylcarbostyril :

The above α-propyl derivative (0.5 g.) was heated with con.sulphuric acid (1 ml.) on a water bath for 1 hr. On working up as before the product crystallised from benzene, m.p. 195°. Yield 0.1 g.

Analysis : Found : C, 72.53; H, 7.19; N, 5.80 %.

$C_{14}H_{17}O_2N$ requires : C, 72.73; H, 7.35; N, 6.06 %.

2,3-Dihydro-2,4,8-trimethyl furo(2,3-b)quinoline

α-Allylacetoacet-o-toluidide (1 g.) described earlier was heated with con.sulphuric acid (2 ml.) on a water bath for 1 hr. The reaction mixture was added to water and the solution made alkaline with sodium hydroxide. The product

which separated crystallised from ether petroleum, m.p. 107°. Yield 0.3 g.

Analysis : Found : C, 78.70; H, 7.53; N, 6.10 %.

$C_{14}H_{15}ON$ requires : C, 78.87; H, 7.04; N, 6.57 %.

α-Allylacetoacet-α-naphthylamide :

Acetoacet-α-naphthylamide (4.4 g.) in dry benzene (50 ml.) was refluxed on a water bath with pulverised sodium (0.46 g.) for 3 hr. Allyl bromide (2.4 g.) was added and the reaction mixture was refluxed further for 6 hr. On working up as before the product crystallised from benzene, m.p. 117°. Yield 2 g.)

Analysis : Found : C, 76.03:, H, 6.71; N, 5.21 %.

$C_{17}H_{17}O_2N$ requires : C, 76.40; H, 6.36; N, 5.24 %.

2,3-Dihydro-2,4-dimethyl-benzo(h) furo(2,3-b)quinoline

The above α-allyl derivative (0.5 g.) was heated on a water bath with con.sulphuric acid (1 ml.) for 2 hr. On working up as before the product crystallised from ether petroleum, m.p. 145°. Yield 0.2 g.

Analysis : Found : C, 81.85; H, 6.16; N, 5.28 %.

$C_{17}H_{15}ON$ requires : C, 81.91; H, 6.02; N, 5.62 %.

α-Allylacetoacet-p-xylidide :

Acetoacet-p-xylidide (4.1 g.) in dry benzene (50 ml.) was refluxed on a water bath with pulverised sodium (0.5 g.) for 4 hr. Allyl bromide (2.4 g.) was added and the reaction mixture was refluxed further for 6 hr. On working up as before the product crystallised from benzene petroleum

ether mixture (1:1), m.p. 128°. Yield 2.5 g.

Analysis : Found : C, 73.18; H, 7.54; N, 5.75 %.

$C_{15}H_{19}O_2N$ requires : C, 73.46; H, 7.75; N, 5.71 %.

2,3-Dihydro-2,4,5,8-tetramethyl furo(2,3-b)quinoline

Theaabove α-allyl derivative (0.5 g.) was heated with con.sulphuric acid (1 ml.) on a water bath for 1 hr. On working up as before the product crystallised from benzene petroleum ether mixture (1:1), m.p. 147°. Yield 0.2 g.

Analysis : Found : C, 79.27; H, 7.21; N, 5.75 %.

$C_{15}H_{17}ON$ requires : C, 79.29; H, 7.48; N, 6.16 %.

6-Methoxy-2,3-dihydro-2,4-dimethyl furo(2,3-b)quinoline

α-Allylacetoacet-p-anisidide (o.5 g.) described earlier was heated on a water bath with con.sulphuric acid (1 ml.) for 1 hr. On working up as before the product crystallised from ether petroleum, m.p. 122°. Yield 0.1 g.

Analysis : Found : C, 73.18; H, 6.44; N, 5.93 %.

$C_{14}H_{15}O_2N$ requires : C, 73.35; H, 6.55; N, 6.11 %.

α-Allylacetoacet-p-chloroanilide :

Acetoacet-p-chloroanilide (4.2 g.) in dry benzene (50 ml.) was refluxed with pulverised sodium (0.46 g.) on a water bath for 6 hr. Allyl bromide (2.4 g.) was added and the reaction mixture was refluxed further for 8 hr. On working up as before the product crystallised from ether petroleum, m.p. 95°. Yield 2.5 g.

Analysis : Found : C, 61.90; H, 5.41; N, 5.69 %.

$C_{13}H_{14}O_2NCl$ requires: C, 62.01; H, 5.56; N, 5.56 %.

6-Chloro-2,3-dihydro-2,4-dimethyl furo(2,3-b)quinoline

The above α-allyl derivative (1 g.) was heated on a water bath with con.sulphuric acid (2 ml.) for 1 hr. On working up as before the product crystallised from ether petroleum, m.p. 130°. Yield 0.3 g.

Analysis : Found : C, 66.68; H, 4.78; N, 5.66 %.

$C_{13}H_{12}ONCl$ requires : C, 66.80; H, 5.13; N, 5.99 %.

2,3-Dihydro-2,4,6-trimethyl furo(3,2-c)quinoline

2,8-Dimethyl-3-allyl-4-hydroxyquinoline (0.5 g.) described earlier was heated on a water bath with con. sulphuric acid (1 ml.) for 1 hr. On working up as before the product crystallised from ether petroleum, m.p. 68°. Yield 0.2 g.

Analysis : Found : C, 78.57; H, 6.80; N, 6.13 %.

$C_{14}H_{15}ON$ requires : C, 78.87; H, 7.04; N, 6.57 %.

2-Methyl-4-allyloxy-7,8-benzoquinoline

2-Methyl-4-hydroxy-7,8-benzoquinoline (3 g.) was dissolved in ethyl methyl ketone (200 ml.) and refluxed with allyl bromide (1.8 g.) in the present of anhydrous potassium carbonate (8 g.) on a water bath for 8 hr. The ethyl methyl ketone was removed and the reaction mixture was added to water. The product which separated crystallised from ether petroleum, m.p. 80°. Yield 1.2 g.

Analysis : Found : C, 81.47; H, 6.41; N, 5.45 %.

$C_{17}H_{15}ON$ requires : C, 81.91; H, 6.02; N, 5.62 %.

2-Methyl-3-allyl-4-hydroxy-7,8-benzoquinoline

The above 4-allyloxy derivative (1 g.) was heated

in an oil bath at 200-10° for 30 minutes. The product after cooling and washing with benzene was crystallised from dilute acetic acid (charcoal), m.p. 289°. Yield 0.6 g.

Analysis : Found : C, 81.66; H, 6.26; N, 5.12 %.

$C_{17}H_{15}ON$ requires : C, 81.91; H, 6.02; N, 5.62 %.

2,3-Dihydro-2,4-dimethyl-benzo(h) furo(3,2-c)quinoline

The above 3-allyl derivative (0.5 g.) was heated on a water bath with con.sulphuric acid (1 ml.) for 1 hr. On working up as before the product crystallised from ether petroleum, m.p. 128°. Yield 0.2 g.

Analysis : Found : C, 81.43; H, 5.63; N, 5.18 %.

$C_{17}H_{15}ON$ requires : C, 81.91; H, 6.02; N, 5.62 %.

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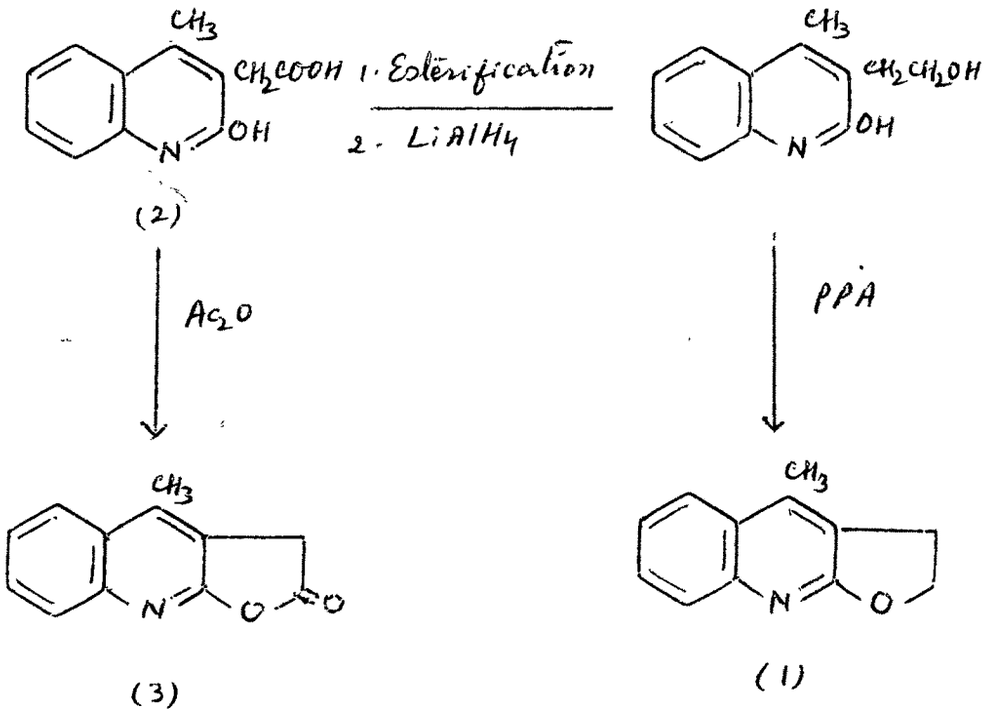
CHAPTER I

Section II

Synthesis of quinolino-lactones and pyranoquinolines

Theoretical

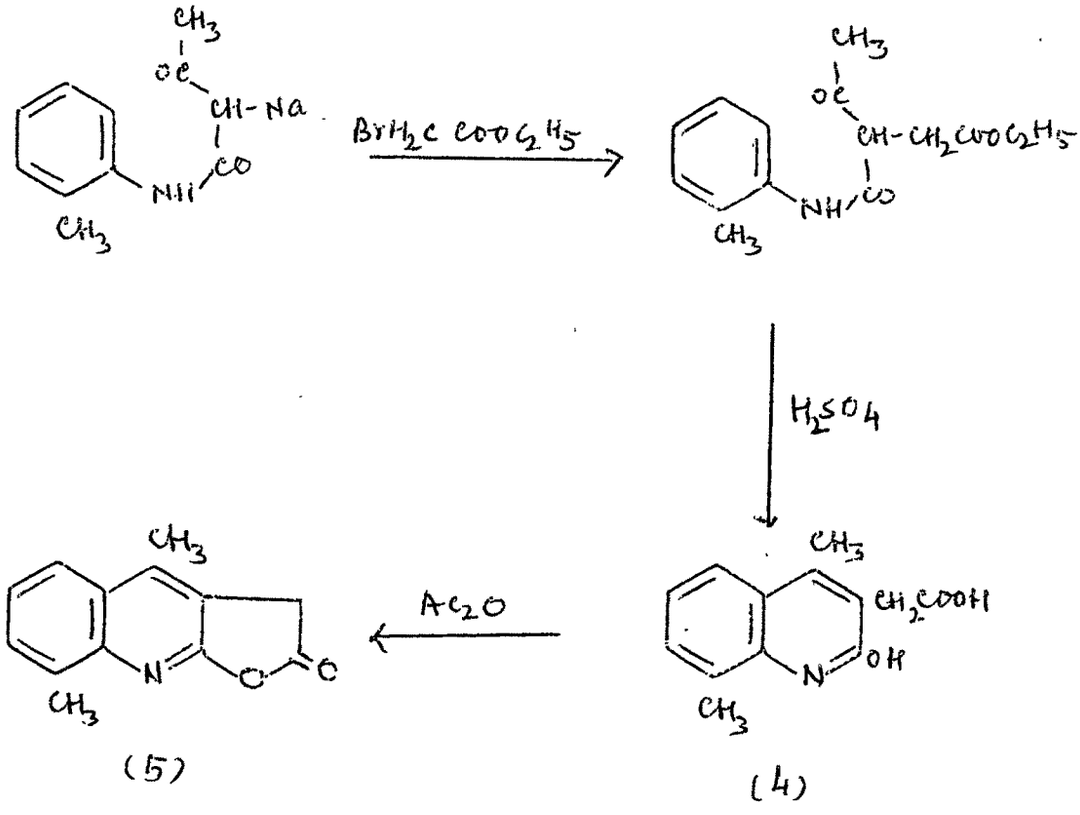
Naturally occurring furoquinoline alkaloids are furo(2,3-b)quinoline derivatives with unsubstituted furan ring. An attempt to prepare such furoquinolines met with failure as ozonolysis of α-allylacetoacetanilide did not succeed. Raman[1] synthesised 2,3-dihydro-4-methyl-furo (2,3-b)quinoline (1) from 4-methyl-2-hydroxyquinoline-3-acetic acid (2). Cyclisation of (2) with acetic anhydride gave a lactone of 4-methyl-2-hydroxyquinoline-3-acetic acid (3). It was therefore, thought of interest to prepare a series of quinoline-3-acetic acid derivatives having



different substituents in the benzene nucleus and convert them into lactone of 4-methyl-2-hydroxyquinoline-3-acetic acid derivatives and 2,3-dihydro-4-methyl furo(2,3-b). quinoline derivatives. As dehydrogenation of dihydro furoquinoline derivatives was unsuccessful and the yield in the reduction of ester of quinoline-3-acetic acid derivative was very poor, the furo(2,3-b)quinoline derivatives could not be synthesised. Therefore, the present investigation describes only the synthesis of lactone of 4-methyl-2-hydroxyquinoline-3-acetic acid derivatives.

Lactone of 4,8-dimethyl-2-hydroxyquinoline-3-acetic acid

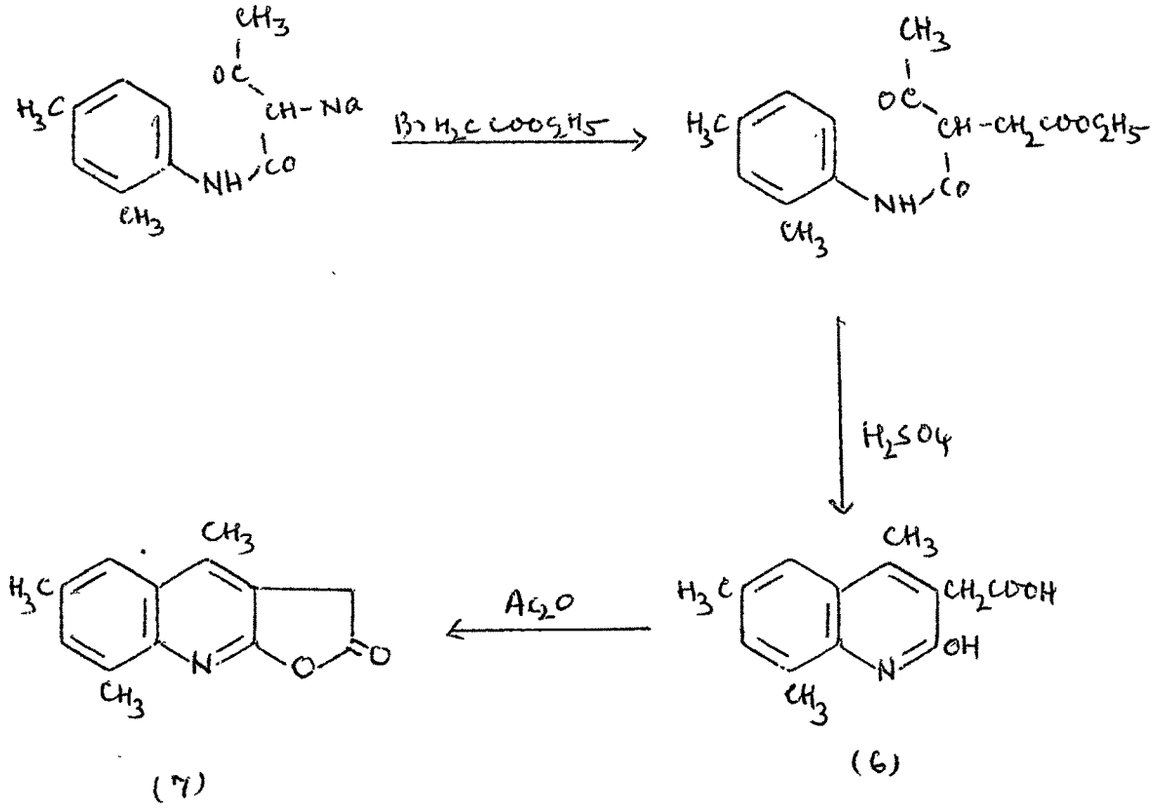
Sodium salt of acetoacet-o-toluidide on condensation with ethyl bromoacetate gave α-carboethoxymethylacetoacet-

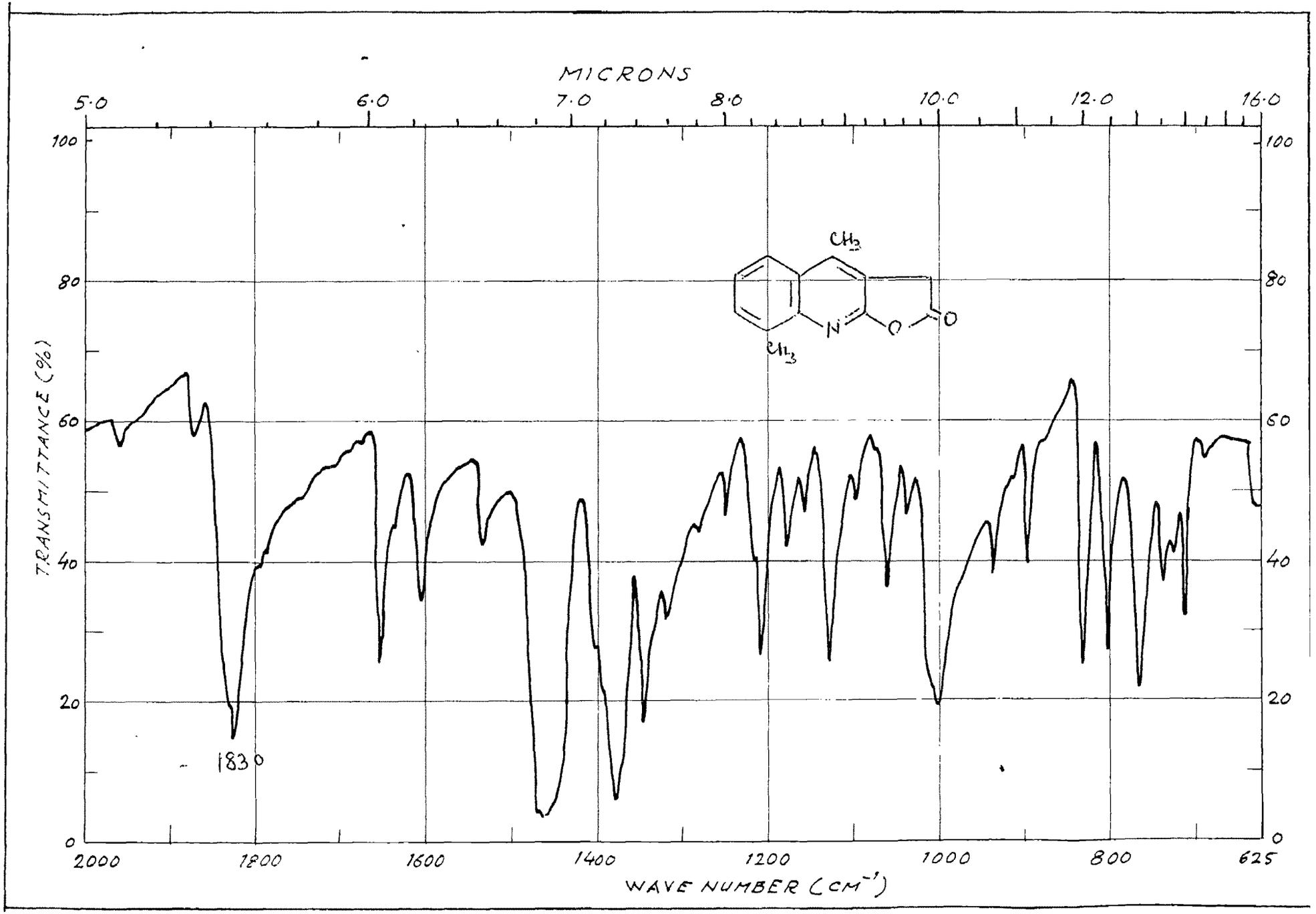


o- toluidide which was then cyclised with concentrated sulphuric acid to 4,8-dimethyl-2-hydroxyquinoline-3-acetic acid (4). This on heating with acetic anhydride in an oil bath at 110° gave a lactone of 4,8-dimethyl-2-hydroxyquinoline-3-acetic acid (5). IR spectrum showed a characteristic lactonyl carbonyl band at 1830 cm^{-1}.

Lactone of 4,6,8-trimethyl-2-hydroxyquinoline-3-acetic acid

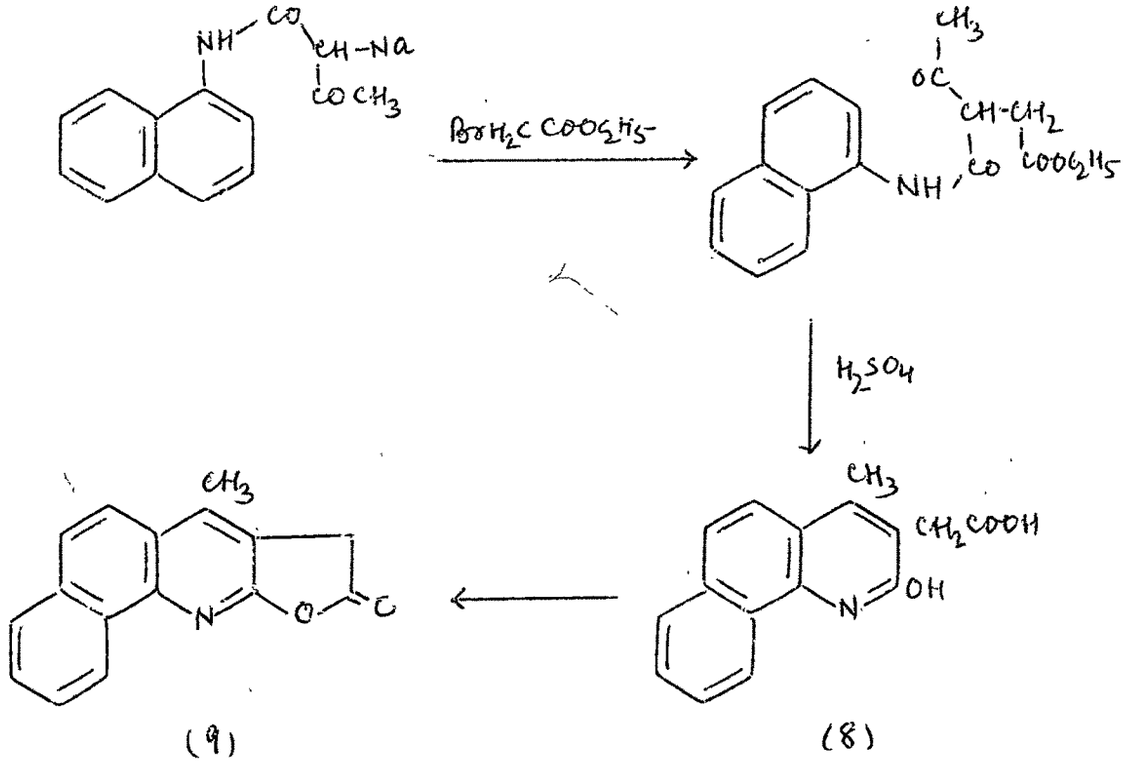
Sodium salt of acetoacet-m-xylidide on condensation with ethyl bromoacetate gave α-carboethoxymethylacetoacet-m-xylidide which on cyclisation with concentrated sulphuric acid gave 4,6,8-trimethyl-2-hydroxyquinoline-3-acetic acid (6). This on heating with acetic anhydride gave a lactone of 4,6,8-trimethyl-2-hydroxyquinoline-3-acetic acid (7).




MICRONS
5·0
6·0
7·0
8·0
10·0
12·0
16·0
100
80
60
40
20
0
TRANSMITTANCE (%)
1830
2000
1800
1600
1400
1200
1000
800
625
WAVE NUMBER (CM⁻¹)
CH₃
CH₃
N
O
O

Lactone of 4-methyl-2-hydroxy-7,8-benzoquinoline-3-acetic acid

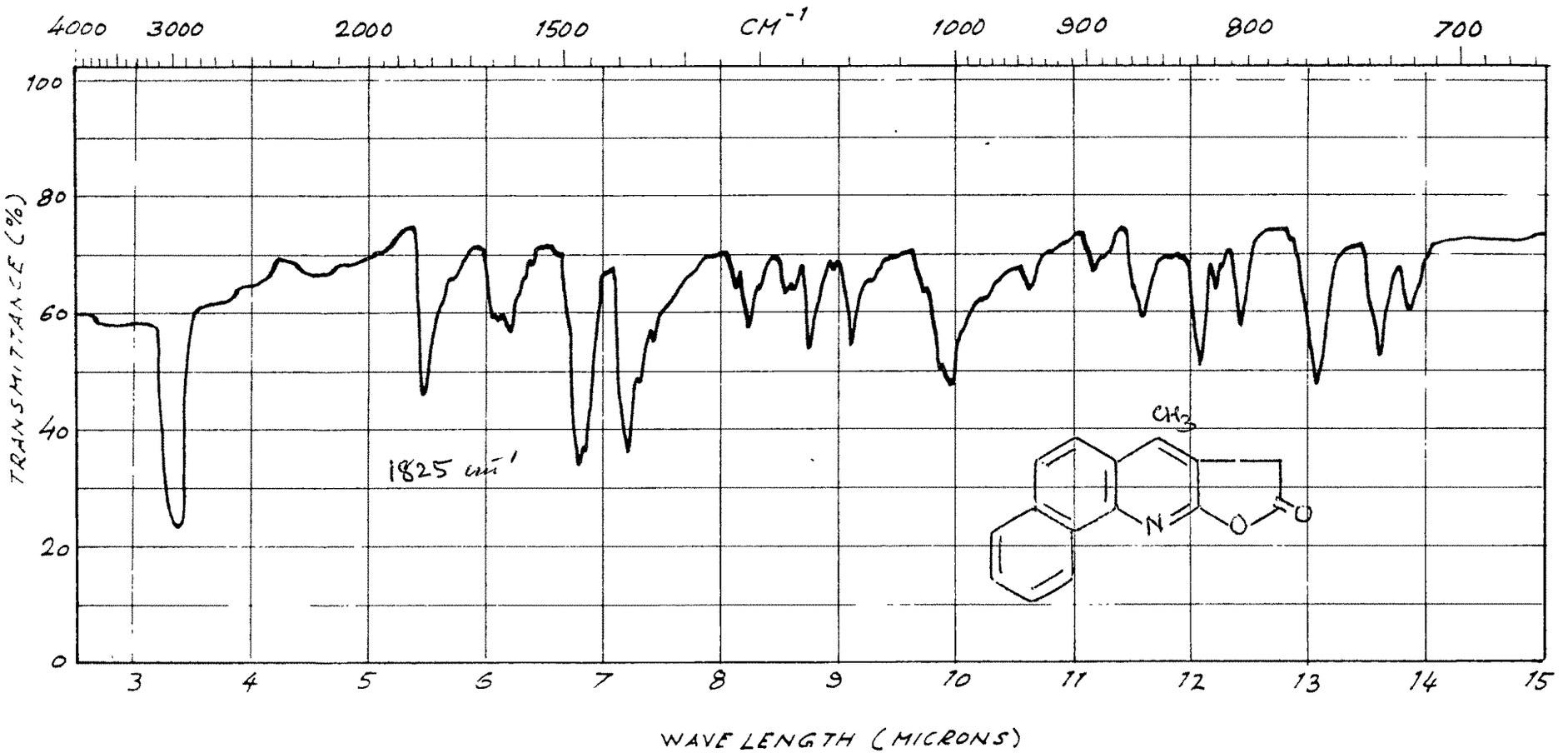
Sodium salt of acetoacet-α-naphthylamide on condensation with ethyl bromoacetate gave α-carboethoxymethylacetoacet-α-naphthylamide. This on cyclisation with concentrated sulphuric acid afforded 4-methyl-2-hydroxy-7,8-benzoquinoline-3-acetic acid (8), which on heating with acetic anhydride yielded a lactone of 4-methyl-2-hydroxy-7,8-benzoquinoline-3-acetic acid (9). IR spectrum showed a characteristic lactonyl carbonyl band at 1825cm^{-1}



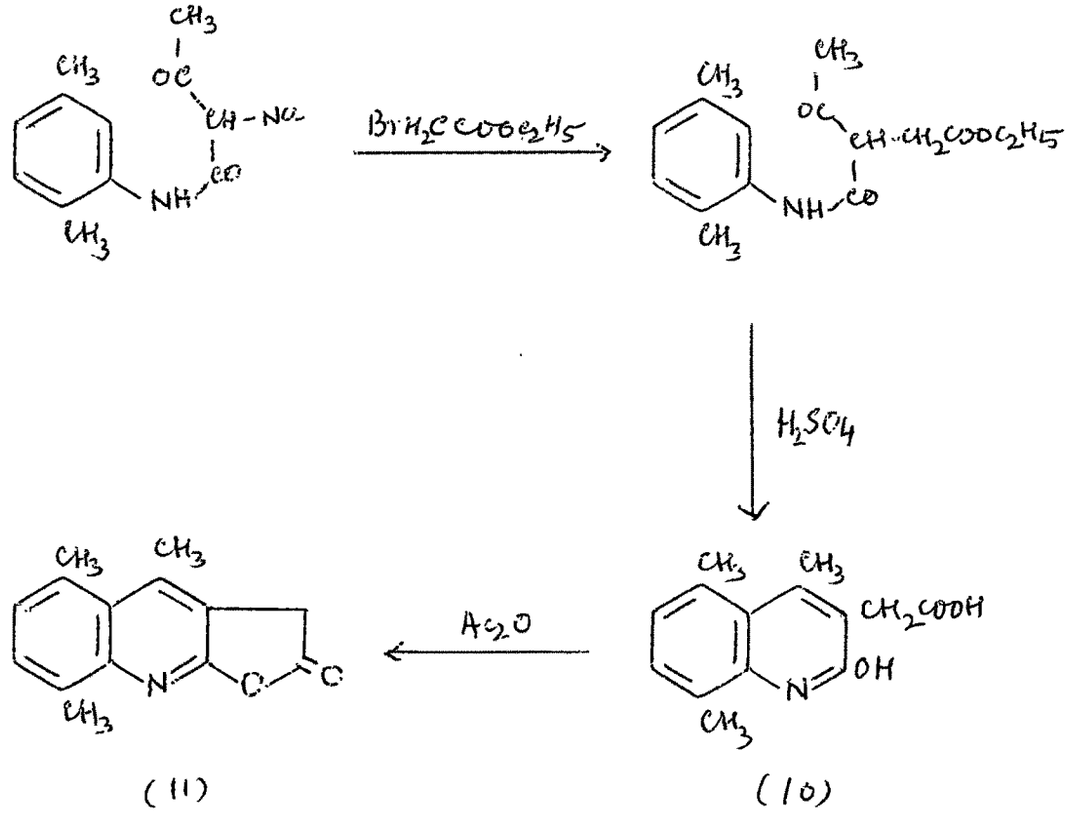
(9) (8)

Lactone of 4,5,8-trimethyl-2-hydroxyquinoline-3-acetic acid

Sodium salt of acetoacet-p-xylidide on condensation with ethyl bromoacetate gave α-carboethoxymethylacetoacet-

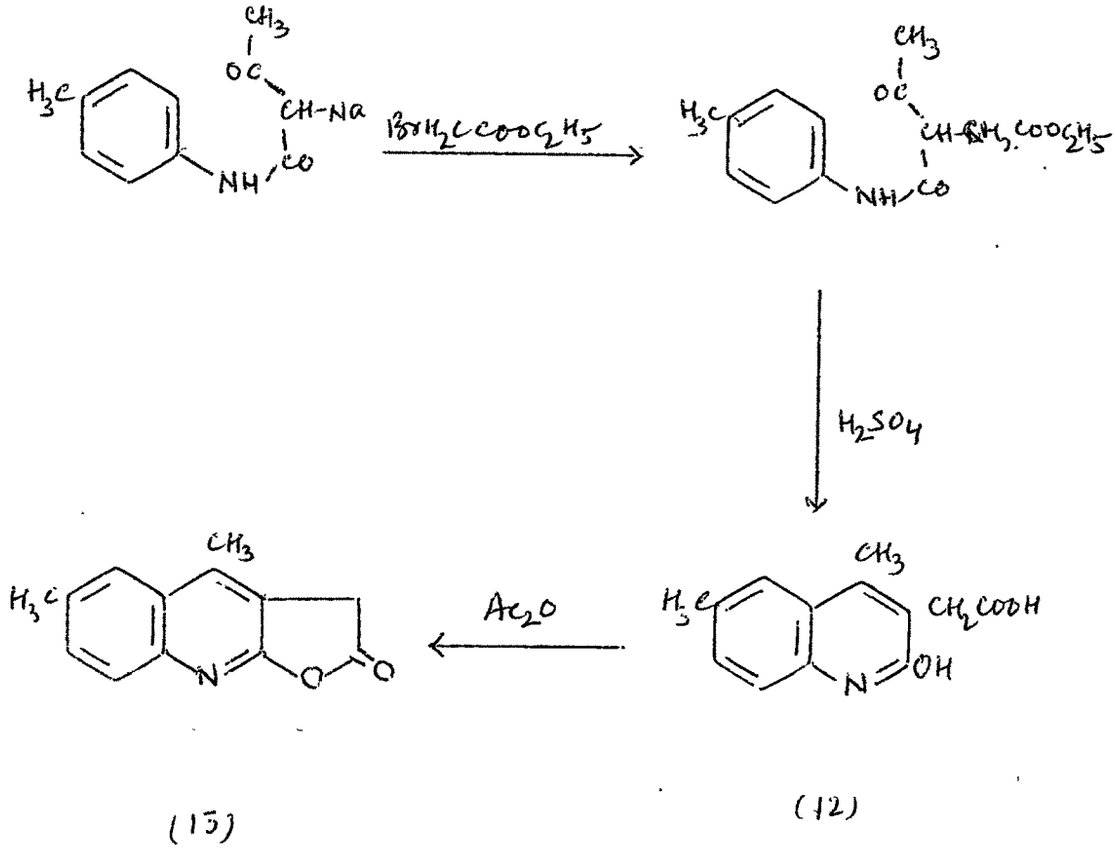

4000
3000
2000
1500
CM⁻¹
1000
900
800
700
100
80
60
40
20
0
TRANSMITTANCE (%)
1825 cm⁻¹
CH3
N
O
O
3
4
5
6
7
8
9
10
11
12
13
14
15
WAVE LENGTH (MICRONS)

p-xylidide. This on cyclisation with concentrated sulphuric acid gave 4,5,8-trimethyl-2-hydroxyquinoline-3-acetic acid (10) which on heating with acetic anhydride gave a lactone of 4,5,8-trimethyl-2-hydroxyquinoline-3-acetic acid (11).



Lactone of 4,6-dimethyl-2-hydroxyquinoline-3-acetic acid

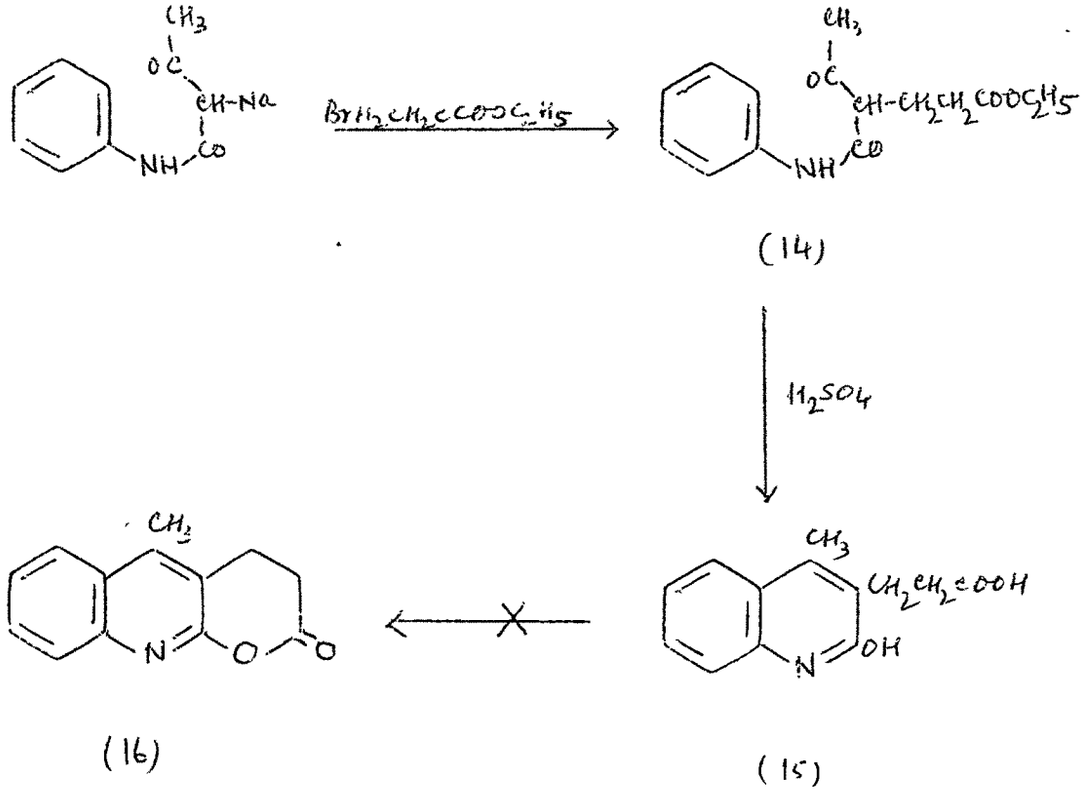
Sodium salt of acetoacet-p-toluidide on condensation with ethyl bromoacetate gave α-carboethoxymethylacetoacet-p-toluidide. This on cyclisation with concentrated sulphuric acid gave 4,6-dimethyl-2-hydroxyquinoline-3-acetic acid (12) which on heating with acetic anhydride gave a lactone of 4,6-dimethyl-2-hydroxyquinoline-3-acetic acid (13).



(15) (12)

Condensation of sodium salt of acetoacetanilide with ethyl bromopropionate

It was also thought of interest to prepare lactones having 6 membered ring by introducing one more methylene group. To prepare this, ethyl bromopropionate was condensed with sodium salt of acetoacetanilide. α-Carboethoxyethyl-acetoacetanilide (14) was obtained and cyclised with concentrated sulphuric acid to 4-methyl-2-hydroxyquinoline-3-propionic acid (15). Cyclisation of (15) to a lactone of 4-methyl-2-hydroxyquinoline-3-propionic acid (16) with acetic anhydride, acetic anhydride and fused sodium acetate or polyphosphoric acid was unsuccessful.

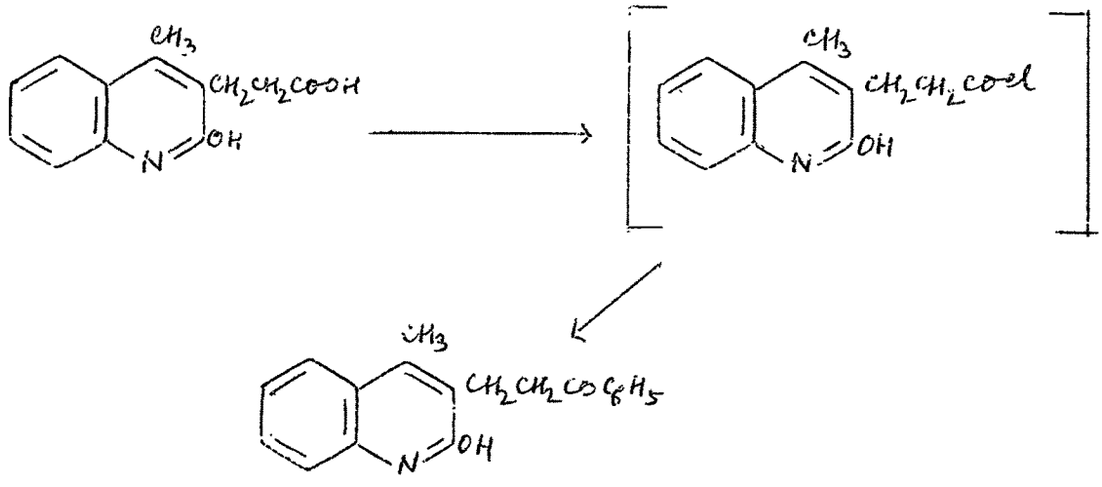


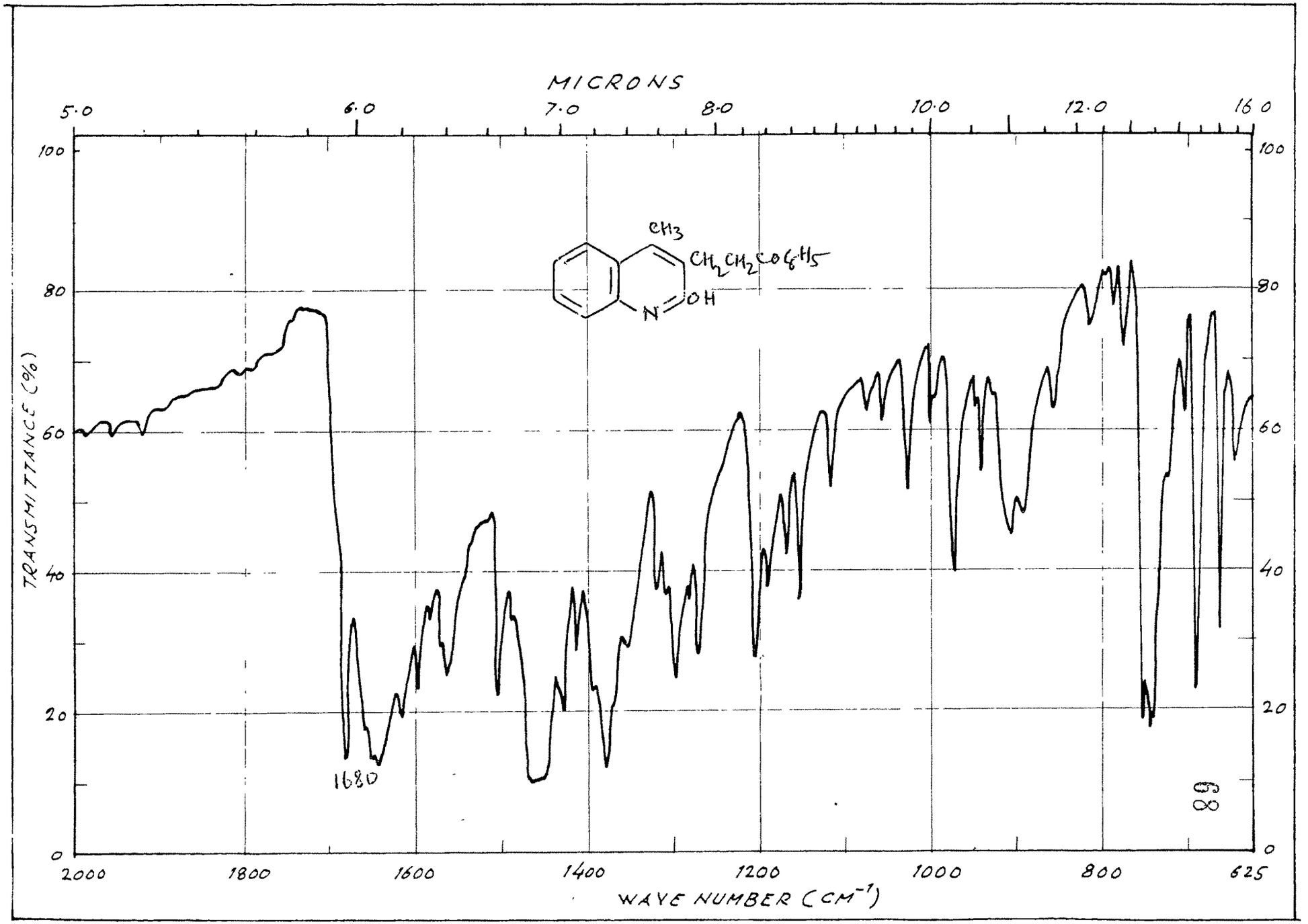
(14)

(16)

(15)

In an attempt to cyclise (15) with thionyl chloride followed by treatment with anhydrous aluminium chloride in dry benzene, the product obtained was assigned (4-methyl-2-hydroxy-3-quinolyl) ethyl phenyl ketone (17) structure on the basis of analytical results. IR spectrum (nujol)

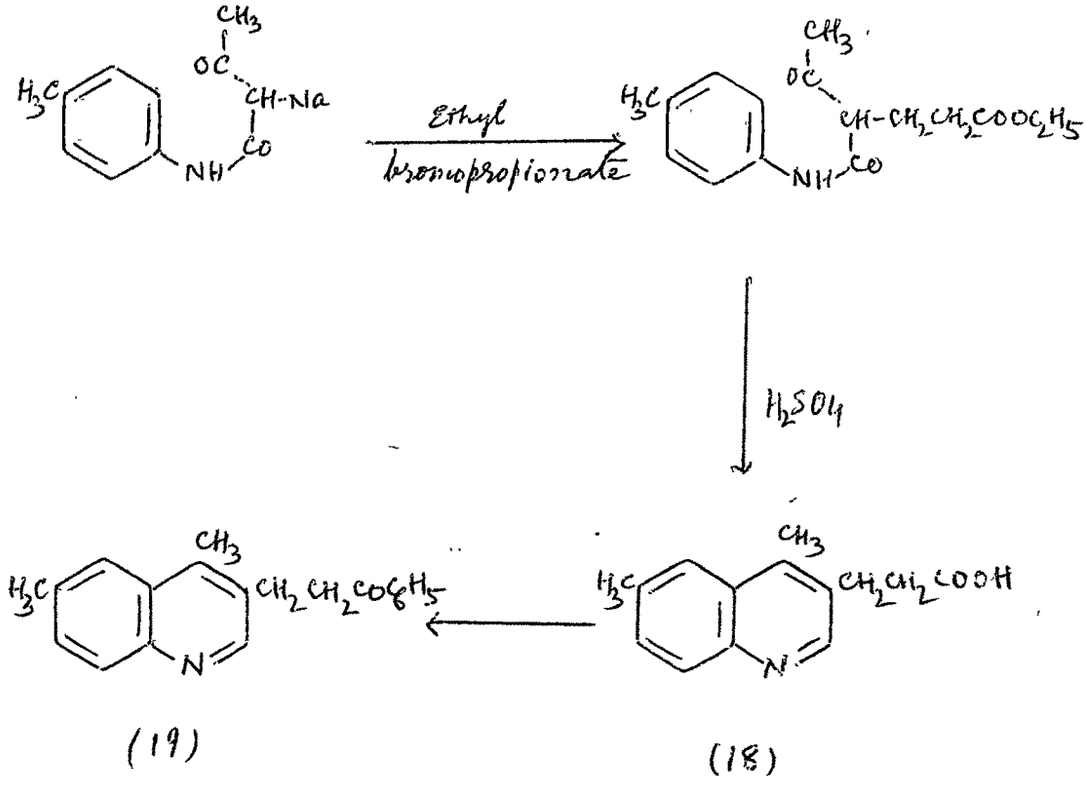



MICRONS
5·0
6·0
7·0
8·0
10·0
12·0
16 0
100
80
60
40
20
0
TRANSMITTANCE (%)
CH3
CH2CH2CO6H5
OH
N
1680
2000
1800
1600
1400
1200
1000
800
625
WAVE NUMBER (CM-1)
88

showed a characteristic carbonyl band at 1680 cm^{-1}. Thus it indicated that the cyclisation did not take place but instead Friedel-Craft reaction took place between benzene and acid chloride.

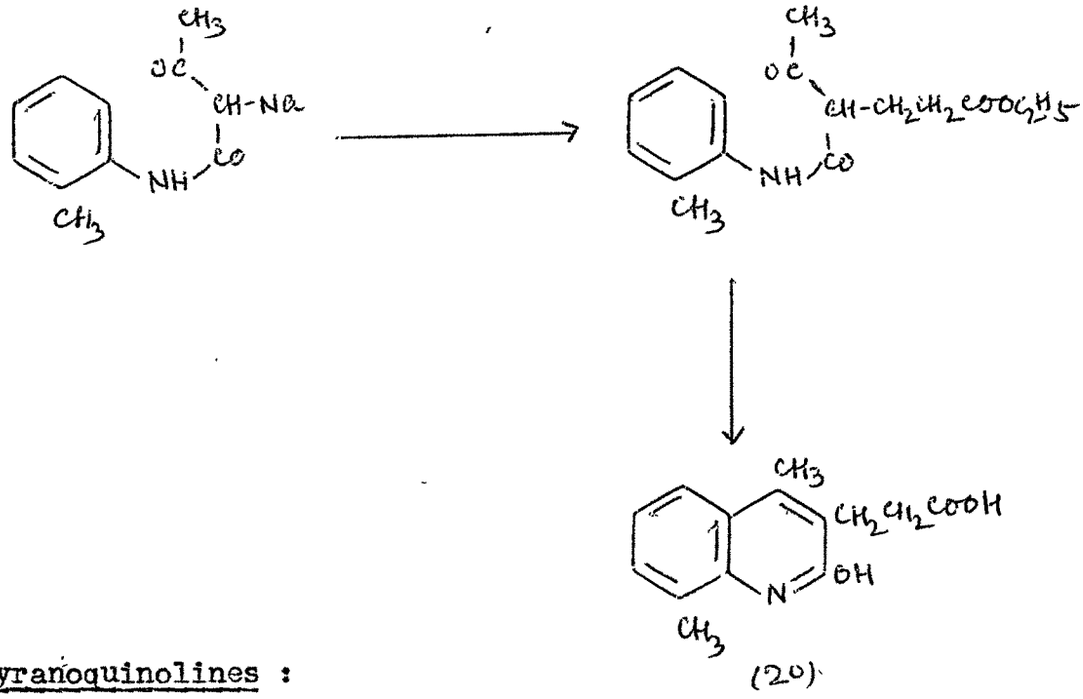
(4,6-Dimethyl-2-hydroxy-3-quinolyl) ethyl phenyl ketone

Sodium salt of acetoacet-p-toluidide on condensation with ethyl bromopropionate gave α-carboethoxyethylacetoacet-p-toluidide which on cyclisation with concentrated sulphuric acid gave 4,6-dimethyl-2-hydroxyquinoline-3-propionic acid (18). This on treatment with thionyl chloride followed by benzene and anhydrous aluminium chloride gave (4,6-dimethyl-2-hydroxy-3-quinolyl) ethyl phenyl ketone (19).



4,8-Dimethyl-2-hydroxyquinoline-3-propionic acid

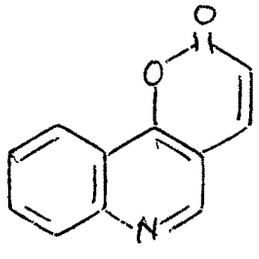
Sodium salt of acetoacet-o-toluidide on condensation with ethyl bromopropionate afforded α-carboethoxyethylacetoacet-o-toluidide. This on cyclisation with con.sulphuric acid gave 4,8-dimethyl-2-hydroxyquinoline-3-propionic acid (20).



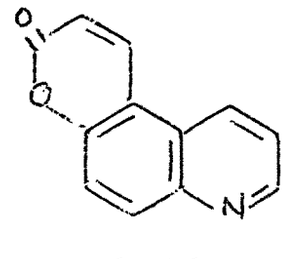
(20)

Pyranoquinolines :

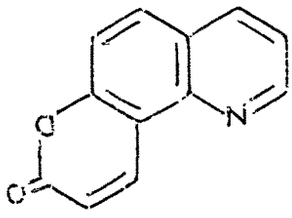
If an α-pyrone ring is build on a suitably substituted quinoline derivative, it leads to the synthesis of pyranoquinolines. Alternatively, one can start with an appropriate coumarin derivative and build up the quinoline ring on it. The following pyranoquinolines are found in the literature.



Type I



Type II



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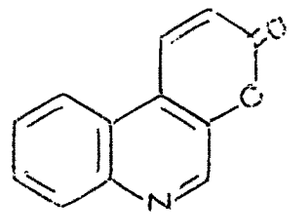
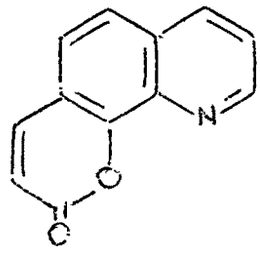
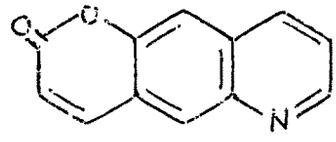


type IV



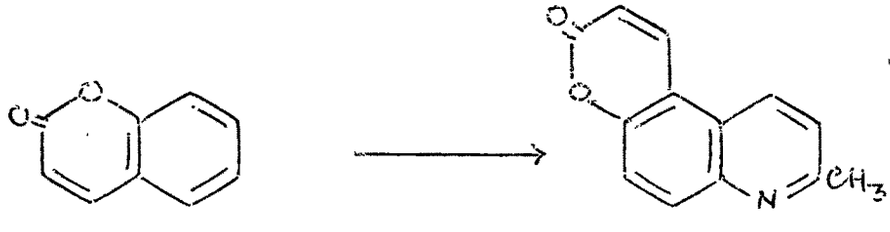
type V



type VI

The methods of synthesis of pyranoquinolines are briefly reviewed here.

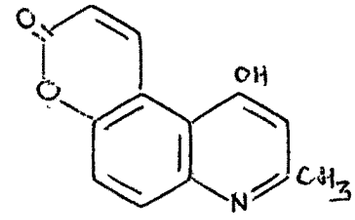
Dey, Sarkar and Seshadri[2] synthesised 2-methyl-quinolino-6,5,a-pyrone (21) [8-methyl-3-oxo-3H-pyrano(3,2-f)



(21)

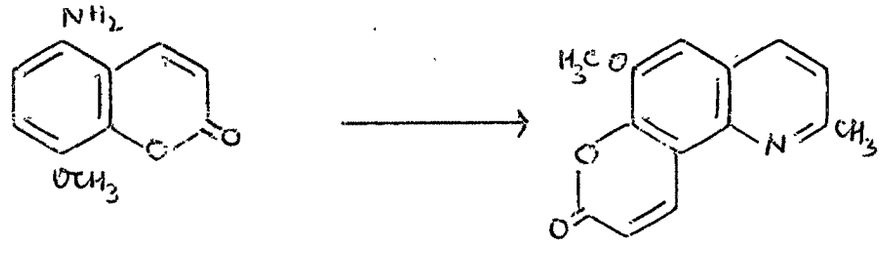
quinoline] by reacting 6-aminocoumarin with paraldehyde in the presence of hydrochloric acid.

Chakravarti, Ahuja and Siddiqui[3] prepared ethyl β-(2-oxo-1,2H-benzopyran-2-ylamino) crotonate by warming 6-aminocoumarin with ethylacetoacetate and a drop of hydrochloric acid. This when cyclised in paraffin preheated to 260° gave 4-hydroxyquinaldino-6,5-α-pyrone (22) [8-methyl-10-hydroxy-3-oxo-3H-pyrano(3,2-f)quinoline] .



(22)

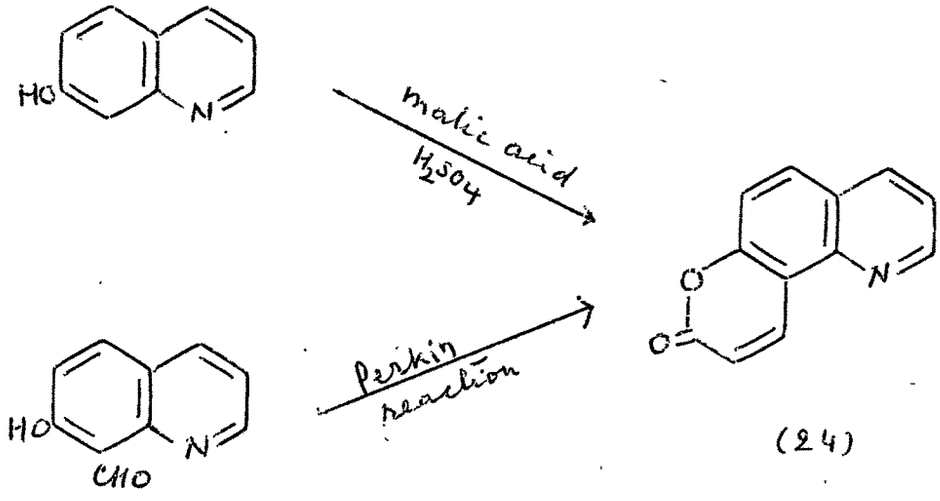
Dey and Ammalkutti[4] prepared 2-methylquinolino-7,8-α-pyrone (23) [6-methoxy-2-methyl-8-oxo-8H-pyrano(2,3-h) quinoline] from 5-amino-8-methoxy coumarin and paraldehyde.



(23)

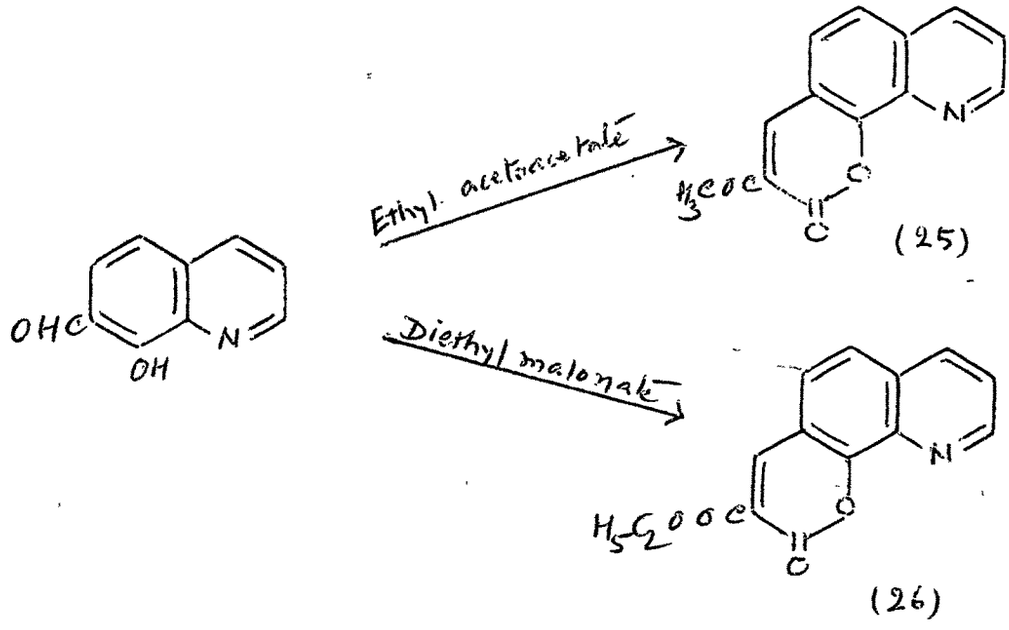
Bobranski and Kochanska[5] carried out the condensation of 7-hydroxyquinoline with malic acid in the presence of conc. sulphuric acid and obtained 2',3'-pyrido-5,6-coumarin (24) [8-oxo-8H-pyrano(2,3-h)quinoline] which was also prepared

from 7-hydroxy-8-formylquinoline by Perkin reaction.



(24)

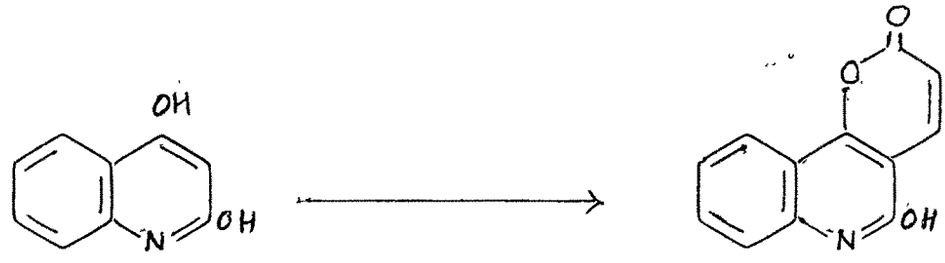
Fiedler[6] synthesised 3-acetyl-2-oxo-2H-pyrano (3,2-h)quinoline (25) and 3-carboethoxy-2-oxo-2H-pyrano-(3,2-h)quinoline (26) from 8-hydroxy-7-formylquinoline with ethylacetoacetate and diethyl malonate in the presence of piperidine respectively.



(25)

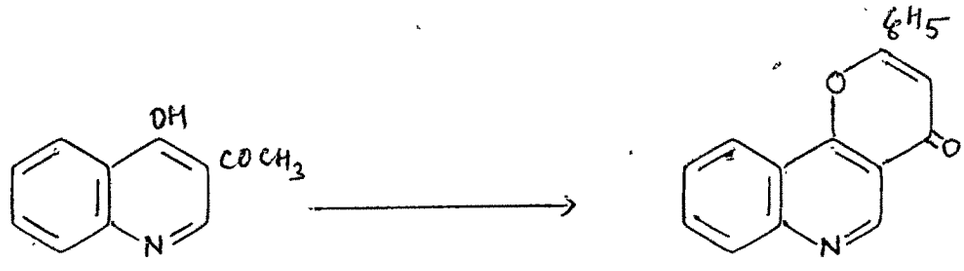
(26)

Brown et al[7] carried out the Pechmann reaction on 2,4-dihydroxyquinoline with malic acid in the presence of conc. sulphuric acid and obtained 5-hydroxy-2-oxo-2H-pyrano (3,2-c)quinoline (27).



(27)

Elliott and Tittensor[8] synthesised 4'-oxo-6'-phenyl pyrano(3':2'-3:4)quinoline (28)[2-phenyl-4-oxo-4H-pyrano (3,2-c)quinoline] from 3-acetyl-4-hydroxyquinoline by application of Kostanecki-Robinson reaction with benzoic anhydride and triethylamine.



(28)

The present work deals with the synthesis of the following pyranoquinoline derivatives from 2-methyl-3-formyl-4-hydroxyquinoline derivatives which were prepared for the synthesis of furo(3,2-c)quinoline derivatives.

(a) 5-Methyl-2-oxo-2H-pyrano(3,2-c)quinoline (29),

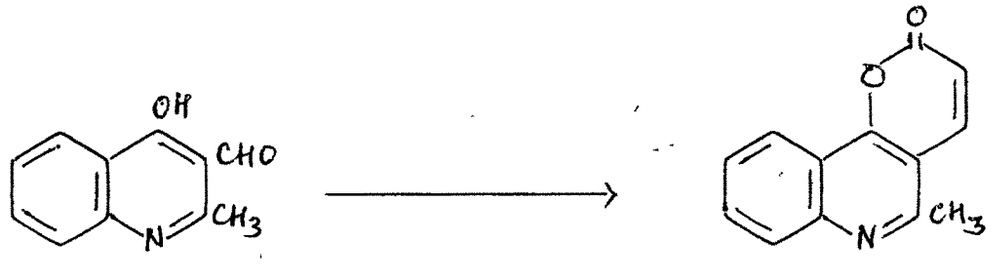
(b) 5-Methyl-3-phenyl-2-oxo-2H-pyrano(3,2-c)quinoline (30),

(c) 5,7-Dimethyl-2-oxo-2H-pyrano(3,2-c)quinoline (31),

(d) 5,7-Dimethyl-3-phenyl-2-oxo-2H-pyrano(3,2-c)quinoline (32).

(a) 5-Methyl-2-oxo-2H-pyrano(3,2-c)quinoline

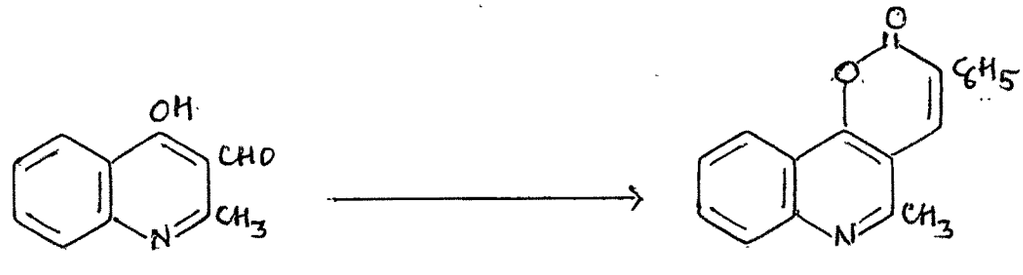
2-Methyl-3-formyl-4-hydroxyquinoline was subjected to Perkin reaction using acetic anhydride and triethylamine. The product obtained was assigned 5-methyl-2-oxo-2H-pyrano (3,2-c)quinoline (29) structure on the basis of analytical results which was also supported by IR spectrum. IR spectrum showed a characteristic lactonyl carbonyl band at 1725 cm^{-1}.



(29)

(b) 5-Methyl-3-phenyl-2-oxo-2H-pyrano(3,2-c)quinoline

2-Methyl-3-formyl-4-hydroxyquinoline on treatment with acetic anhydride, phenylacetic acid and triethylamine gave a product to which 5-methyl-3-phenyl-2-oxo-2H-pyrano (3,2-c)quinoline (30) structure was assigned on the basis of



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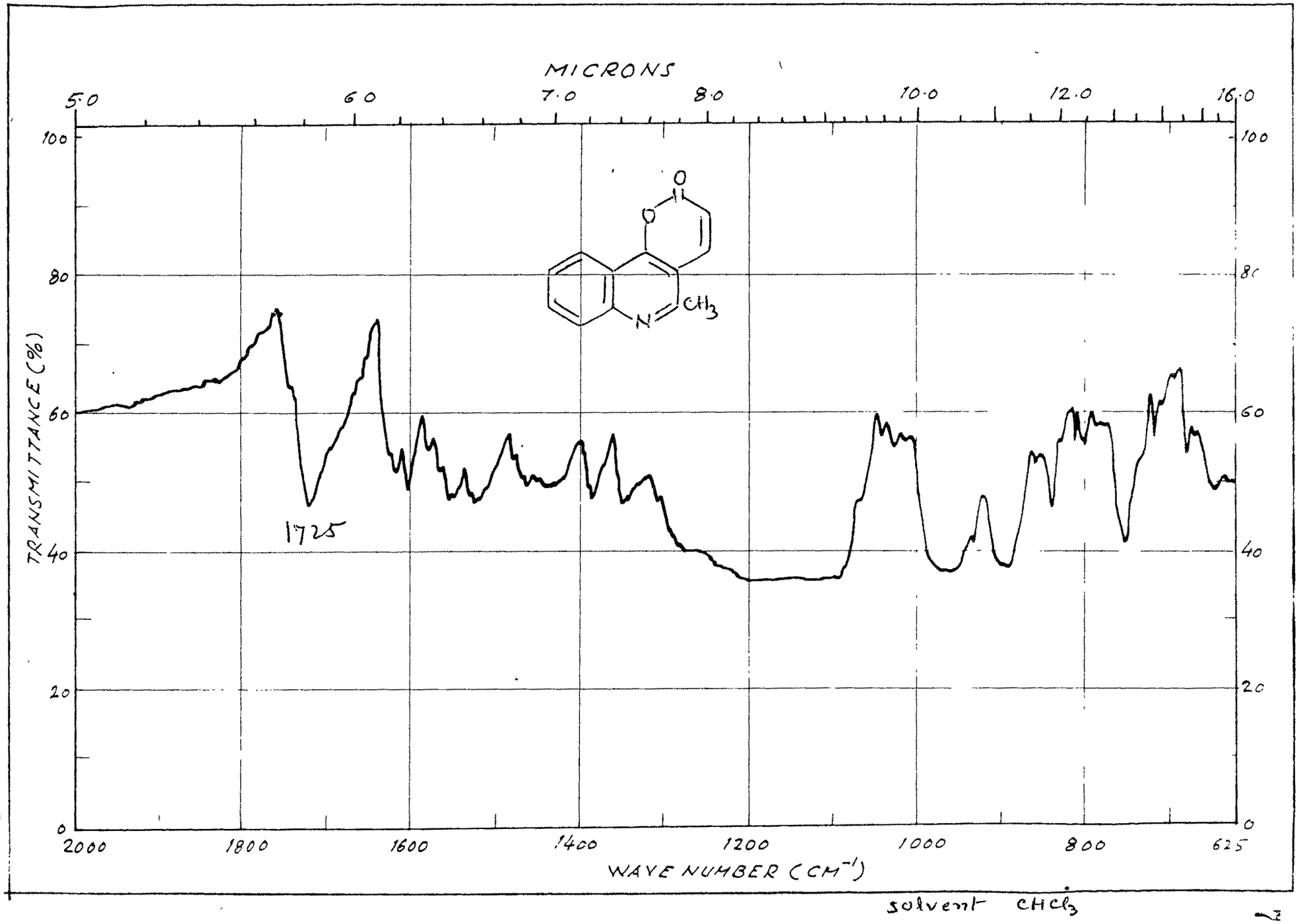
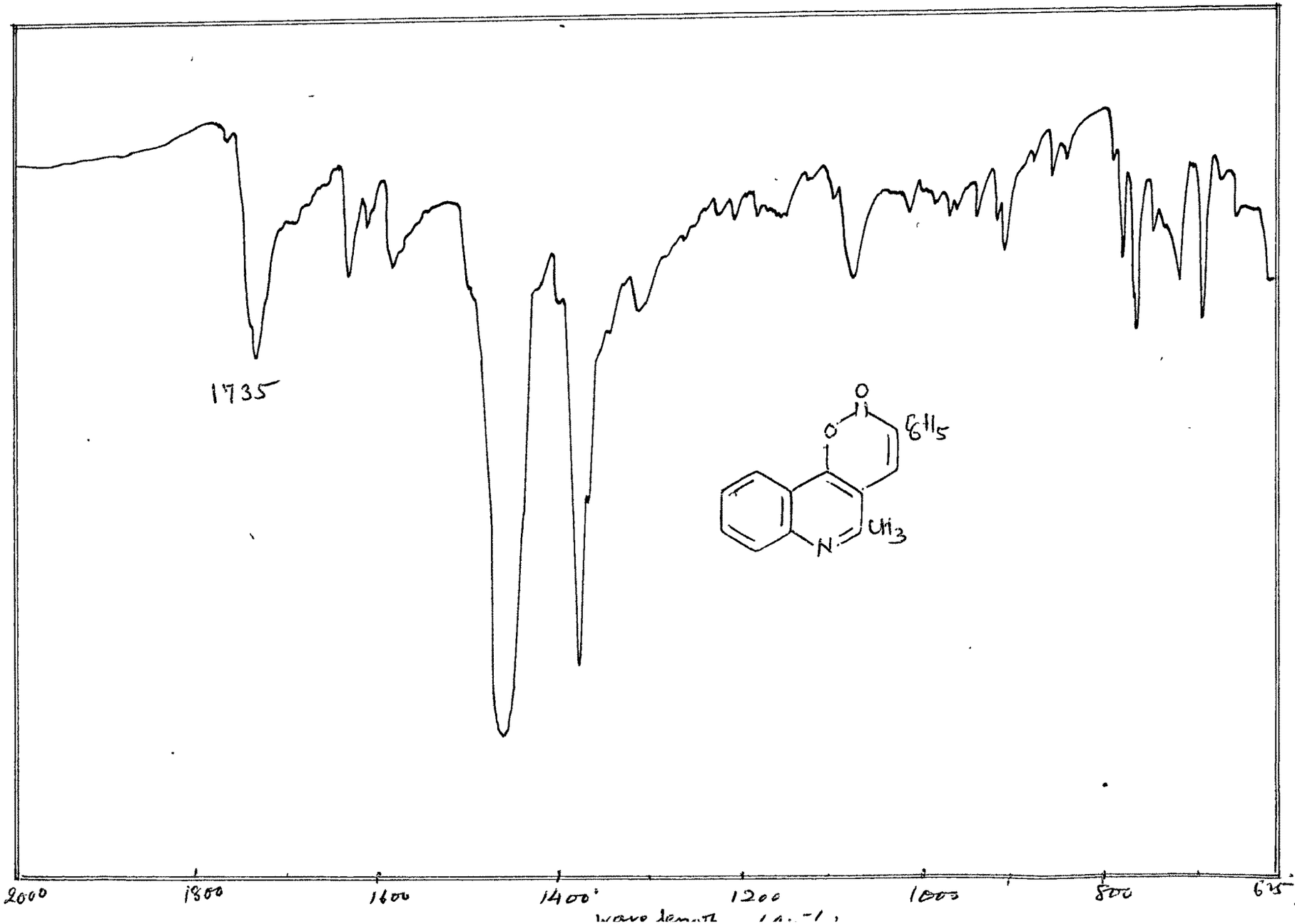


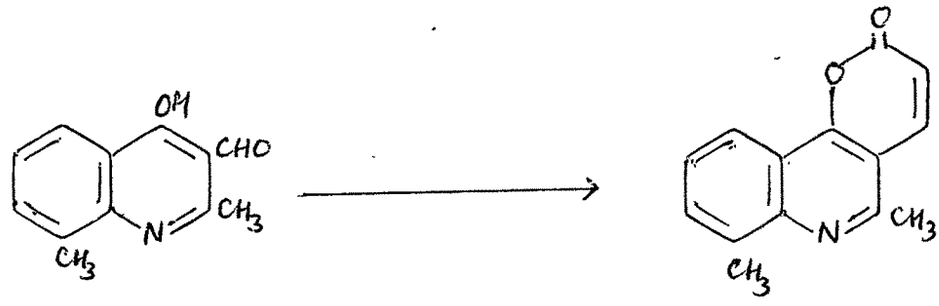
solvent $CHCl_3$


1735
O
O
C_6H_5
CH_3
N
2000
1800
1600
1400
1200
1000
800
wave length

analytical results. IR spectrum showed a characteristic lactonyl carbonyl band at 1735 cm^{-1}.

(c) 5,7-Dimethyl-2-oxo-2H-pyrano(3,2-c)quinoline

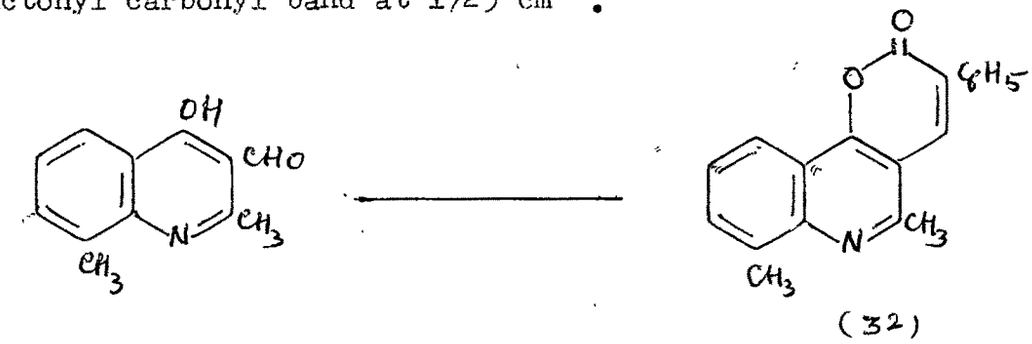
2,8-Dimethyl-3-formyl-4-hydroxyquinoline on treatment with acetic anhydride and triethylamine gave a product to which 5,7-dimethyl-2-oxo-2H-pyrano(3,2-c)quinoline (31) structure was assigned. IR spectrum showed a characteristic lactonyl carbonyl band at 1740 cm^{-1}.



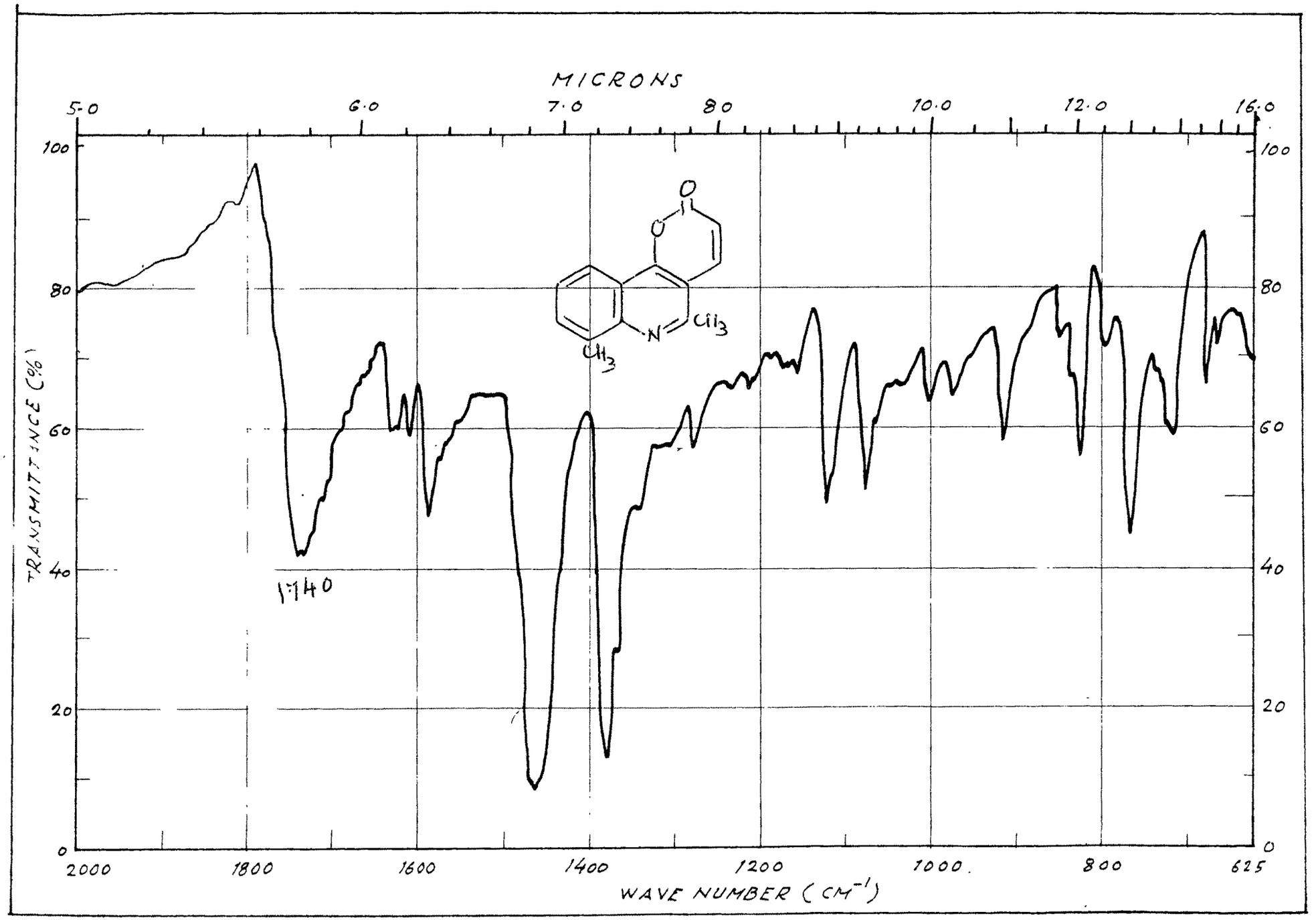
(31)

(d) 5,7-Dimethyl-3-phenyl-2-oxo-2H-pyrano(3,2-c) quinoline

2,8-Dimethyl-3-formyl-4-hydroxyquinoline on treatment with acetic anhydride, phenylacetic acid and triethylamine gave a product to which 5,7-dimethyl-3-phenyl-2-oxo-2H-pyrano (3,2-c)quinoline (32) structure was assigned on the basis of analytical results. IR spectrum showed a characteristic lactonyl carbonyl band at 1725 cm^{-1}.



(32)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7·0
8·0
10·0
12·0
16·0
100
80
60
40
20
0
TRANSMITTANCE (%)
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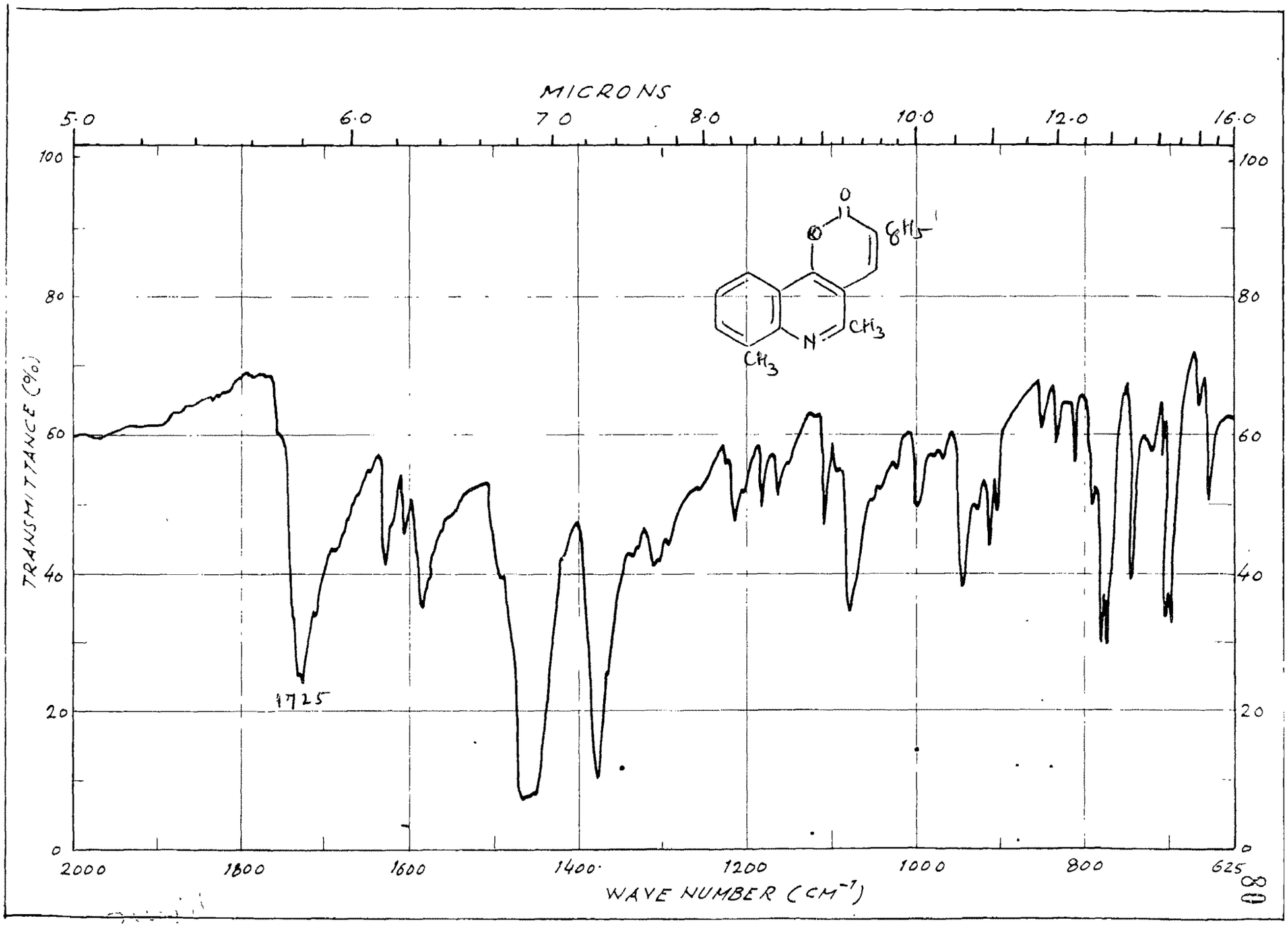
O
N
CH3
CH3
2000
1800
1600
1400
1200
1000
800
625
WAVE NUMBER (CM-1)


MICRONS
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6·0
7·0
8·0
10·0
12·0
16·0
100
80
60
40
20
0
TRANSMITTANCE (%)
1725
2000
1800
1600
1400
1200
1000
800
625
WAVE NUMBER (CM⁻¹)
O
O
CH3
N
CH3
CH3

EXPERIMENTAL

IR spectra (nujol) were recorded on Perkin Elmer 237 grating spectrophotometer.

Condensation of sodium salt of acetoacet-o-toluidide with ethyl bromoacetate: α-Carboethoxymethyl acetoacet-o-toluidide

Acetoacet-o-toluidide (5.7 g.) in dry benzene (70 ml.) was refluxed with pulverised sodium (0.7 g.) for 5 hr. and cooled to room temperature. Ethyl bromoacetate (4.8 ml.) was added and the reaction mixture was refluxed further for 4 hr. It was cooled and diluted with water. The two layers were separated and aqueous layer was extracted with benzene. The combined benzene extracts were washed with water and dried with anhydrous calcium chloride. The solvent was removed and the product obtained crystallised from benzene petroleum ether mixture (1:1), m.p. 82°. Yield 4.5 g.

Analysis : Found : C, 64.89; H, 6.71; N, 5.14 %.

$C_{15}H_{19}O_4N$ requires : C, 64.99; H, 6.86; N, 5.05 %.

4,8-Dimethyl-2-hydroxyquinoline-3-acetic acid

α-Carboethoxymethyl acetoacet-o-toluidide (4.5 g.) was treated with concentrated sulphuric acid (12 ml.) and left overnight. It was heated on water bath for 45 min. The reaction mixture was added to water and the product which separated crystallised from glacial acetic acid, m.p. 295°. Yield 3 g.

Analysis : Found : C, 67.43; H, 5.50; N, 5.95 %.

$C_{13}H_{13}O_3N$ requires : C, 67.53; H, 5.62; N, 6.06 %.

Lactone of 4,8-dimethyl-2-hydroxyquinoline-3-acetic acid

4,8-Dimethyl-2-hydroxyquinoline-3-acetic acid (2 g.) was heated with acetic anhydride (5 ml.) in an oil bath at 110° for 4 hr. The cooled mixture was diluted with ice water and stirred well. The separated product was filtered and washed with water. The product was stirred with sodium bicarbonate solution and the insoluble solid crystallised from dilute acetone, m.p. 199°. Yield 1.1 g.

Analysis : Found : C, 72.86; H, 5.01; N, 6.12 %.

$C_{13}H_{11}O_2N$ requires : C, 73.23; H, 5.16; N, 6.57 %.

Condensation of sodium salt of acetoacet-m-xylidide with ethyl bromoacetate : α-Carboethoxymethyl acetoacet-m-xylidide

Pulverised sodium (0.7 g.) in dry benzene (80 ml.) and acetoacet-m-xylidide (6.1 g.) were heated on a water bath for 5 hr. and cooled to room temperature. Ethyl bromoacetate (4.8 ml.) was added and the reaction mixture was refluxed further for 4-5 hr. The product obtained on working up as before crystallised from benzene-petroleum ether mixture (1:1), m.p. 126°. Yield 5 g.

Analysis : Found : C, 65.84; H, 7.10; N, 4.40 %.

$C_{16}H_{21}O_4N$ requires : C, 65.97; H, 7.21; N, 4.81 %.

4,6,8-Trimethyl-2-hydroxyquinoline-3-acetic acid

α-Carboxyethoxymethyl acetoacet-m-xylidide (5 g.) was treated with concentrated sulphuric acid (12 ml.) and

left overnight. It was then heated on a water bath for 1 hr. The reaction mixture was added to water and the product which separated crystallised from glacial acetic acid, m.p. 308°. Yield 3.5 g.

Analysis : Found : C, 68.36; H, 5.96; N, 5.55 %.

$C_{14}H_{15}O_3N$ requires : C, 68.57; H, 6.12; N, 5.17 %.

Lactone of 4,6,8-trimethyl-2-hydroxyquinoline-3-acetic acid

4,6,8-Trimethyl-2-hydroxyquinoline-3-acetic acid (2 g.) was treated with acetic anhydride (6 ml.) and heated in an oil bath at 110° for 4 hr. The product separated on dilution with water was taken in sodium bicarbonate solution and the insoluble solid crystallised from acetone, m.p. 268°. Yield 1 g.

Analysis : Found : C, 74.43; H, 5.96; N, 6.30 %.

$C_{14}H_{13}O_2N$ requires : C, 74.00; H, 5.72; N, 6.16 %.

Condensation of sodium salt of acetoacet-α-naphthylamide with ethyl bromoacetate : α-Carboethoxymethyl acetoacet-α-naphthylamide

Acetoacet-α-naphthylamide (6 g.) in dry benzene (60 ml.) was refluxed with pulverised sodium (0.6 g.) for 5 hr. Ethyl bromoacetate (4.1 ml.) was added and the reaction mixture was refluxed further for 6 hr. On working up as before the product crystallised from methyl alcohol, m.p. 130°. Yield 4.5 g.

Analysis : Found : C, 68.89; H, 6.21; N, 4.07 %.

$C_{18}H_{19}O_4N$ requires : C, 69.03; H, 6.07; N, 4.47 %.

4-Methyl-2-hydroxy-7,8-benzoquinoline-3-acetic acid

α-Carboethoxymethylacetoacet-α-naphthylamide (4.5 g.) was treated with concentrated sulphuric acid (12 ml.) and left overnight. It was heated on a water bath for 1 hr. The reaction mixture was added to water and the product which separated crystallised from glacial acetic acid, m.p. 308°. Yield 2 g.

Analysis : Found : C, 71.68; H, 4.97; N, 4.92 %.

$C_{16}H_{12}O_3N$ requires : C, 71.91; H, 4.86; N, 5.24 %.

Lactone of 4-methyl-2-hydroxy-7,8-benzoquinoline-3-acetic acid

The above acid (2 g.) was treated with acetic anhydride (6 ml.) and heated in an oil bath at 110° for 4 hr. The reaction mixture was added to water and the product which separated was washed with sodium bicarbonate solution to remove unreacted product. The cyclised product crystallised from dilute acetone, m.p. 256°. Yield 1 g.

Analysis : Found : C, 77.63; H, 4.37; N, 5.36 %.

$C_{16}H_{11}O_2N$ requires : C, 77.73; H, 4.45; N, 5.66 %.

Condensation of sodium salt of acetoacet-p-xylidide with ethyl bromoacetate: α-Carboethoxymethyl acetoacet-p-xylidide

Acetoacet-p-xylidide (4.1 g.) in dry benzene (80 ml.) and pulverised sodium (0.5 g.) were refluxed on a water bath for 5 hr. Ethyl bromoacetate (3.2 ml.) was added and the reaction mixture was refluxed further for 4 hr. On working up as before the product obtained in liquid form (3 g.).

4,5,8-Trimethyl-2-hydroxyquinoline-3-acetic acid

The above oily product (3 g.) was treated with concentrated sulphuric acid (8 ml.) and left overnight. It was then heated on a water bath for 1 hr. The reaction mixture was added to water and the product which separated crystallised from glacial acetic acid, m.p. 278°. Yield 1.5 g.

Analysis : Found : C, 68.53; H, 6.04; N, 5.37 %.

$C_{14}H_{15}O_3N$ requires : C, 68.57; H, 6.12; N, 5.17 %.

Lactone of 4,5,8-trimethyl-2-hydroxyquinoline-3-acetic acid

The above acid (1 g.) was heated with acetic anhydride (5 ml.) in an oil bath at 110° for 4 hr. On working up as before the product crystallised from acetone, m.p. 238°. Yield 0.4 g.

Analysis : Found : C, 73.64; H, 5.64; N, 6.46 %.

$C_{14}H_{13}O_2N$ requires : C, 74.00; H, 5.73; N, 6.16 %.

Condensation of sodium salt of acetoacet-p-toluidide with ethyl bromoacetate : α-Carboethoxymethyl acetoacet-p-toluidide

Acetoacet-p-toluidide (5.7 g.) in dry benzene (80 ml.) was refluxed with pulverised sodium (0.7 g.) for 5 hr. Ethyl bromoacetate (4.8 ml.) was then added and the reaction mixture refluxed further for 5 hr. On working up as before the product obtained in liquid form (3.5 g.).

4,6-Dimethyl-2-hydroxyquinoline-3-acetic acid

The above oily product (3 g.) was treated with concentrated sulphuric acid (8 ml.) and left overnight.

It was then heated on a water bath for 1 hr. The product which separated on dilution with water crystallised from glacial acetic acid, m.p. 305°. Yield 2 g.

Analysis : Found : C, 67.98; H, 6.00; N, 6.43 %.

$C_{13}H_{13}O_3N$ requires : C, 67.53; H, 5.62; N, 6.06 %.

Lactone of 4,6-dimethyl-2-hydroxyquinoline-3-acetic acid

The above acid (2 g.) was heated with acetic anhydride (5 ml.) in an oil bath at 105-10° for 4 hr. On working up as before the product crystallised from acetone, m.p. 230°. Yield 0.8 g.

Analysis : Found : C, 73.45; H, 5.12; N, 6.10 %.

$C_{13}H_{11}O_2N$ requires : C, 73.23; H, 5.16; N, 6.57 %.

Condensation of sodium salt of acetoacetanilide with ethyl bromopropionate : α-Carboethoxyethyl acetoacetanilide

Acetoacetanilide (5.1 g.) in dry benzene (50 ml.) was refluxed on a water bath with pulverised sodium (0.7 g.) for 6 hr. To the cooled solution was added ethyl bromopropionate (5.4 ml.) and the reaction mixture was refluxed further for 5 hr. It was added to water. The two layers formed were separated and the aqueous layer was extracted with benzene. The combine benzene extracts were dried over anhydrous calcium chloride. On removal of benzene the product separated in a liquid form (5 g.).

4,Methyl-2-hydroxyquinoline-3-propionic acid

The above oily product (5 g.) was treated with concentrated sulphuric acid (10 ml.) and left overnight.

It was then heated on a water bath for 1 hr. and poured over ice water. The product which separated crystallised from alcohol, m.p. 237°. Yield 3 g.

Analysis : Found : C, 68.82; H, 5.58; N, 6.30 %.

$C_{13}H_{13}O_3N$ requires : C, 68.43; H, 5.70; N, 6.14 %.

Attempted cyclisation of 4-methyl-2-hydroxyquinoline-3-propionic acid

(a) With acetic anhydride

The above acid (1.5 g.) was heated with acetic anhydride (5 ml.) in an oil bath at 110° for 4 hr. On dilution with water the product which separated was found to be original acid.

(b) With acetic anhydride and fused sodium acetate

The above acid (1 g.) was treated with acetic anhydride (5 ml.) and fused sodium acetate (1.5 g.) and refluxed for 4 hr. On dilution with water the product which separated was found to be original acid.

(c) With polyphosphoric acid

The above acid (1 g.) was heated with polyphosphoric acid (5 g. phosphorus pentoxide and 3 ml. of o-phosphoric acid) in an oil bath at 120° for 3 hr. The product which separated on dilution with water was found to be original acid.

(d) With thionyl chloride followed by treatment with anhydrous aluminium chloride in dry benzene: (4-Methyl-2-hydroxy-3-quinolyl) ethyl phenyl ketone

4-Methyl-2-hydroxyquinoline-3-propionic acid (1 g.) was heated with thionyl chloride (5 ml.) on a water bath

for 2 hr. After removing excess of thionyl chloride, dry benzene (15 ml.) and anhydrous aluminium chloride (2 g.) was slowly added and heating continued for further 2 hr. Benzene was removed and the reaction mixture was poured over ice water and hydrochloric acid (3 ml.). The product which separated was filtered and crystallised from glacial acetic acid, m.p. 237°. Yield 0.2 g.

Analysis : Found : C, 78.58; H, 5.57; N, 4.98 %.

$C_{19}H_{17}O_2N$ requires : C, 78.34; H, 5.84; N, 4.81 %.

Condensation of sodium salt of acetoacet-p-toluidide with ethyl bromopropionate : α-Carboethoxyethyl acetoacet-p-toluidide

Acetoacet-p-toluidide (3.8 g.) in dry benzene (40 ml.) was refluxed on a water bath with pulverised sodium (0.5 g.) for 5 hr. Ethyl bromopropionate (3.6 g.) was added and the reaction mixture was refluxed further for 5 hr. On working up as before the product separated in a liquid form. (4 g.).

4,6-Dimethyl-2-hydroxyquinoline-3-propionic acid

The above oily product (4 g.) was treated with concentrated sulphuric acid (8 ml.) and left overnight. It was then heated on a water bath for 1 hr. and poured over ice water. The product which separated crystallised from alcohol, m.p. 252°. Yield 2 g.

Analysis : Found : C, 68.68; H, 6.32; N, 6.00 %.

$C_{14}H_{15}O_3N$ requires : C, 68.56; H, 6.12; N, 5.71 %.

(4,6-Dimethyl-2-hydroxy-3-quinolyl) ethyl phenyl ketone

4,6-Dimethyl-2-hydroxyquinoline-3-propionic acid (1 g.) was heated on a water bath with thionyl chloride (5 ml.) for 2 hr. After removing excess of thionyl chloride dry benzene (15 ml.) and anhydrous aluminium chloride (2 g.) were added and heating continued for further 2 hr. Benzene was removed and the reaction mixture was poured over ice water and hydrochloric acid (3 ml.). The product which separated was filtered and crystallised from benzene, m.p. 178°. Yield 0.3 g.

Analysis : Found : C, 78.61; H, 6.32; N, 5.02 %.

$C_{20}H_{19}O_2N$ requires : C, 78.69; H, 6.23; N, 4.59 %.

Condensation of acetoacet-o-toluidide with ethyl bromopropionate : α-Carboethoxyethyl acetoacet-o-toluidide

Acetoacet-o-toluidide (3.8 g.) in dry benzene (40 ml.) was refluxed on a water bath with pulverised sodium (0.5 g.) for 4 hr. To the cooled solution was added ethyl bromopropionate (3.6 g.) and the reaction mixture was refluxed further for 5 hr. On working up as before the product crystallised from ether petroleum, m.p. 85°. Yield 3 g.

Analysis : Found : C, 65.58; H, 6.97; N, 5.04 %.

$C_{16}H_{21}O_4N$ requires : C, 65.98; H, 7.21; N, 4.81 %.

4,8-Dimethyl-2-hydroxyquinoline-3-propionic acid

α-Carboethoxyethyl acetoacet-o-toluidide (3 g.) was treated with concentrated sulphuric acid (6 ml.) and left overnight. It was then heated on a water bath for 1 hr. and

poured over ice water. The product which separated was filtered and crystallised from alcohol, m.p. 244°. Yield 1.5 g.

Analysis : Found : C, 68.89; H, 6.21; N, 5.40 %.

$C_{14}H_{15}O_3N$ requires : C, 68.56; H, 6.12; N, 5.71 %.

Perkin acetylation of 2-methyl-3-formyl-4-hydroxyquinoline : 5-Methyl-2-oxo-2H-pyrano(3,2-c)quinoline

A mixture of 2-methyl-3-formyl-4-hydroxyquinoline (1 g.), acetic anhydride (10 ml.) and triethylamine (4 ml.) was heated in an oil bath at 110° for 16 hr. It was then poured in ice cold water and the product which separated crystallised from benzene petroleum ether mixture (1:1), m.p. 180°. Yield 0.3 g.)

Analysis : Found : C, 73.77; H, 4.18; N, 6.50 %.

$C_{13}H_9O_2N$ requires : C, 73.93; H, 4.26; N, 6.63 %.

5-Methyl-3-phenyl-2-oxo-2H-pyrano(3,2-c)quinoline

A mixture of 2-methyl-3-formyl-4-hydroxyquinoline (1 g.), phenylacetic acid (1 g.), acetic anhydride (10 ml.) and triethylamine (4 ml.) was heated in an oil bath at 110° for 16 hr. The reaction mixture was then poured in ice cold water and the product which separated crystallised from alcohol, m.p. 204°. Yield 0.4 g.

Analysis: : Found : C, 78.97; H, 4.45; N, 4.81 %.

$C_{19}H_{13}O_2N$ requires : C, 79.43; H, 4.52; N, 4.87 %.

Perkin acetylation of 2,8-dimethyl-3-formyl-4-hydroxyquinoline : 5,7-Dimethyl-2-oxo-2H-pyrano(3,2-c) quinoline

A mixture of 2,8-dimethyl-3-formyl-4-hydroxyquinoline

(1 g.), acetic anhydride (10 ml.) and triethylamine (4 ml.) was heated in an oil bath at 110° for 16 hr. The reaction mixture was then poured in ice cold water and the product which separated crystallised from methyl alcohol, m.p. 170°. Yield 0.3 g.

Analysis : Found : C, 74.62; H, 5.08; N, 5.99 %.

$C_{14}H_{11}O_2N$ requires : C, 74.66; H, 4.88; N, 6.22 %.

5,7-Dimethyl-3-phenyl-2-oxo-2H-pyrano(3,2-c)quinoline

A mixture of 2,8-dimethyl-3-formyl-4-hydroxyquinoline (1 g.), phenylacetic acid (1 g.), acetic anhydride (10 ml.) and triethylamine (4 ml.) was heated in an oil bath at 110° for 16 hr. The reaction mixture was then poured in ice cold water and the product which separated crystallised from alcohol, m.p. 178°. Yield 0.3 g.

Analysis : Found : C, 79.63; H, 4.96; N, 4.46 %.

$C_{20}H_{15}O_2N$ requires : C, 79.71; H, 4.98; N, 4.65 %.

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