CHAPTER- I

STUDIES IN THE SYNTHESIS OF PYRANOQUINOLINES

CHAPTER - I

SECTION - I

Studies in the synthesis of Pyranoquinolines.

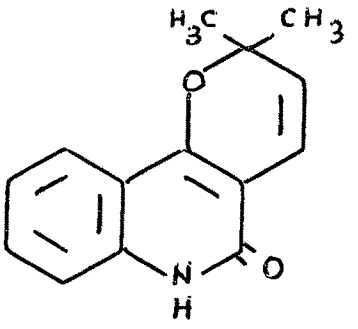
Synthesis of pyrano (3,2-c)quinoline derivatives :

Theoretical

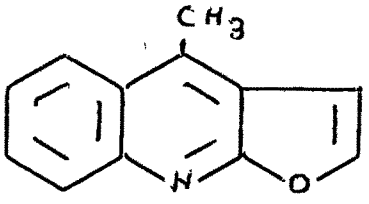
In the Literature two methods are known to synthesise pyranoquinoline derivatives, one method is to get pyranoquinoline by starting with an appropriate amino-coumarin derivative and to build up the pyridine ring on it by known methods. In the second method, pyran ring is built on quinoline ring.

It will be interesting to note here that in recent years pyranoquinolines have received considerable importance because they are occuring in nature and also possess good therapeutic properties. For example, pyrano quinoline derivative " flindersine "(1) is isolated from the plant Rutacease (especially from Australian species) along with a furoquinoline alkaloid " Dictamine "(2). Several new pyrano quinoline alkaloids have been recently isolated and also obtained synthetically, such alkaloids are Khaplofoline (3), Ribalinine (4), Oricine (5), Heplamine (6), Pteleflorine (7), Ptelefolidone (8), Haplobucharine

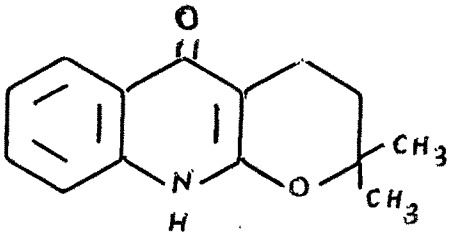
(9), Isobalfourodine (10), Ribalinidine (11), Psuedo-isobalfourodine (12) and isodubinidine (13).



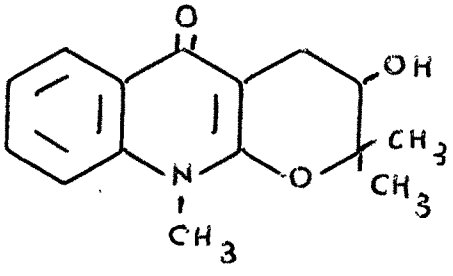
(1)



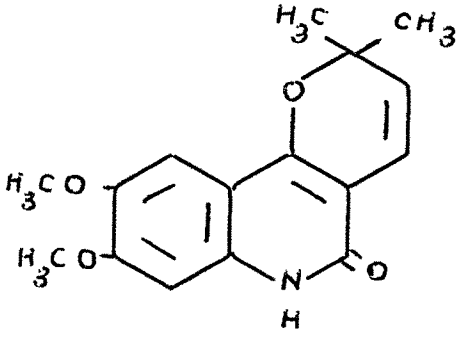
(2)



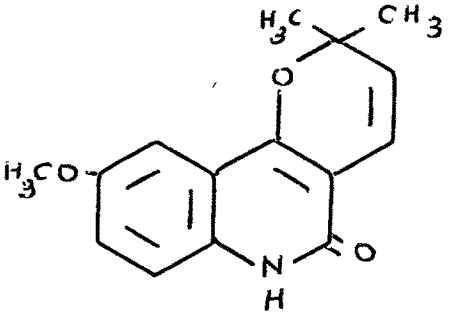
(3)



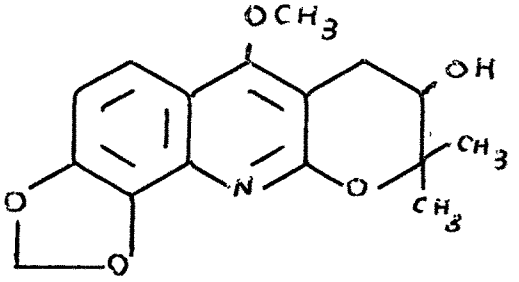
(4)



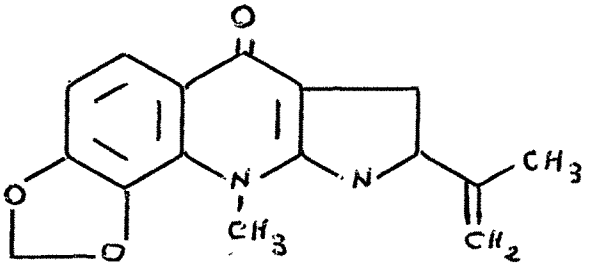
(5)



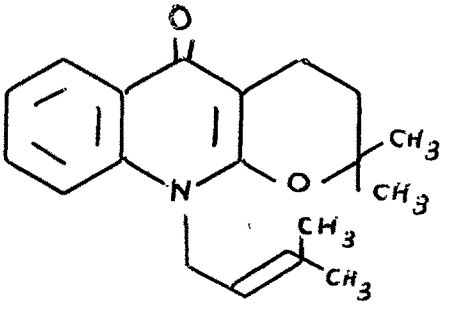
(6)



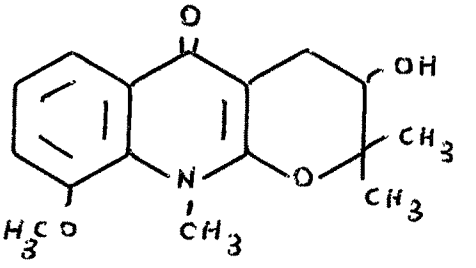
(7)



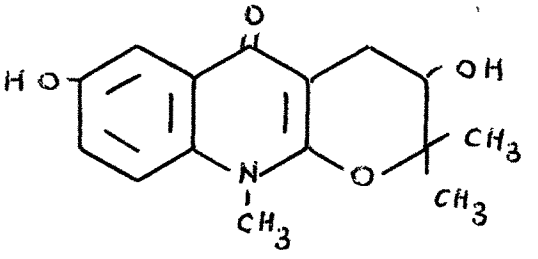
(8)



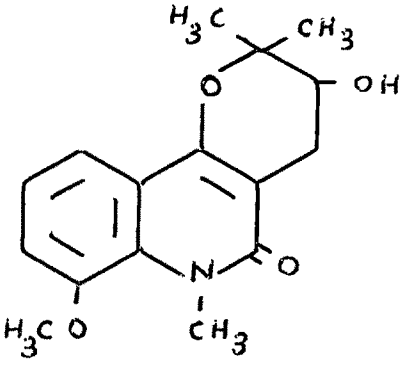
(9)



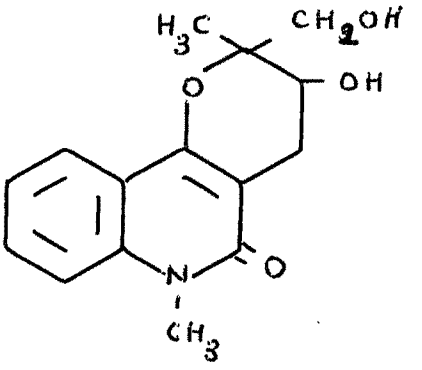
(10)



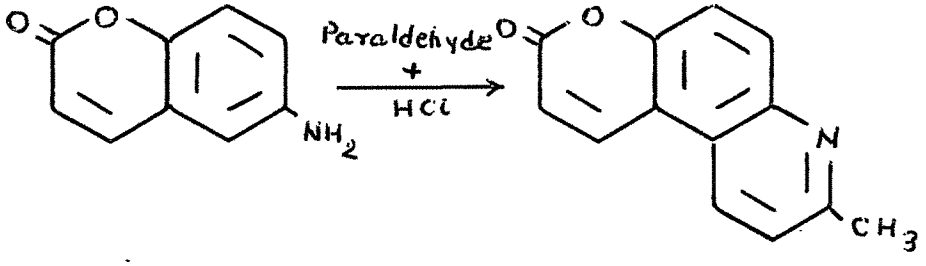
(11)



(12)



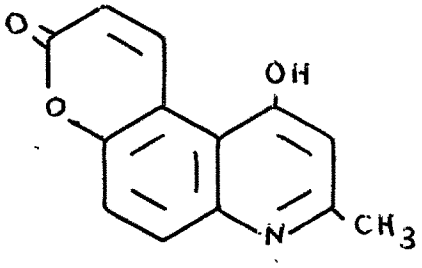
Dey, Sarkar and Seshadri[1] synthesised 2-methyl-quinolino-(6,5-a)pyrone (14) by reacting 6-amino-coumarin with paraldehyde in the presence of hydrochloric acid.



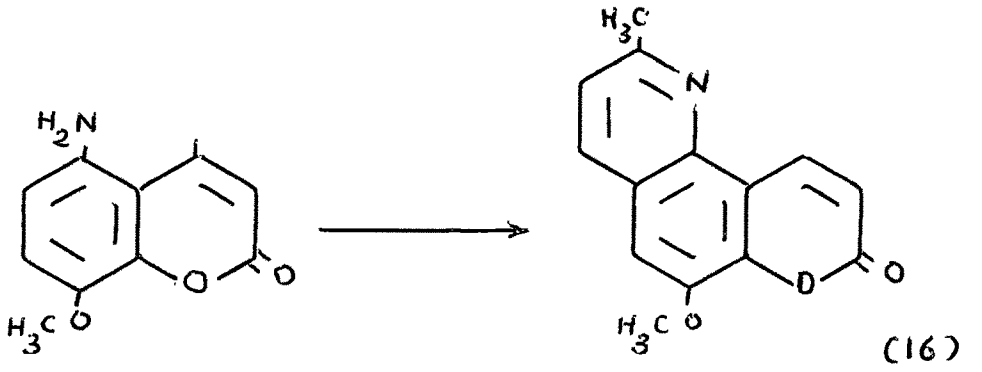
(14)

Chakravarti, Ahuja and Siddiqui[2] prepared ethyl β-(2-oxo-1,2-H-benzopyran-2-ylamino) crotonate by warming 6-amino coumarin with ethylacetoacetate and a drop of hydrochloric acid. This when cyclised in paraffine preheated to 260° gave 4-hydroxyquinaldino-(6,5-a) pyrone (15).

(15)



Dey and Ammalkutti[3] prepared 6-methoxy-2-methyl-8-oxo-8 H-pyrano (2,3-h) quinoline (16) from 5-amino-8-methoxy coumarin and paraldehyde.

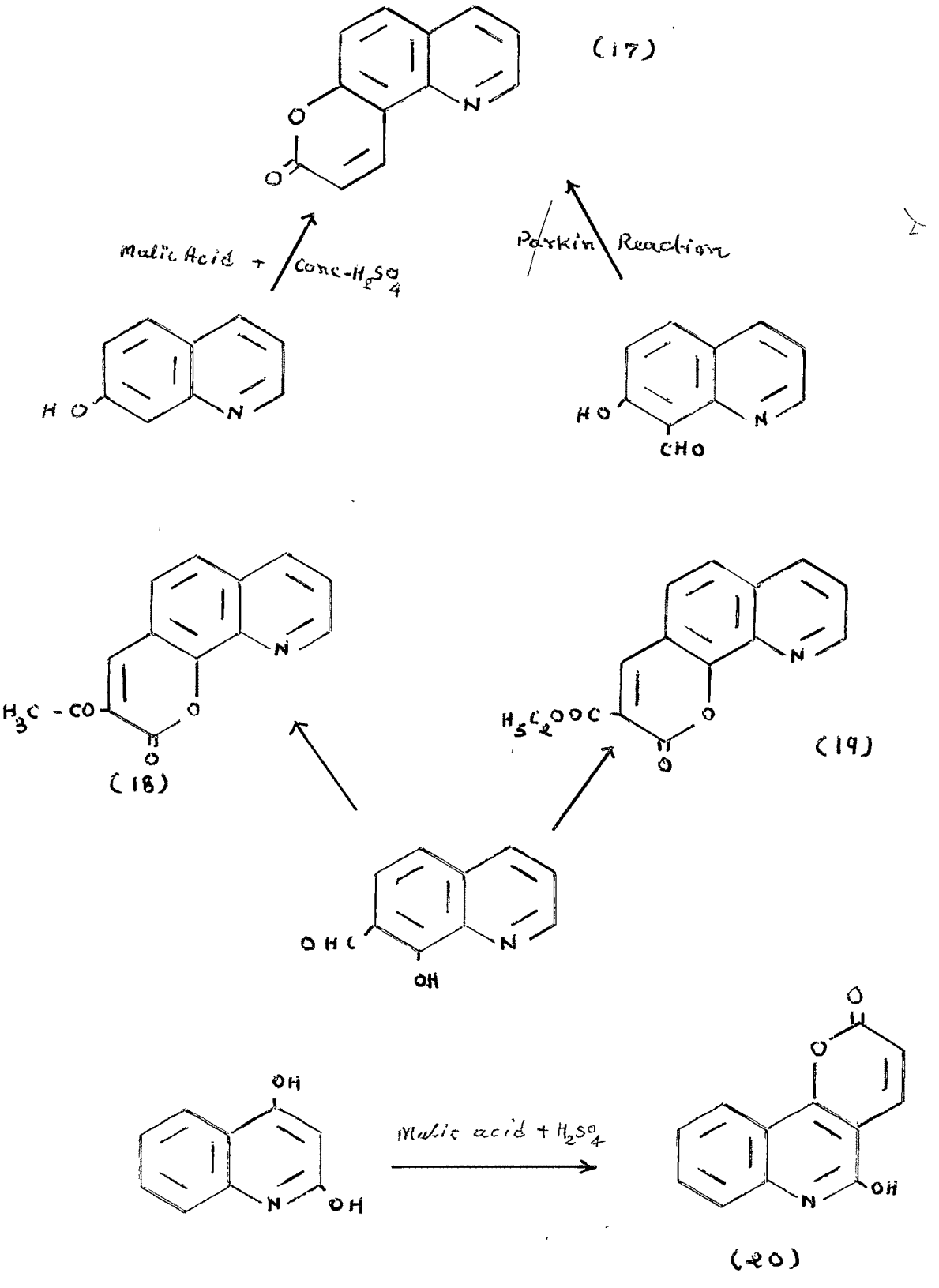


(16)

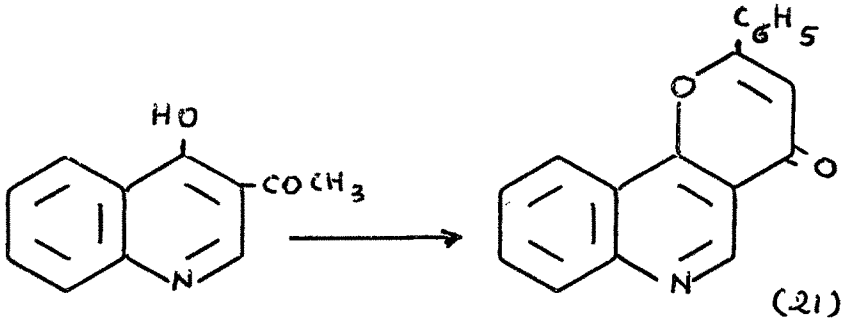
Bobranski and Kochanska[4] carried out the condensation of 7-hydroxyquinoline with malic acid in the presence of conc. sulphuric acid and obtained 8-oxo-8 H-pyrano-(2,3-h) quinoline (17) which was also prepared from 7-hydroxy-8-formylquinoline by Perkin reaction.

Fiedler[5] synthesised 3-acetyl-2-oxo-2 H-pyrano-(2,3-h) quinoline (18) and 3-carboethoxy-2-oxo-2 H-pyrano-(3,2-h) quinoline (19) from 8-hydroxy-7-formylquinoline with ethylacetoacetate and diethylmalonate in the presence of piperidine, respectively.

Brown et. al[6] 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-2 H-pyrano-(3,2-c) quinoline (20).


(17)
Malic Acid + Conc-H_2SO_4
Parkin Reaction
HO
N
HO
CHO
N
H_3C - CO
O
O
(18)
N
H_5C_2OOC
O
O
(19)
N
OHC
OH
OH
N
OH
Malic acid + H_2SO_4
O
O
N
OH
(20)

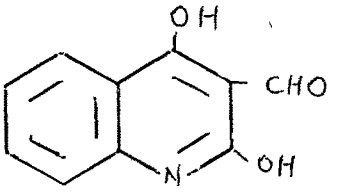
Ellilott and Tittenson[7] synthesised 4'-oxo-6'-phenyl pyrano-(3':2'- 3:4) quinoline (21) from 3-acetyl-4-hydroxyquinoline by application of Kostanecki-Robinson reaction with benzoic anhydride and triethylamine.



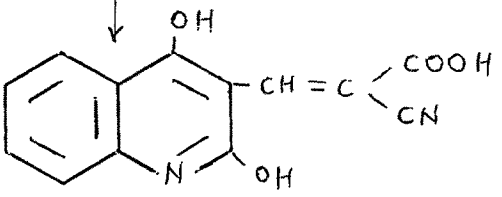
(21)

5-Hydroxy-2-oxo-2 H-pyrano-(3,2-c) quinoline-3-carboxylic acid (22) was obtained by Yashuiko Asahina and Mototaro Inubuse[8] by reacting cyanoacetic acid in warm 10 % KOH with nordictamnal (23) to get nordictamnal cyanoacetic acid (24) which on further treatment with conc. sulphuric acid gave a compound (22). Clarke and Grundon[9] observed that acid cyclizations of the 3-methyl-2-butenyl quinolones (25) furnish the angular pyrano-quinoline (26) and the linear pyranoquinoline (27), which equilibrate on prolonged treatment with acid. Same authors[10] reported that by cyclization of 4-hydroxy-3-(3-methyl-2-butenyl) quinolone with peroxylauric acid furnished balfourodine (28).

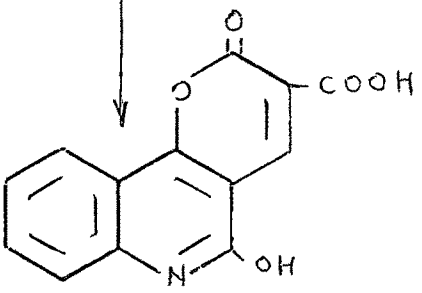
(23)

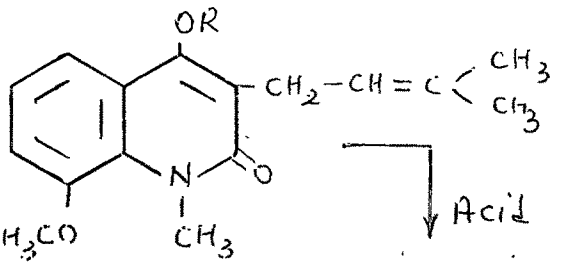


(24)



(22)

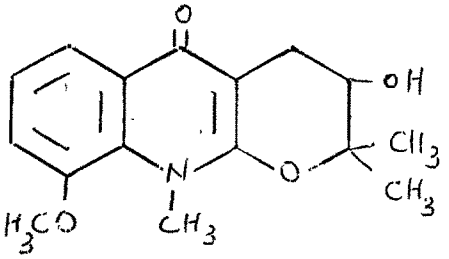


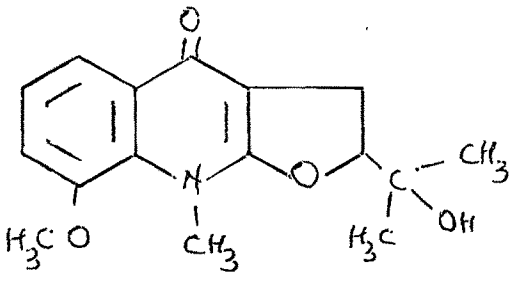


(25)

Peroxyl auric acid

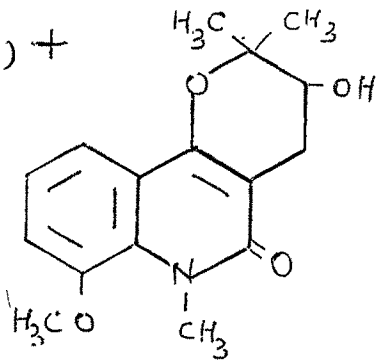
Acid





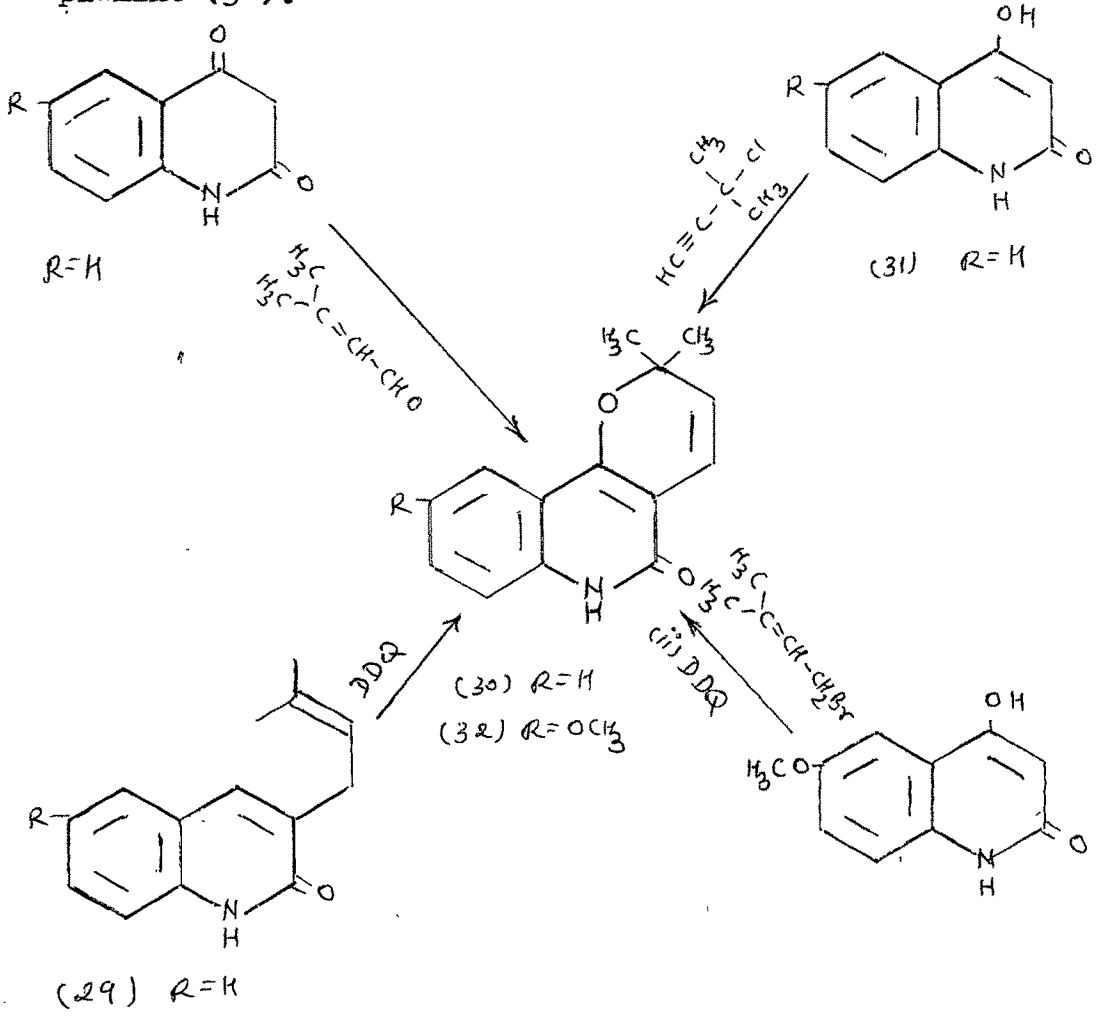
(28)

(27) +



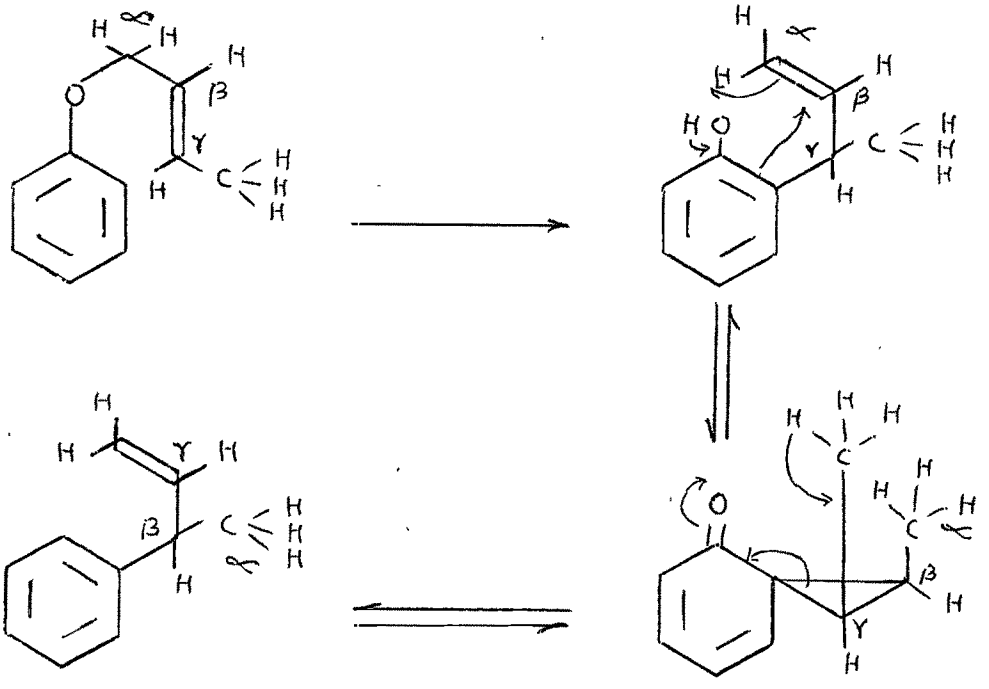
(26)

Franco, Pietro and Aurora[11] synthesised flindersine (30) by the action of DDQ on 3(Y,Y-dimethyl allyl)-4-hydroxy-2-quinolone (29). Huffman and Hsu[12] synthesised findersine (30) by one step synthesis. The condensation of thallous salt of (31) with 3-chloro-3-methyl-but-1-yne gave findersine (30). De Groot and Janson[13] prepared same compound (30) by condensing 1,2,3,4-tetrahydroquinolone with 3-methyl-2-butenal (Me_2-C=CH-CHO). By condensing 4-hydroxy-6-methoxy-2-quinolone with 3-methyl-1-bromo-but-2-ene, followed by cyclisation using DDQ, Venturella and Franco[14] synthesised Haplamine (32).



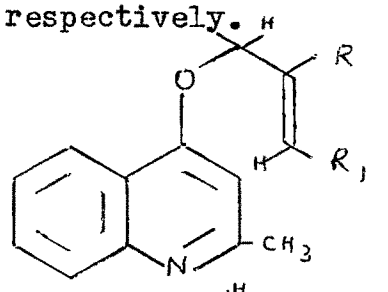
Work done in the synthesis of pyranoquinoline derivatives reveals two main types of reaction paths (i) C-alkylation, ortho to hydroxyl group and followed by cyclisation by different agents, (ii) ether formation, followed by Claisen rearrangement and cyclisation. During Claisen rearrangement variety of rearranged products are obtained. These are mainly of two types, normally rearranged product and abnormally rearranged one. The mechanism of normal rearrangement was studied long back by various group of chemists and that of abnormal one was studied in detail in last 10-15 years. The Claisen rearrangement in which the C-atom linked with the oxygen in the ether attaches with the nucleus in migrated product, is generally referred to as abnormal Claisen rearrangement. The abnormal rearrangement leading to structural [15,16,17,18,19] and geometric[20,21,22] isomerisation, in the migrating allyl group is generally observed to accompany the ortho-rearrangement of ethers bearing γ-alkyl substituents on the allyl group. The abnormal product obtained in a subsequent rearrangement of the normal o-allylphenols[23] is formed through an intermediate spirocyclopropyl cyclohexadienone resulting from hydrogen transfer from the phenolic function to the terminal carbon atom of the allyl group. Reversal of this process a 1,5-hydrogen shift, but involving a hydrogen from γ-alkyl group, leads to

the abnormal product[19,23,24]. Thus in an abnormal product, the original β-carbon atom of the side chain is attached to the ring and the original α-carbon atom becomes saturated. β-Substituent and the double bond shifts to a position between the original β-carbon atom and its hydrogen bearing allyl group. The interconversion of normal and abnormal product through such acyl cyclopropyl intermediate is quite common[25] and is recognised as a enoline rearrangement[26].



Most of the abnormal rearrangements are considerably slower than the formation of the normal o-allyl phenol.

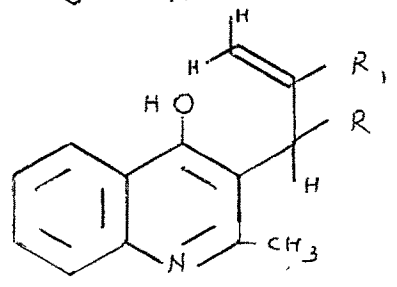
Yasuo Makisumi[27] reported the ortho-Claisen rearrangement of allyl, meth-allyl and crotyl ethers of 2-methyl-4-hydroxyquinoline. A detailed study of the rearrangement was done by carrying out reactions without solvent by heating for periods of 30 min. at 190°, 30 min. at 200° and 30 min. at 230° in separate experiments. The product was digested with benzene to give benzene insoluble fraction (34) and the benzene soluble fraction was chromatographed on Al_2O_3 to give unchanged (33) and then (35). Similarly (36) and (39) gave (37) and (40) as migrated product and (38) and (41) as cyclic products, respectively.



(33) R = R_1 = H

(36) R = Me, R_1 = H

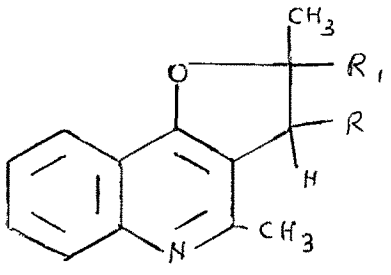
(39) R = H, R_1 = Me



(34) R = R_1 = H

(37) R = H, R_1 = Me

(40) R = Me, R_1 = H

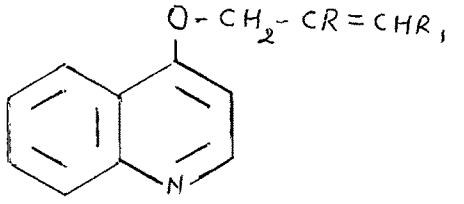


(35) R = R_1 = H

(38) R = Me, R_1 = H

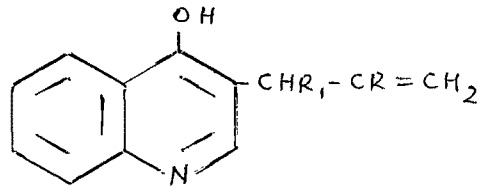
(41) R = H, R_1 = Me

Similar observation were made, when (42) and (43) were pyrolysed at 200° gave (44) and (45) respectively.



(42) R = R_1 = H

(43) R = Me, R_1 = H



(44) R = R_1 = H

(45) R = Me, R_1 = H

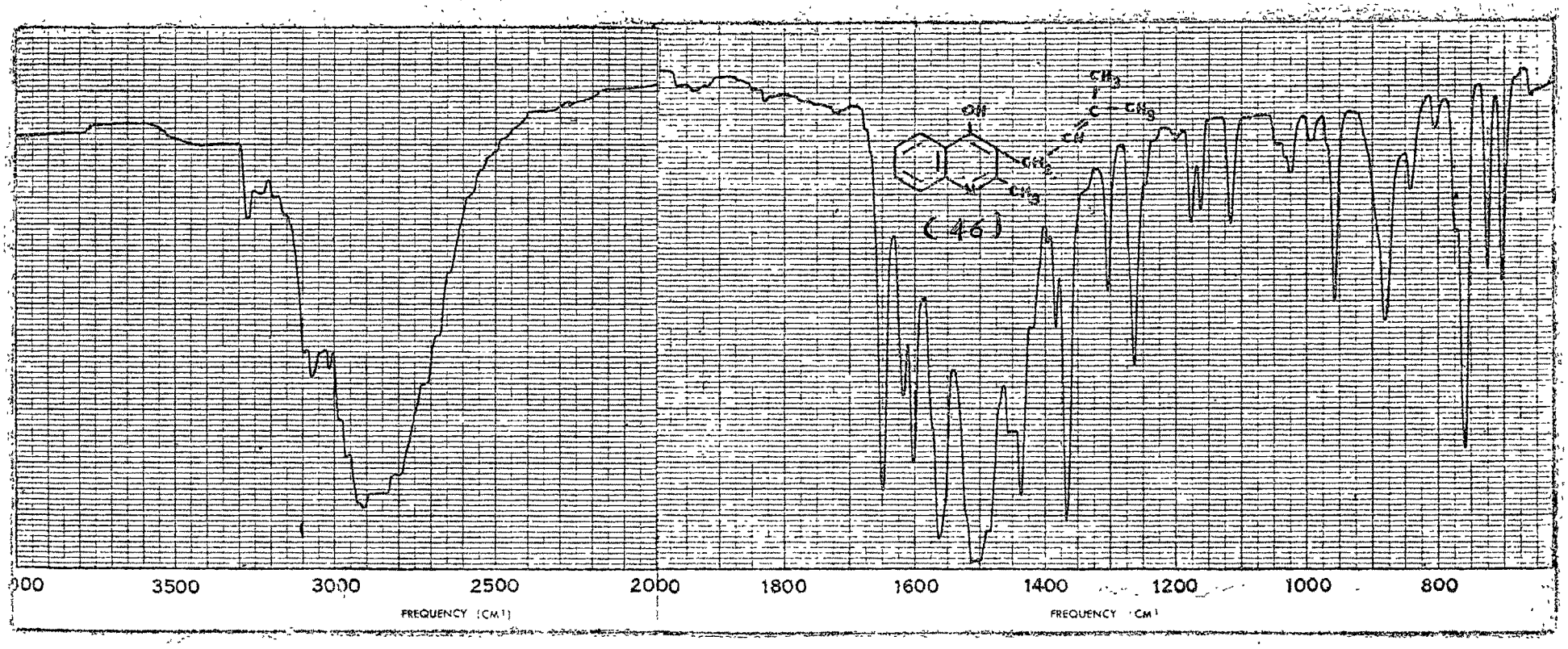
In the present work, Claisen rearrangement of 2-methyl-4-hydroxy quinoline derivatives was carried out which gave abnormally rearranged products. The structure of these compounds were confirmed by NMR spectra. The attempted dehydrogenation of the rearranged products with DDQ in dioxan failed to give the compound pyranoquinoline derivatives. It was also observed that, if pyrolysis of ether was carried out for longer period i.e. more than 30-40 minutes, original 2-methyl-4-hydroxyquinoline derivatives were obtained.

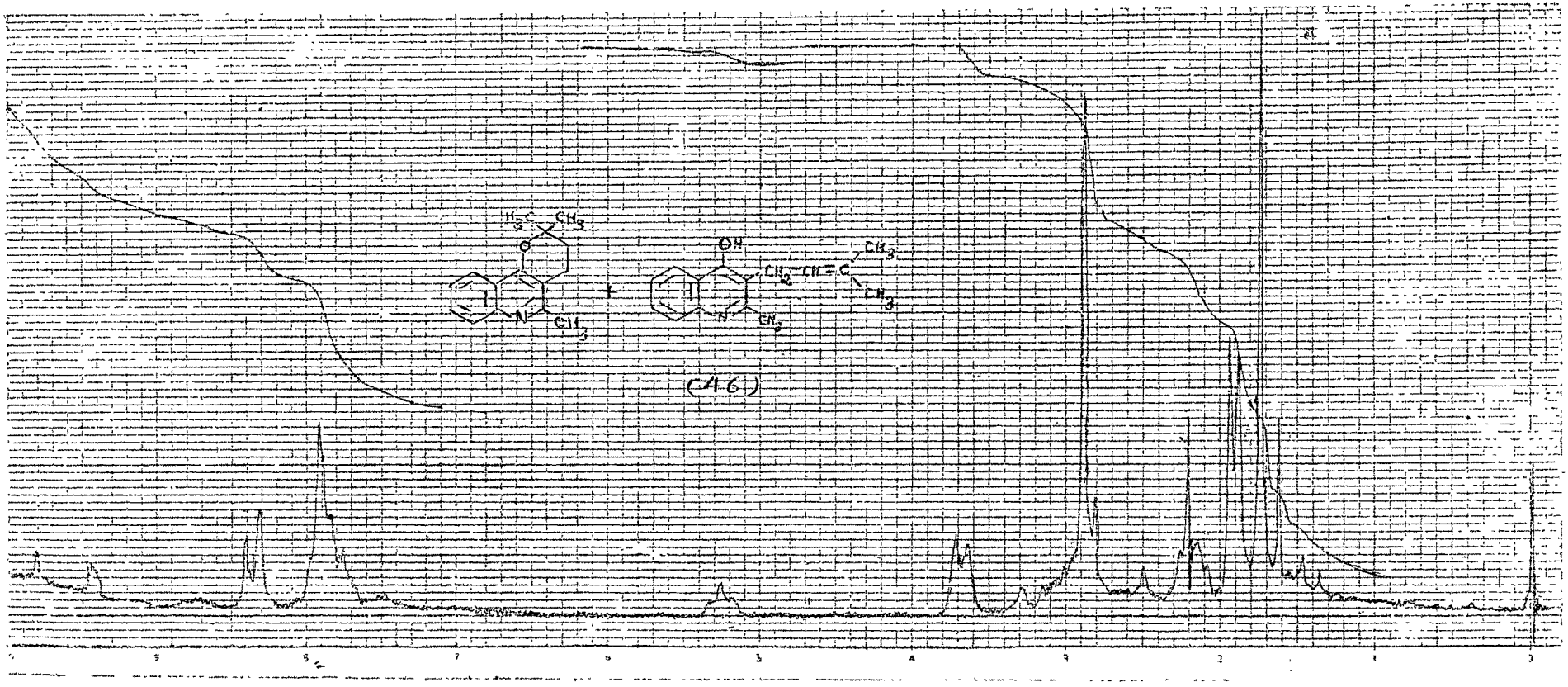
The rearranged products were cyclised with polyphosphoric acid as cyclising agent to give dihydro pyrano (3,2-c) quinoline derivatives. The structure of these pyrano quinolines were confirmed on the basis of their NMR spectra. Dehydrogenation of these dihydro pyranoquinolines using DDQ in dry benzene was next attempted

but it failed to give pyranoquinolines. The synthesis of such pyranoquinoline derivative was finally achieved by carrying out the condensation of 2-methyl-4-hydroxy-quinoline with 3-methyl-3-chloro-1-butyne in the presenee of potassium carbonate.

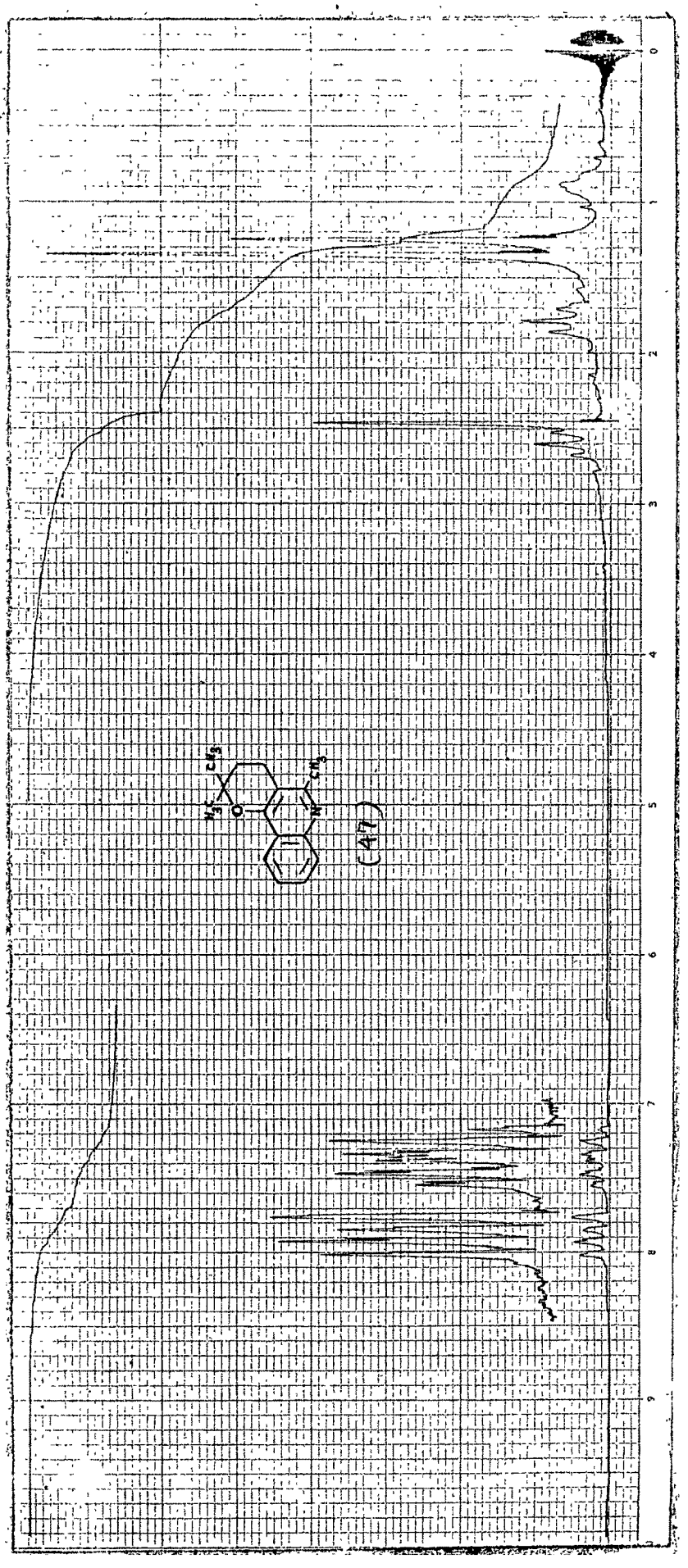
2,2,5-Trimethyl-3,4-dihydro pyrano(3,2-c)quinoline (47) :

3-Methyl-4-hydroxyquinoline, when condensed with 3-methyl-1-chloro-but-2-ene in ethylmethylketone in the presence of potassium carbonate and potassium iodide gave 2-methyl-4-(3-methyl-but-2-enyloxy)quinoline, which when pyrolysed at 190-200° gave the migrated product 2-methyl-3-(3-methyl-but-2-enyl)-4-hydroxyquinoline (46) as benzene insoluble fraction. ~~The structure of migrated product (46) as benzene insoluble fraction.~~ The structure of migrated product (46) was confirmed on the basis of NMR spectrum. NMR spectrum (CF_3COOH) of (46) showed signals at δ; 1.9, doublet, J = 7Hz, 6H, geminal dimethyl group ; 2.89, singlet, 3H, -CH_3 group at C_2 ; 3.7, doublet, J = 8Hz, 2H, -CH_2- gfoup at C_2 ; 327 2.25, triplet, J = 8Hz, 1H, -CH = group and 7.8 -8.4 multiplet, 4H, aromatic. NMR spectrum also showed some additional signals at δ; 1.72, singlet, 6H, geminal dimethyl group ; 2.2, triplet, J = 8Hz, 2H, -CH_2- group at C_4 and a triplet at δ; 2.9 with coupling constant J = 8Hz for -CH_2- group merged with a singlet at δ, 2.9 of methyl group indicating the presence of a cyclic product 2,2,5-trimethyl-3,4-dihydro-pyrano (3,2-c)quinoline. All attempts to separate this mixture met with failure. The (46) was cyclised by using polyphosphoric acid at 140° for about 3 hrs gave cyclic

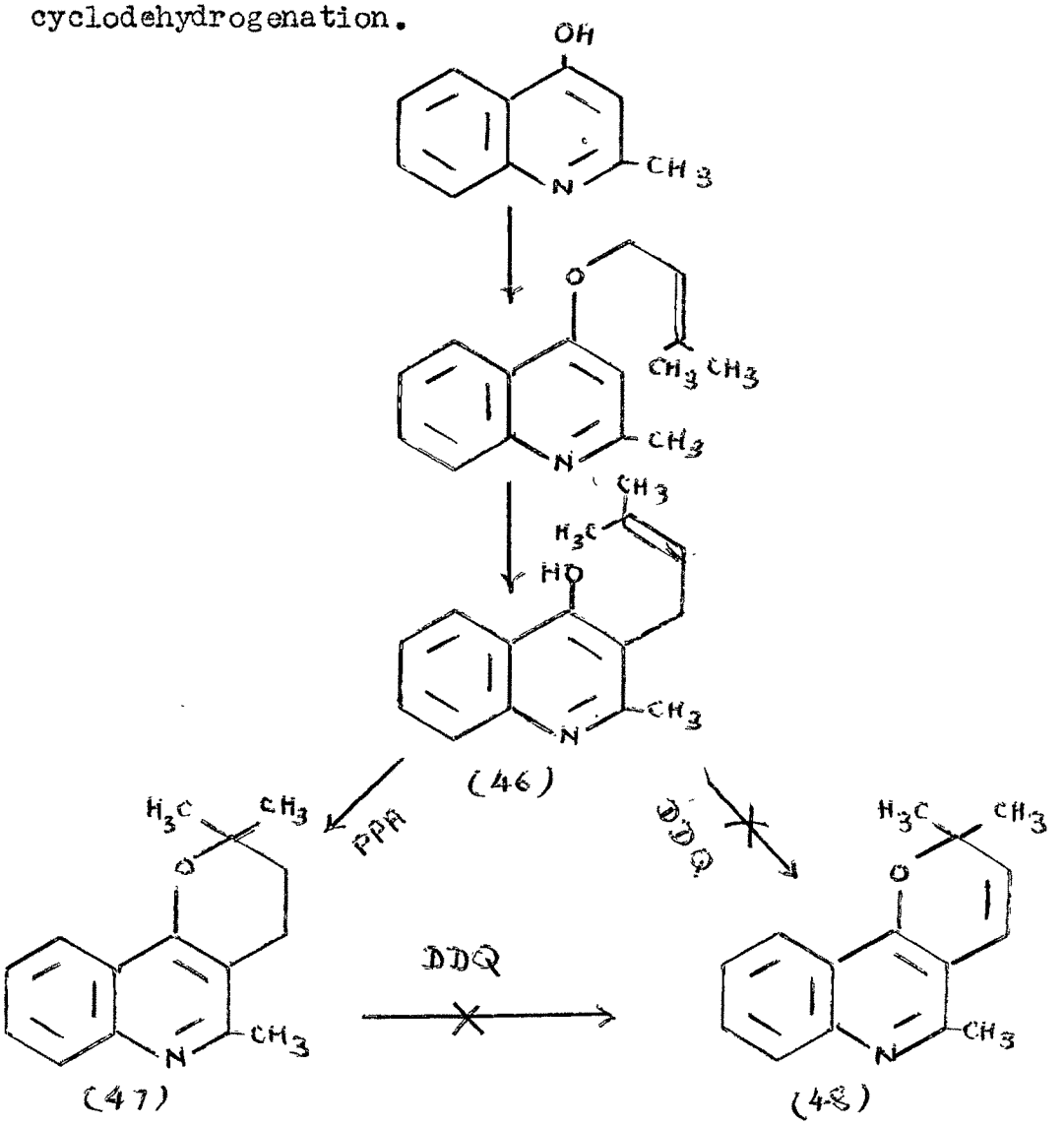

OH
CH3
C
CH3
CH2
CH3
(46)
00
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
FREQUENCY CM-1



(46)

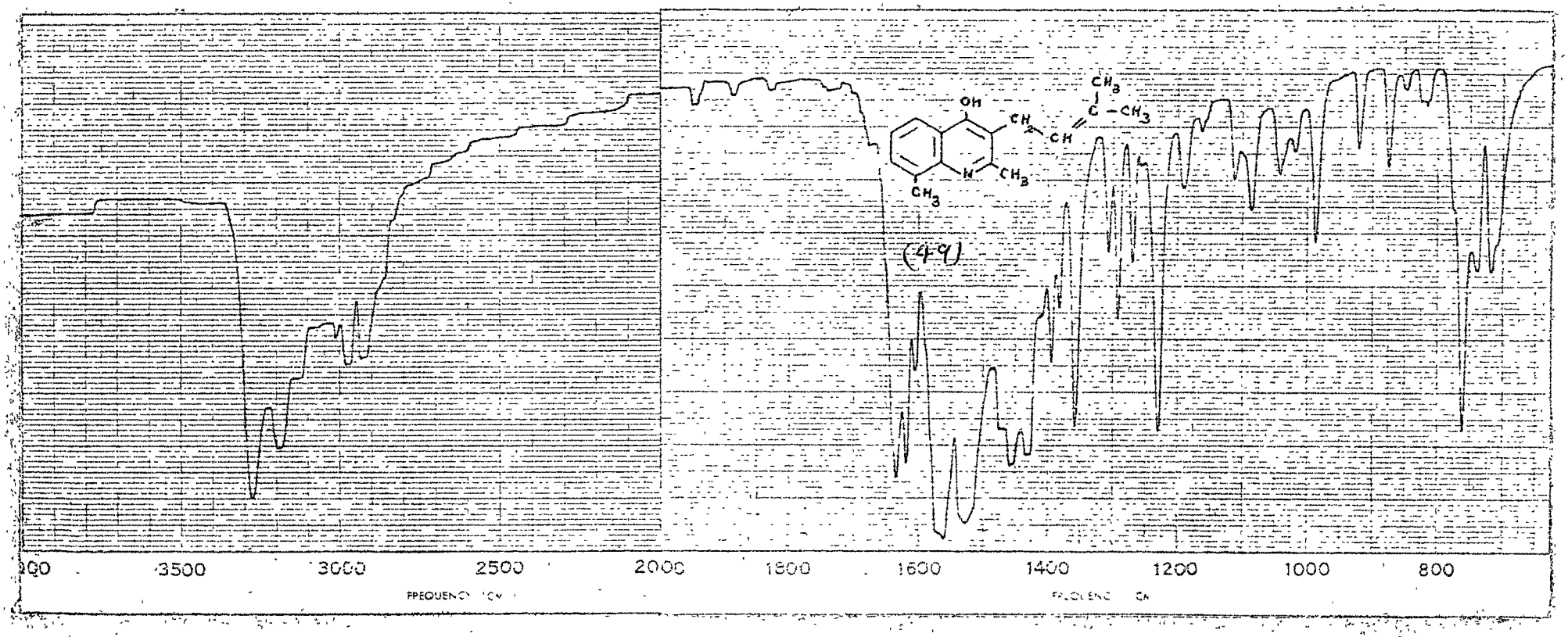

(47)

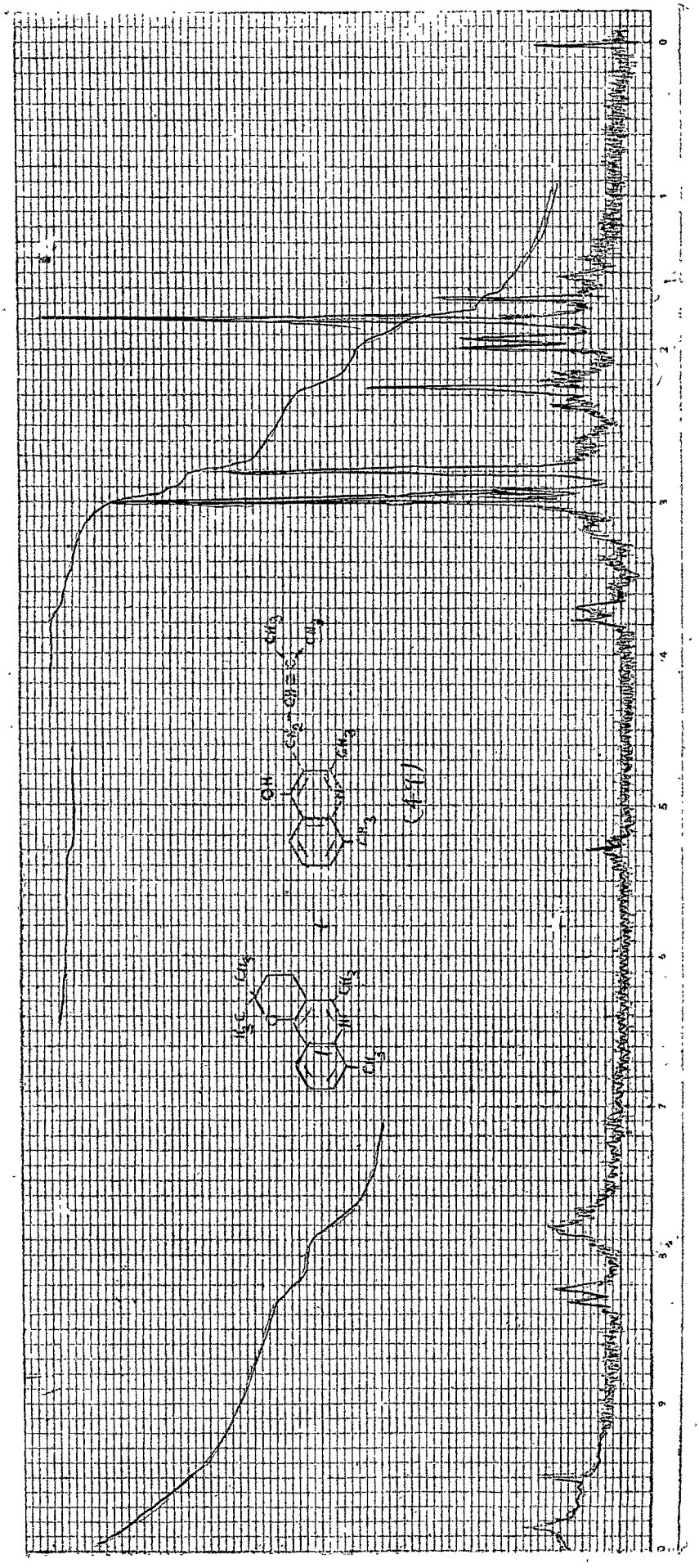
product. 2,2,5-trimethyl-3,4-dihydro pyrano (3,2-c) quinoline (47). NMR spectrum of (47) (CCl_4) showed signals at δ, 1.25 and 1.35, two singlets, 6H, geminal dimethyl group ; 2.46, singlet, 3H, $-CH_3$ group at $-C_5$; 1.80, triplet, J = 8Hz, 2H, $-CH_2-$ group at C_4, 2.60, triplet, J = 8Hz, 2H, $-CH_2-$ group at C_3 and 7.2 -8.05, multiplet, 4-H aromatic. The pyranoquinoline (47) was reacted with DDQ using dry benzene as solvent, but dehydrogenation could not be affected. Similarly (46) was also treated with DDQ in dry dioxan but failed to undergo cyclodehydrogenation.

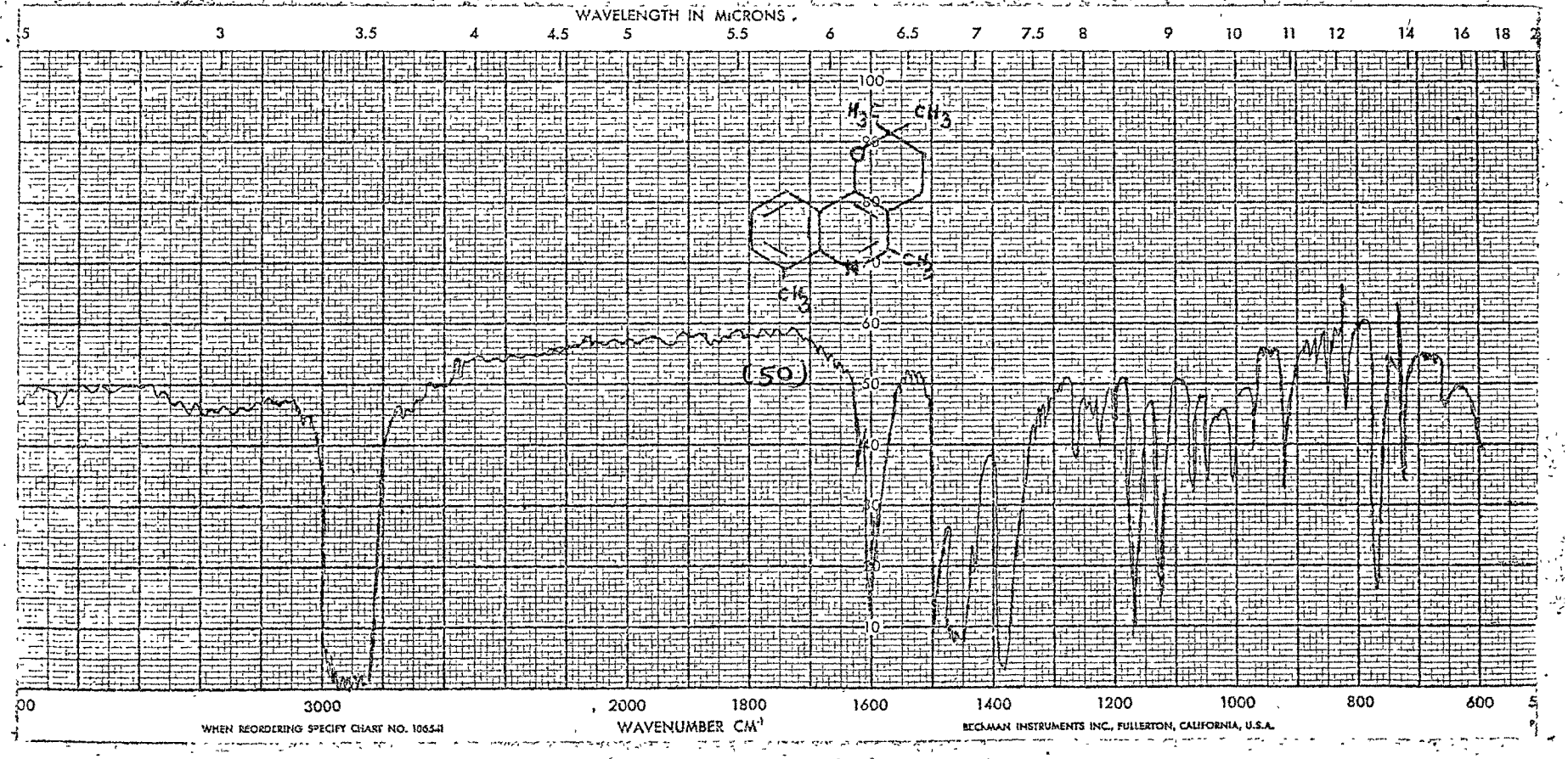


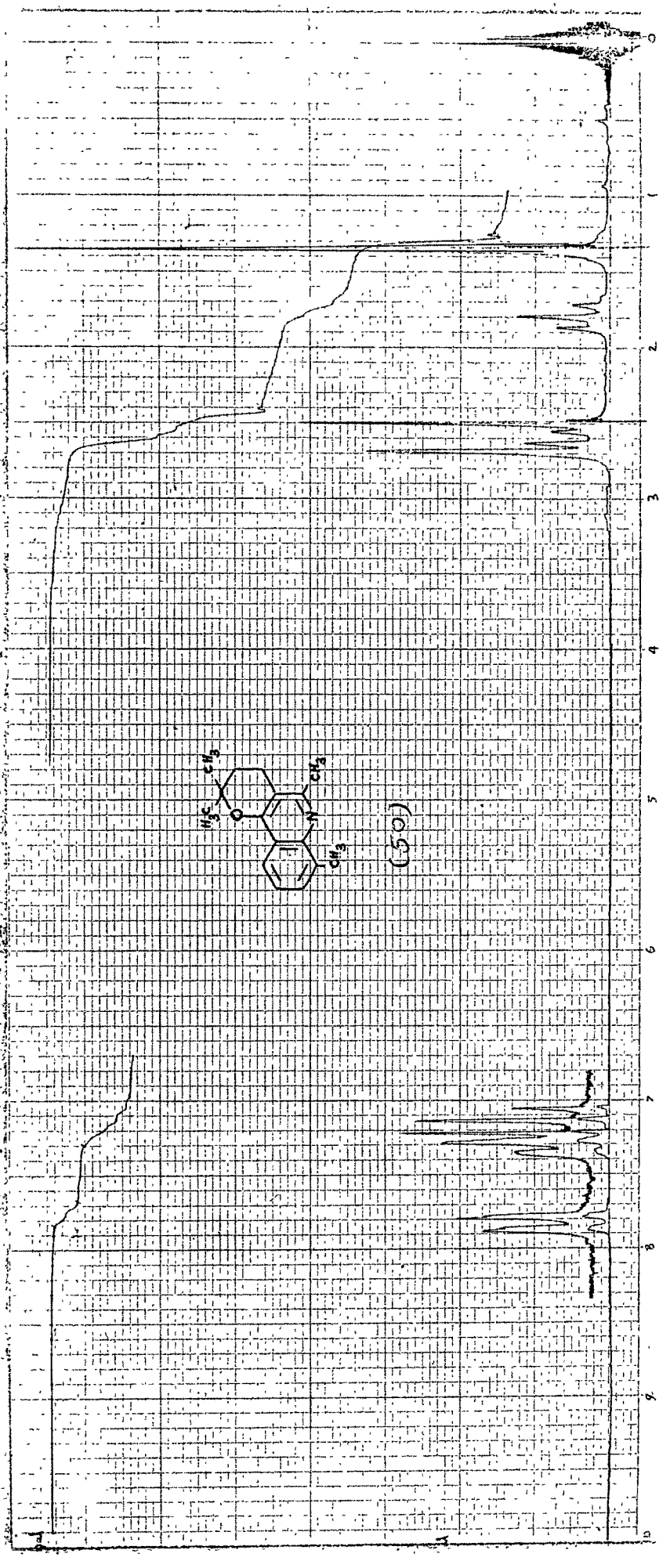
2,2,5,7-Tetramethyl-3,4-dihydro pyrano(3,2-c)quinoline (50):

2,8-Dimethyl-4-hydroxyquinoline on condensation with 3-methyl-1-chloro-but-2-ene in ethylmethylketone in the presence of potassium carbonate and potassium iodide gave 2,8-dimethyl-4-(3-methylbut-2-enyloxy)quinoline, which on pyrolysis at 190-200° gave the migrated product 2,8-dimethyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline (49). The structure of (49) was confirmed by IR and NMR spectra. IR spectrum (KBr) showed characteristic bands at 3270 cm^{-1} for OH group and at 1635 cm^{-1} for >C=C< group. NMR spectrum (CF_3COOH) of (49) showed resonance signals at δ, 1.95, doublet, J = 7Hz, 6H, geminal dimethyl group, 2.8, singlet, 3H, $-CH_3$ group at C_8 ; 3.0, singlet, 3H, $-CH_3$ group at C_2 ; 3.75, doublet, J = 8Hz, 2H, $-CH_2-$ group ; 5.3, triplet, J = 8Hz, 1H, -CH = group at C_2 and 7.7 - 8.35, multiplet, 3H, aromatic. NMR spectrum also showed some additional signals at δ, 1.8, singlet, 6H, geminal dimethyl group ; 2.25, triplet, J = 8Hz, 2H, $-CH_2-$ group at C_4 and a triplet at δ, 2.98 with the coupling constant J = 8Hz for $-CH_2-$ group merged with a strong singlet of methyl group ; indicating the presence of cyclic product 2,2,5,7-tetramethyl-3,4-tetramethyl-3,4-dihydro pyrano(3,2-c) quinoline. All attempts to separate this mixture met with failure. The (49) when cyclised with PPA at 140° to give 2,2,5,7-tetramethyl-3,4-dihydro pyrano (3,2-c)quinoline (50). NMR spectrum of (50), (CCl_4) showed signals at δ, 1.35, singlet, 6H, geminal dimethyl group at C_2 ; 1.8, triplet, J = 8Hz, 2H, $-CH_2-$ at C_4 ; 2.50, singlet, 3H, $-CH_3$ group at C_7 ; 2.62, triplet, J = 8Hz, 2H, $-CH_2-$ at C_3, 2.68, singlet, 3H, $-CH_3$ group at C_5 and 7.05 - 7.9, multiplet, 3H, aromatic


OH
CH2
CH
CH3
CH3
CH3
C
CH3
(49)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800

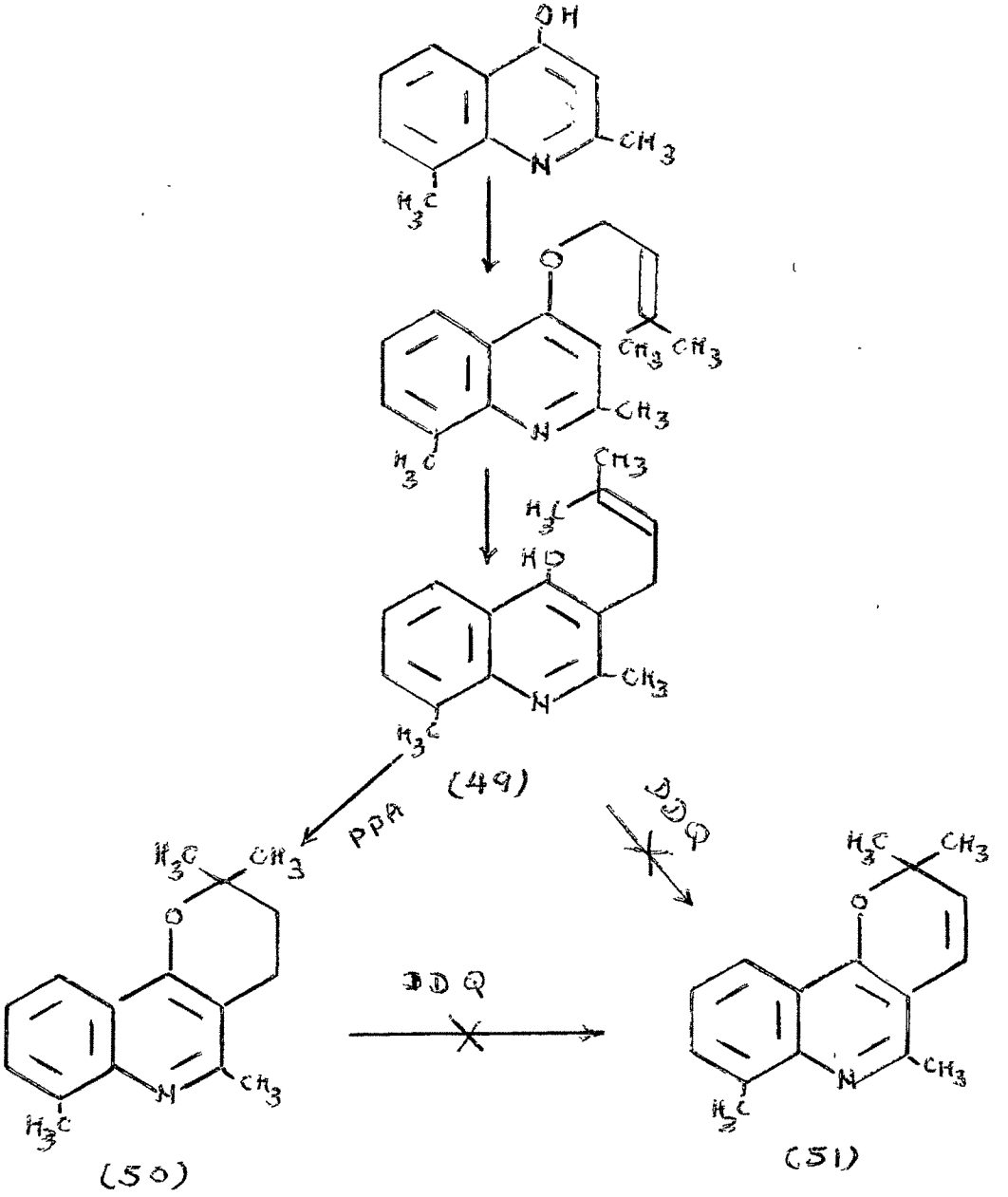



WAVELENGTH IN MICRONS
5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
100
90
80
70
60
50
40
30
20
10
(50)
00
3000
2000
1800
1600
1400
1200
1000
800
600
WHEN REORDERING SPECIFY CHART NO. 1065-H
WAVENUMBER CM⁻¹
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.



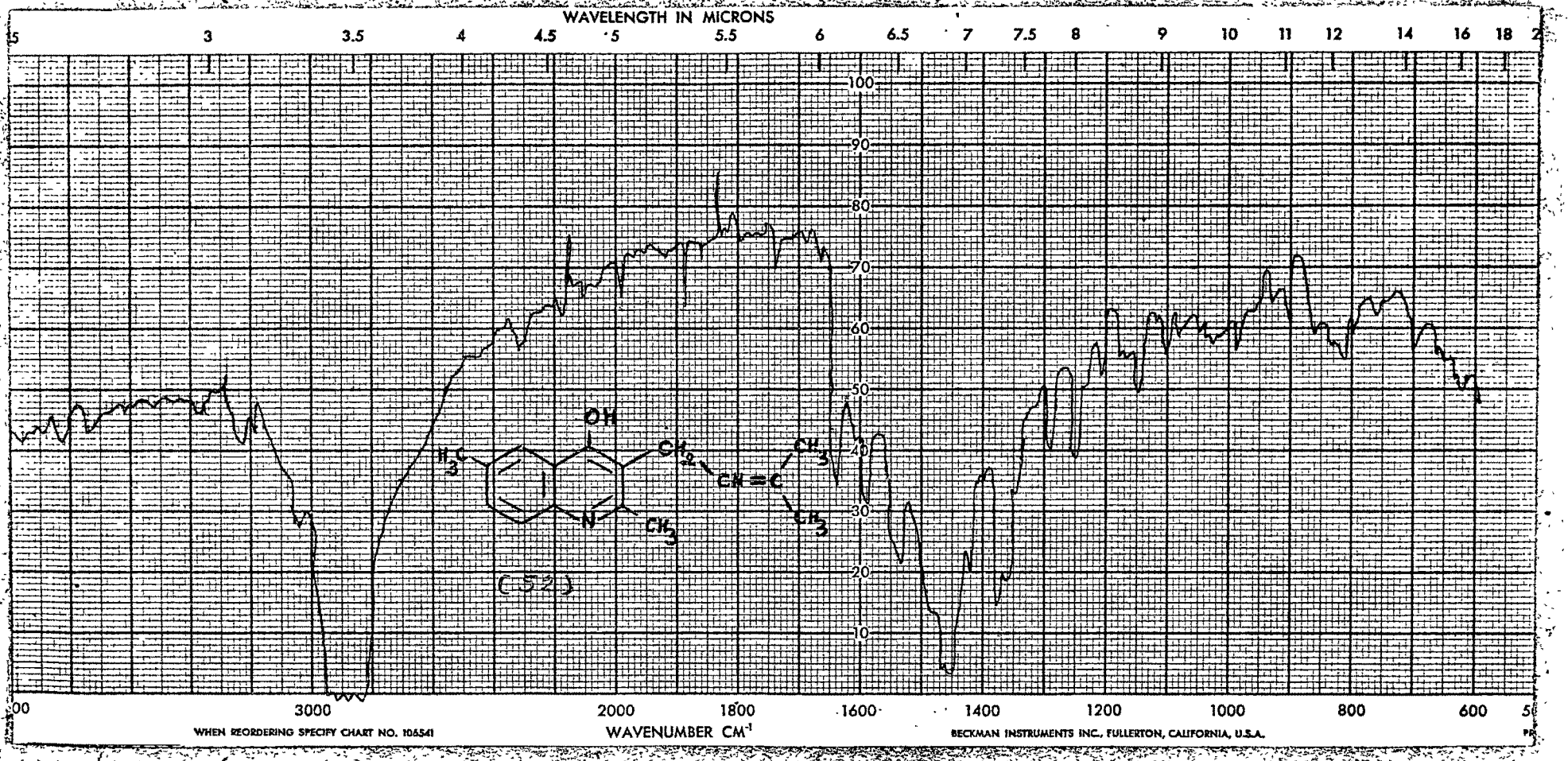
(50)

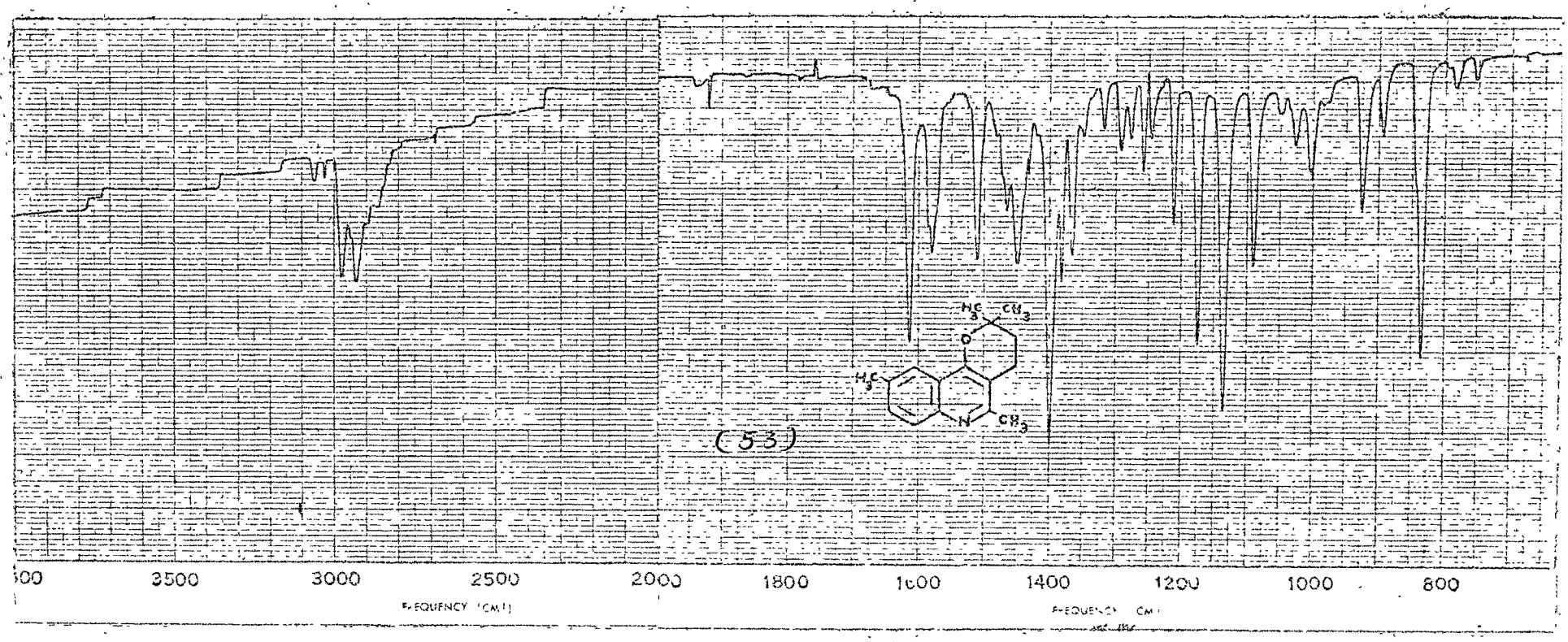
The pyranoquinoline (50) was treated with DDQ using dry benzene as solvent, but dehydrogenated (51) was not obtained. Similarly (49) was also treated with DDQ in dry dioxan but failed to undergo cyclo-dehydrogenation.

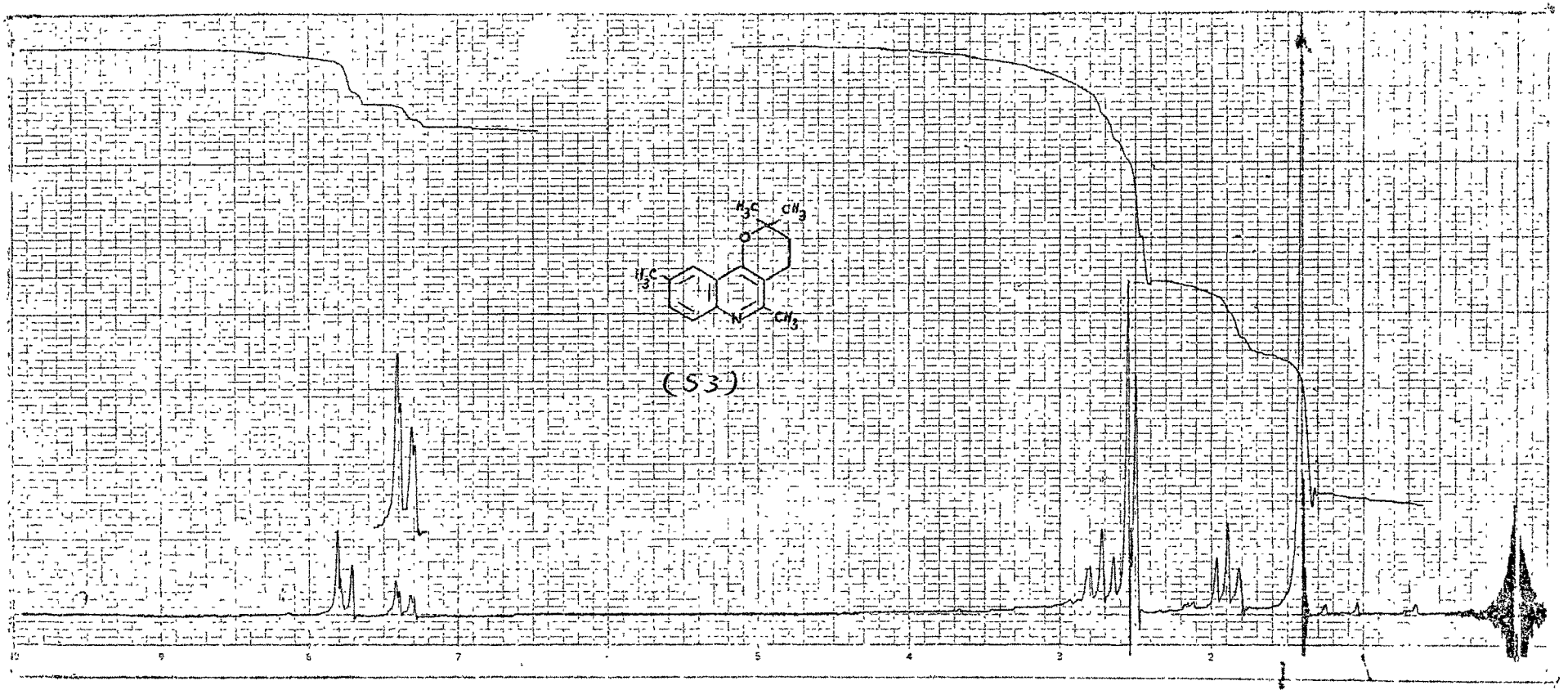


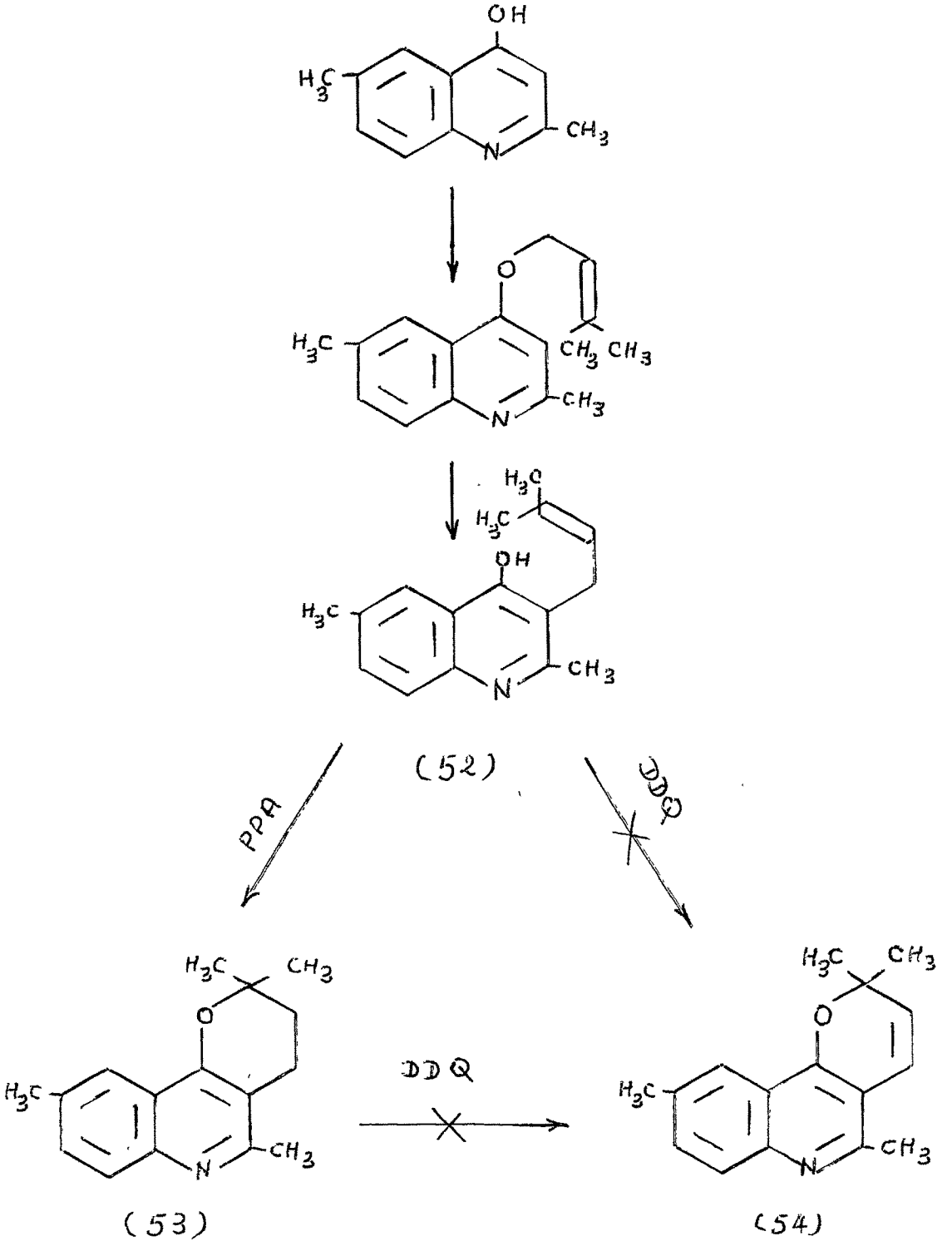
2,2,5,9-Tetramethyl-3,4-dihydro-pyrano(3,2-c)quinoline (53) :

2,6-Dimethyl-4-hydroxyquinoline when condensed with 3-methyl-1-chloro-but-2-ene in ethylmethylketone in the presence of potassium carbonate and potassium iodide, as before, gave 2,6-dimethyl-4-(3-methyl-but-2-enyloxy) quinoline, which on pyrolysis at 190-200° gave the migrated product 2,6-dimethyl-3-(3-methyl-but-2-enyl) -4-hydroxyquinoline (52). The structure of (52) was confirmed by IR spectrum. The IR spectrum (KBr) showed characteristic bands at 3300 cm^{-1} for OH group and 1640 cm^{-1} for >C=C< group. The (52) was cyclised by using PPA at 140° to give 2,2,5,9-tetramethyl-3,4-dihydro-pyrano(3,2-c)quinoline (53). NMR spectrum (C_6Cl_4) of (53).showed signals at δ; 1.4, singlet, 6H, geminal dimethyl group at C_2 ; 1.9, triplet, J = 8Hz, 2H, $-CH_2-$ group at C_4 ; 2.72, triplet, J = 8Hz, 2H, $-CH_2-$ group at C_3 ; 2.5 ; singlet, 3H, $-CH_3$ group at C_9 ; 2.55, singlet, 3H, $-CH_3-$ group at C_5 and 7.3 - 7.8, multiplet, 3H, aromatic protons. The pyranoquinoline (53) was treated with DDQ using dry benzene as solvent, but dehydrogenated product (54) was not obtained. Similarly (52) was also treated with DDQ in dry dioxan but failed to undergo cyclo-dehydrogenation.


WAVELENGTH IN MICRONS
5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
100
90
80
70
60
50
40
30
20
10
OH
H_3C
CH_2
$CH=C$
CH_3
CH_3
N
CH_3
(52)
00
3000
2000
1800
1600
1400
1200
1000
800
600
WHEN REORDERING SPECIFY CHART NO. 106541
WAVENUMBER CM^{-1}
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.


3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
(53)


H3C
CH3
O
H3C
N
CH3
(53)
10
9
8
7
6
5
4
3
2
1



(52)

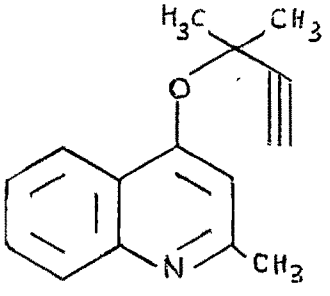
(53)

(54)

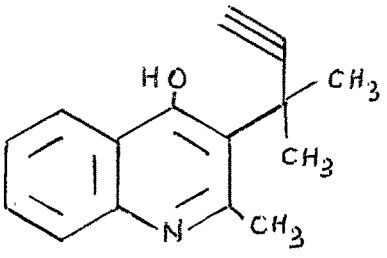
Synthesis of 2,2,5-Trimethylpyrano (3,2-c) quinoline derivative (48) :

As it was observed that 2-methyl-3-(3-methyl-but-2-enyl)-4-hydroxyquinoline derivatives as well as 2,2,5-trimethyl-3,4-dihydro pyrano (3,2-c) quinoline derivatives failed to undergo cyclo-dehydrogenation and dehydrogenation, respectively, to give 2,2,5-trimethyl-pyrano~~quinoline~~ (3,2-c) quinoline derivatives, the condensation of 3-methyl-3-chloro-but-1-yne with 2-methyl-4-hydroxyquinoline was next tried. Thus when 2-methyl-4-hydroxyquinoline was condensed with 3-methyl-3-chloro-but-1-yne in the presence of potassium carbonate and potassium iodide using ethylmethylketone as solvent, the cyclic product 2,2,5-trimethyl pyrano (3,2-c) quinoline was obtained directly. The intermediate 2-methyl-4-(2-methyl-but-3-yneloxy) quinoline (54), or its rearranged product 2-methyl-3(2-methyl-but-3-ynyl)-4-hydroxyquinoline (55) or 2-methyl-3-(3-methyl-but-1,2-diene) (56) could not be isolated. Similar results were obtained by Huffman and Hsu[12]. They found that when thallous salt of 4-hydroxy-8-methoxy-2-quinolone condensed with 3-chloro-3-methyl-1-butyne, two products were obtained but none of them was corresponding to ether. One of these product was 2,2-dimethyl-7-methoxy-4-oxo-4H-pyrano (3,2-c) quinoline (57). The NMR spectrum of (57) showed vinyl doublets at δ; 6.78 and 5.58 with coupling constant J = 10Hz and six proton methyl singlet at δ = 1.56. The NMR spectrum (C_6Cl_4) of (48) also showed signal at δ;

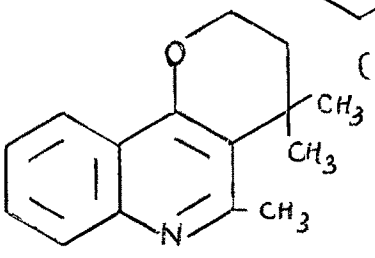
6.58 and 5.58, two doublet, J = 10Hz, 2H, vinyl protons, 1.5, singlet, 6H, geminal methyl groups, 2.58, singlet, 3H, $-CH_3$ group at C_5 and 7.28 - 8.0, multiplet, 4H, aromatic. Hence it is suggested that first ether (54) might have formed which underwent antimarkovnikoff cyclisation and results into a cyclic product, 2,2,5-trimethyl pyrano (3,2-c)quinoline. It is certain that this is not the case of C-alkylation followed cyclisation to give pyranoquinoline. If it would have been the case the compound would have either structure (58) or (59), which would have shown different NMR signals.



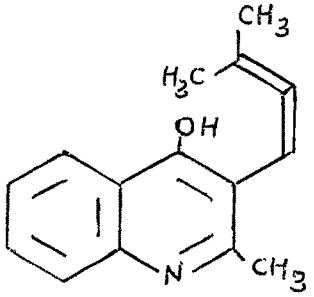
(54)



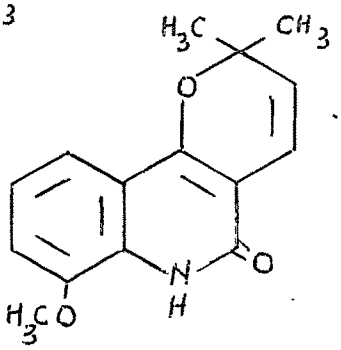
(55)



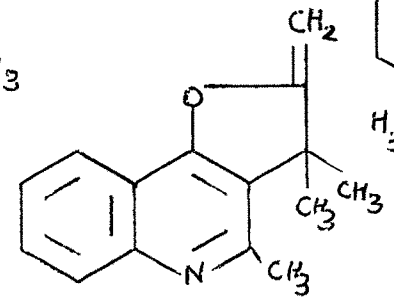
(58)



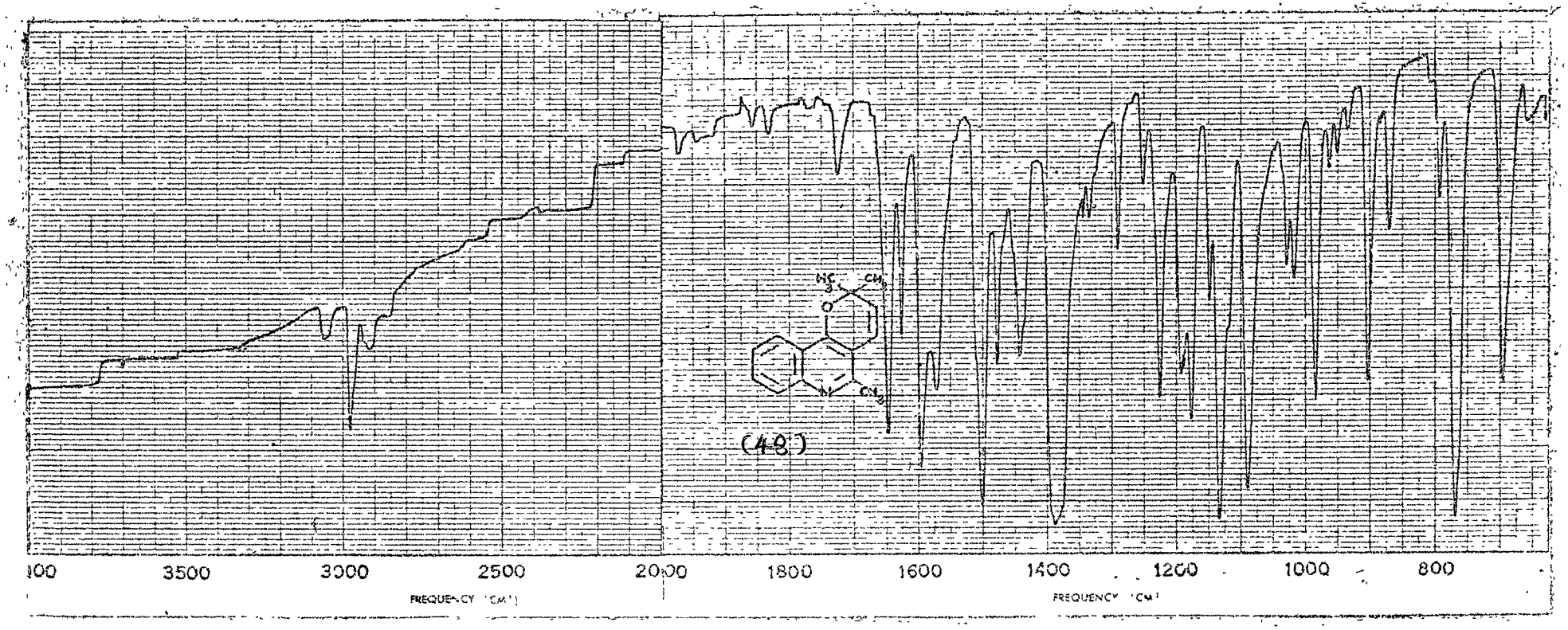
(56)

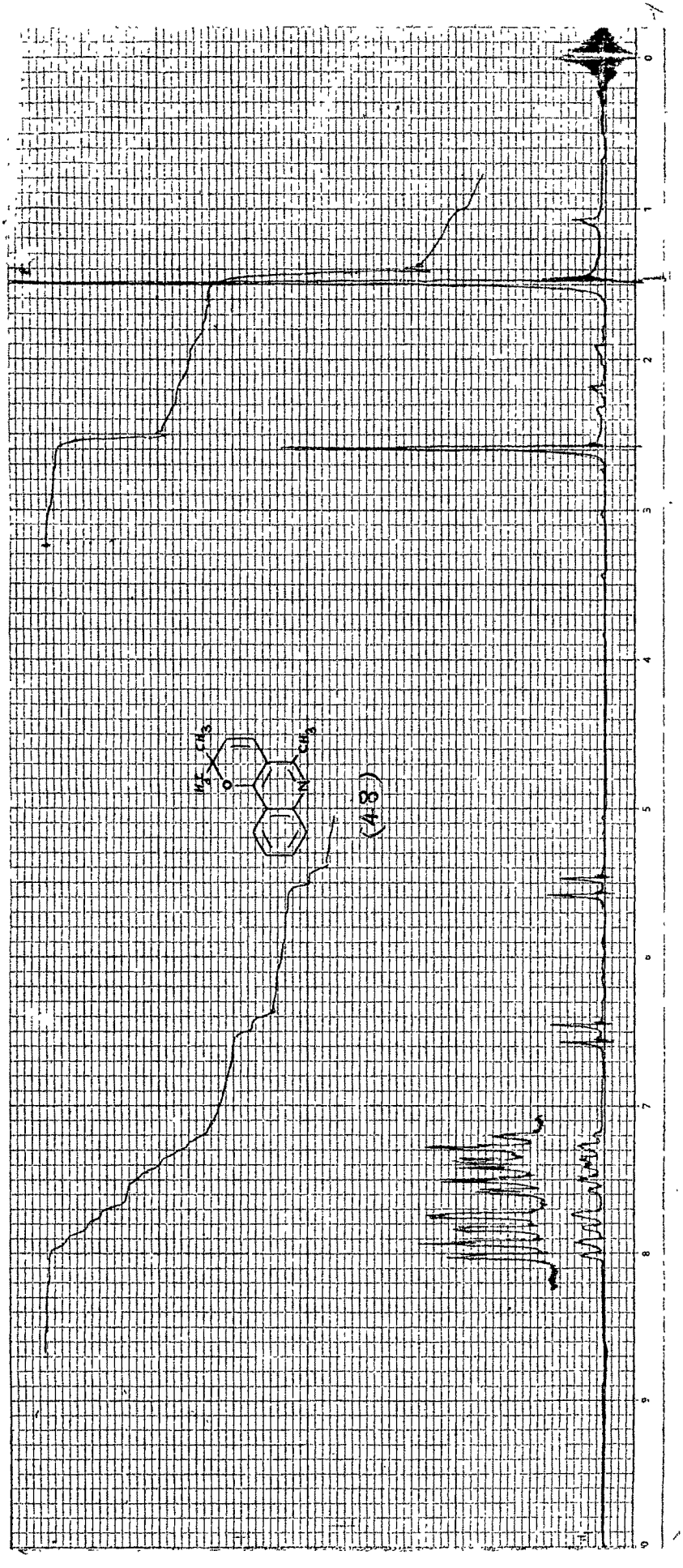


(57)

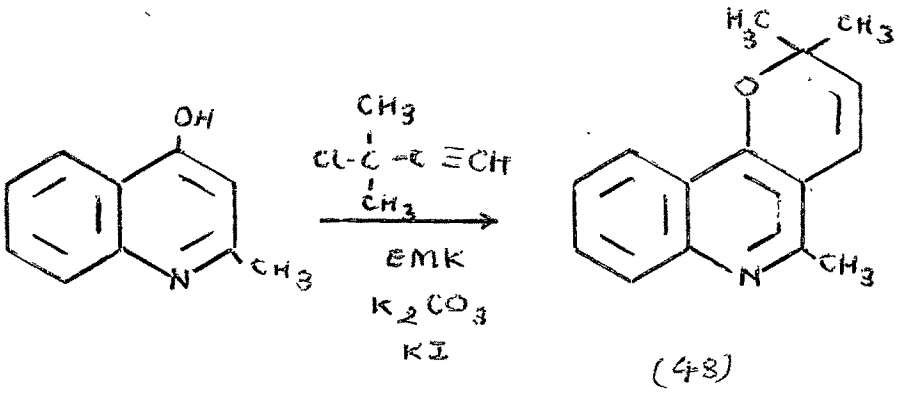


(59)


(48)
100
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY (CM⁻¹)


(48)

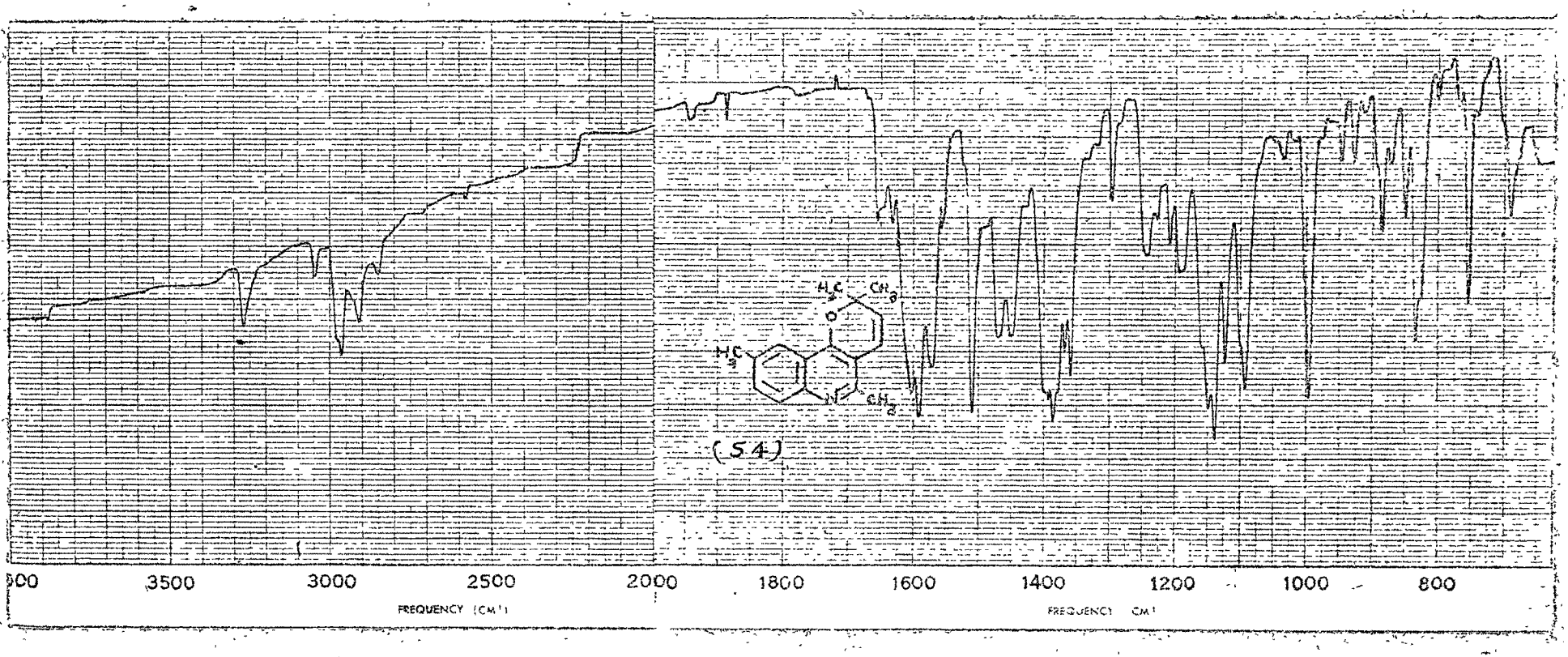
Thus on the basis of NMR spectrum the structure of cyclic compound obtained by condensation of 2-methyl-4-hydroxyquinoline with 3-methyl-3-chloro-but-1-yne was assigned as (48) and not (58) or (59).



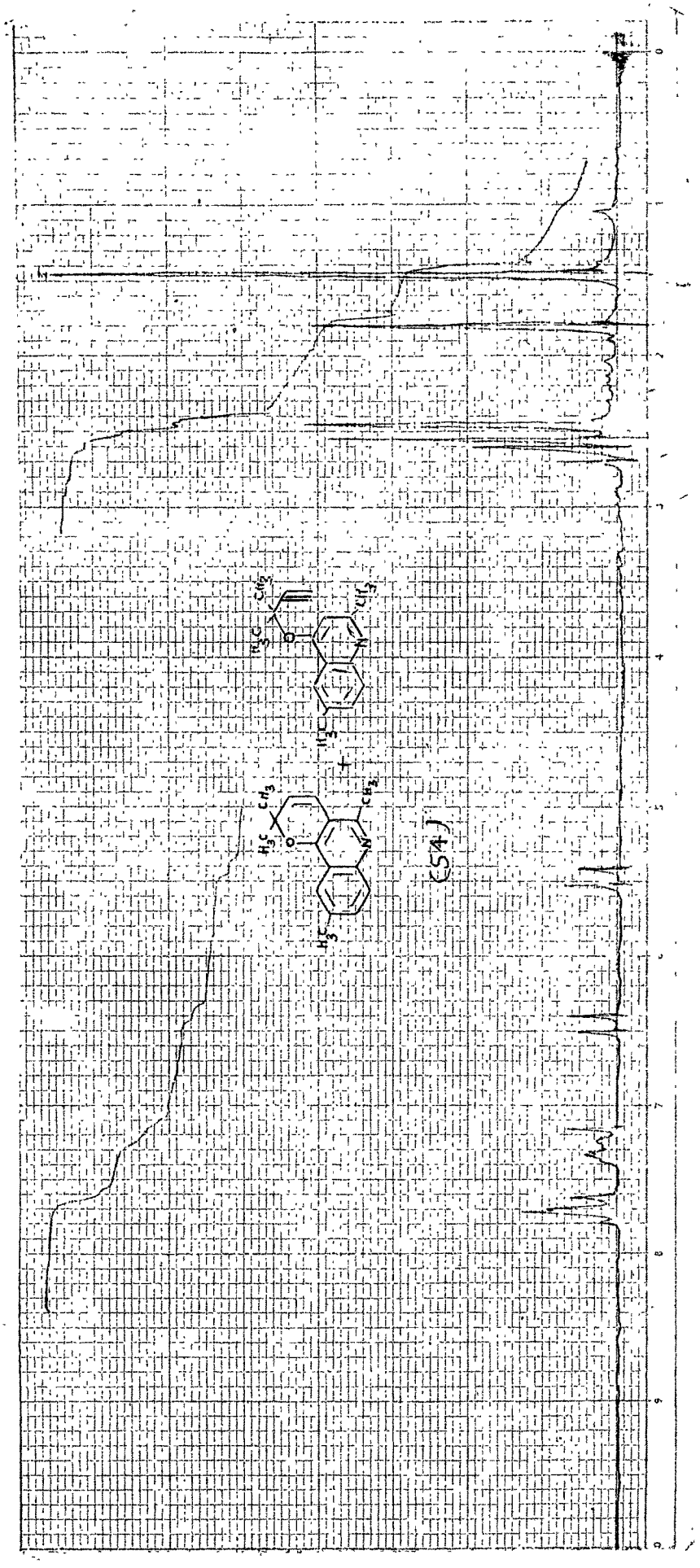
(48)

2,2,5,9-Tetramethyl pyrano(3,2-c)quinoline (54) :

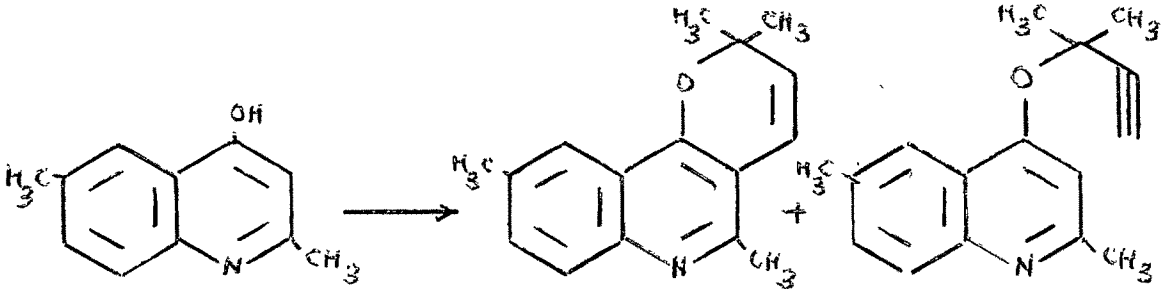
2,6-Dimethyl-4-hydroxyquinoline when condensed with 3-chloro-3-methyl-1-butyne in the presence of potassium carbonate and potassium iodide using ethylmethylketone as solvent gave the 2,2,5,9-tetramethyl pyrano (3,2-c)quinoline (54). NMR spectrum (C Cl_4) of (54) showed signals at δ, 1.45, singlet, 6H, geminal dimethyl group at C_2 ; 2.48, singlet, 3H, $-CH_3$ group at C_9 ; 2.56, singlets, 3H, $-CH_3$ group at C_5 ; 5.1 and 6.5, two doublets, J = 11Hz, vinylic protons and 7.15 - 7.8, multiplet, 3H, aromatic. The NMR spectrum also showed some additional signals at δ, 1.8, singlet, 6H, geminal dimethyl group and a singlet at δ, 2.6 for 1H of methyne ≡ CH group : indicating the presence of


3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY CM⁻¹

(54)


(54)

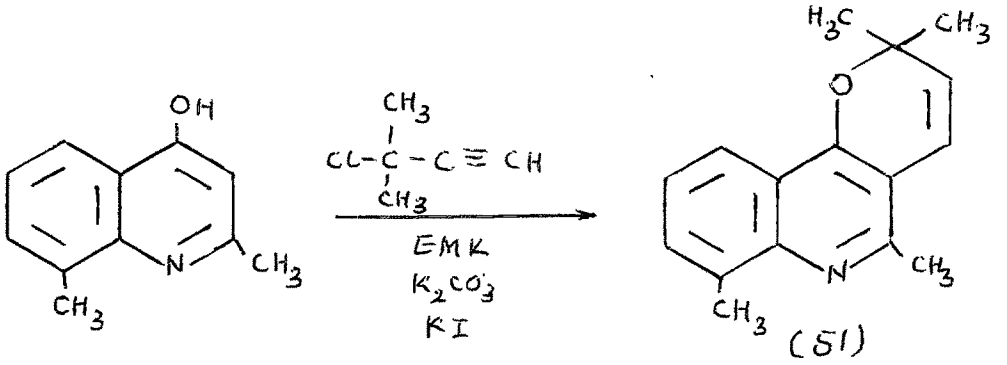
2,6-dimethyl-4-(2-methyl-3-butynyl-2-oxy)quinoline (54-A) along with cyclic product (54). IR spectrum of the (54) also showed one charactoristic band at 3270 cm^{-1} for C ≡ CH stretching, supporting the presence of (54-A) along with (54). All attempts to separate the mixture met with failure.



(54) (54-A)

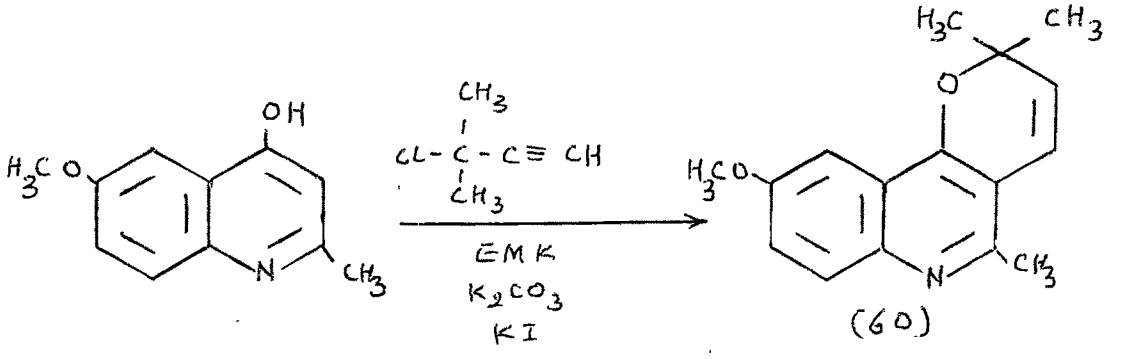
2,2,5,7-Tetramethylpyrano (3,2-c)quinoline (51) :

2,8-Dimethyl-4-hydroxyquinoline was similarly condensed with 3-chloro-3-methyl-1-butyne in the presence of potassium carbonate and potassium iodide using ethylmethylketone as solvent gave 2,2,5,7-tetramethyl pyrano (3,2-c)quinoline (51). The structure of (51) was assigned on the basis of analogy with the above products.



2,2,5-Trimethyl-9-methoxypyrano (3,2-c)quinoline (60) :

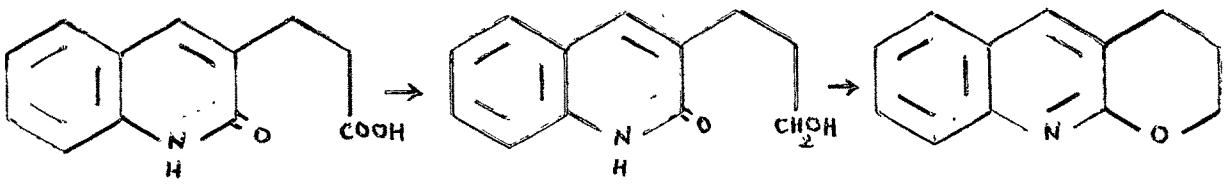
2-Methyl-6-methoxy-4-hydroxyquinoline was condensed with 3-chloro-3-methyl-1-butyne in the presence of potassium carbonate and potassium iodide using ethylmethylketone as solvent gave (60). The structure of (60) was assigned on the basis of analogy with the above products.



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

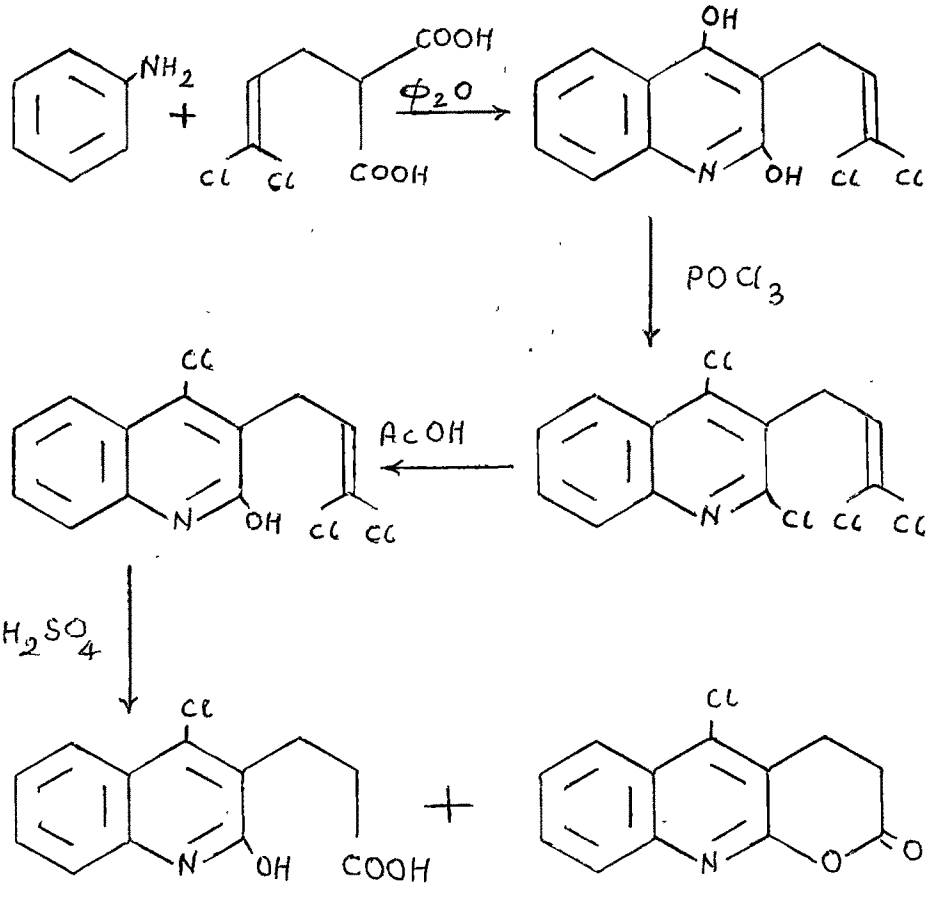
In literature various methods are available for the synthesis of pyrano (3,2-c)quinoline derivatives but few are known to prepare pyrano (2,3-b)quinoline derivatives. Generally, pyrano (3,2-b)quinoline derivatives were obtained from 4-allyloxy quinoline derivatives, followed by Claisen rearrangement and cyclisation. But pyrano (2,3-b)quinoline derivatives could not be obtained by subjecting 2-allyloxy quinoline derivatives to Claisen rearrangement, followed by cyclisation. Many attempts were made for the synthesis of pyrano (2,3-b)quinoline derivatives by preparing ∝-allyl-acetoacetanilide derivatives, followed by cyclisation. But such attempts lead to the formation of furo (2,3-b) quinoline instead of pyrano (2,3-b) quinoline derivatives.

Shanmugam and Ramkrishnan[28] obtained 1,2-dihydro-2-oxo-3-quinoline-propionic acid (61) from o-aminobenzaldehyde, which after esterification and followed by reduction using $LiAlH_4$ in THF gave 1,2-dihydro-2-oxo-3-quinoline propanol (62). The cyclisation of (62) by PPA gave 3,4-dihydro-2 H-pyrano (2,3-b)quinoline (63).



(61) (62) (63)

Gyul'budagyan and Durgaryan[29] prepared 2-oxo-pyrano (2,3-b)quinolines (64) by the condensation of aniline with diethyl-3',3'-dichloro-propenyl malonate (Cl_2-C=CH-CH_2-CH ($COOC_2H_5$)$_2$) in boiling diphenyl oxide followed by $POCl_3$ chlorination and acid hydrolysis by mixture of acetic acid and sulphuric acid.

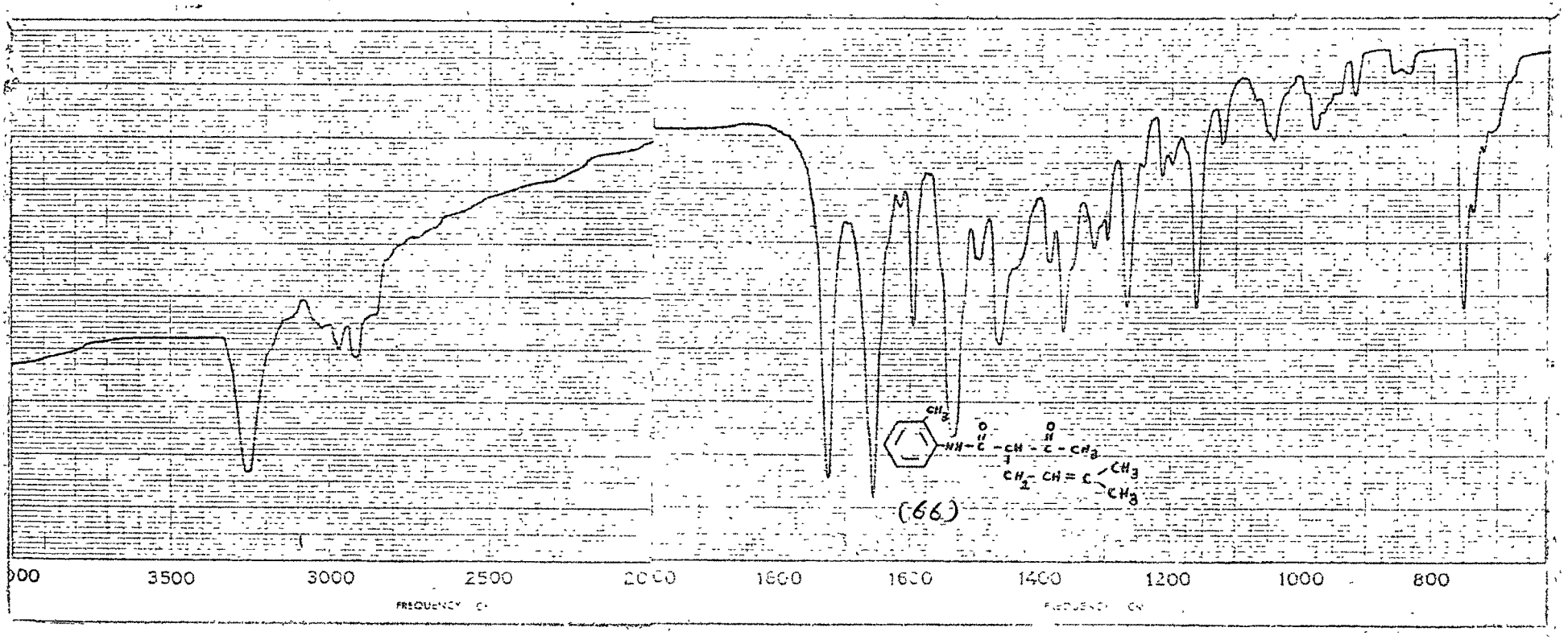


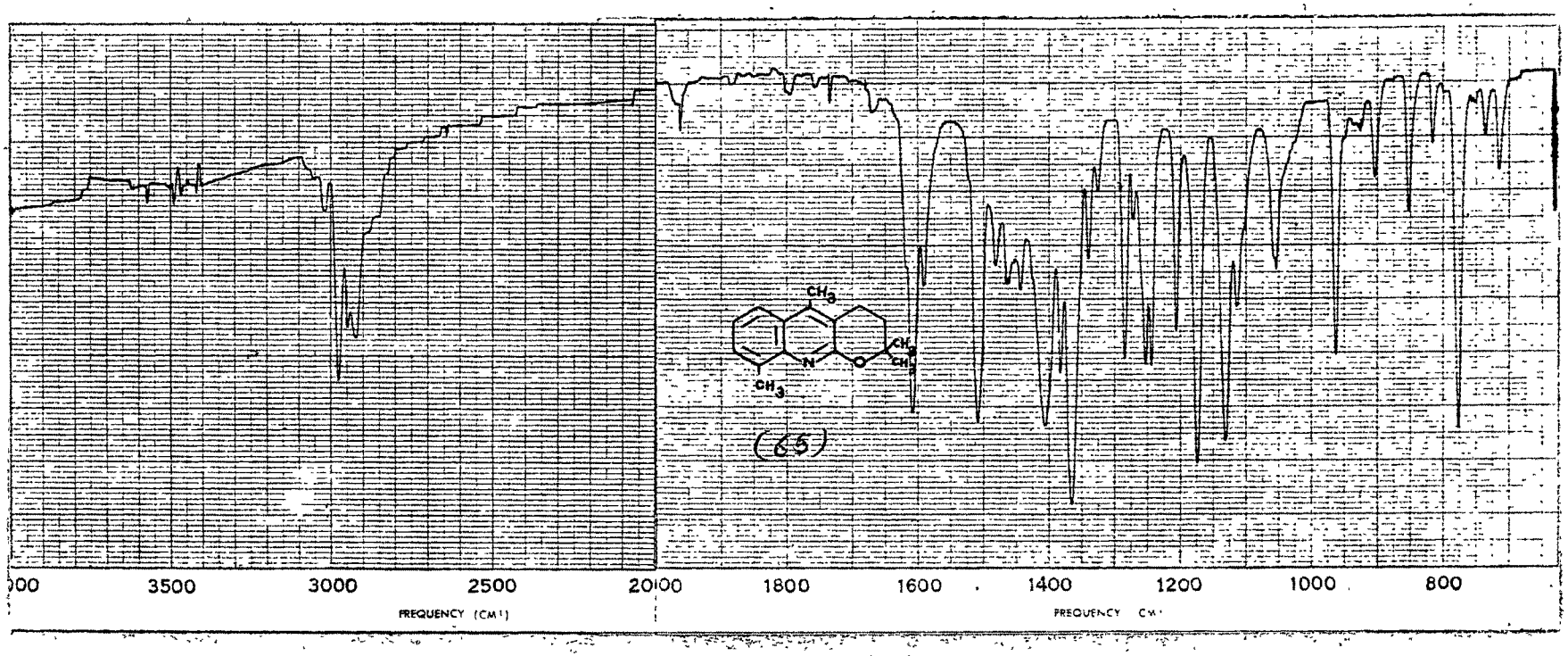
(64)

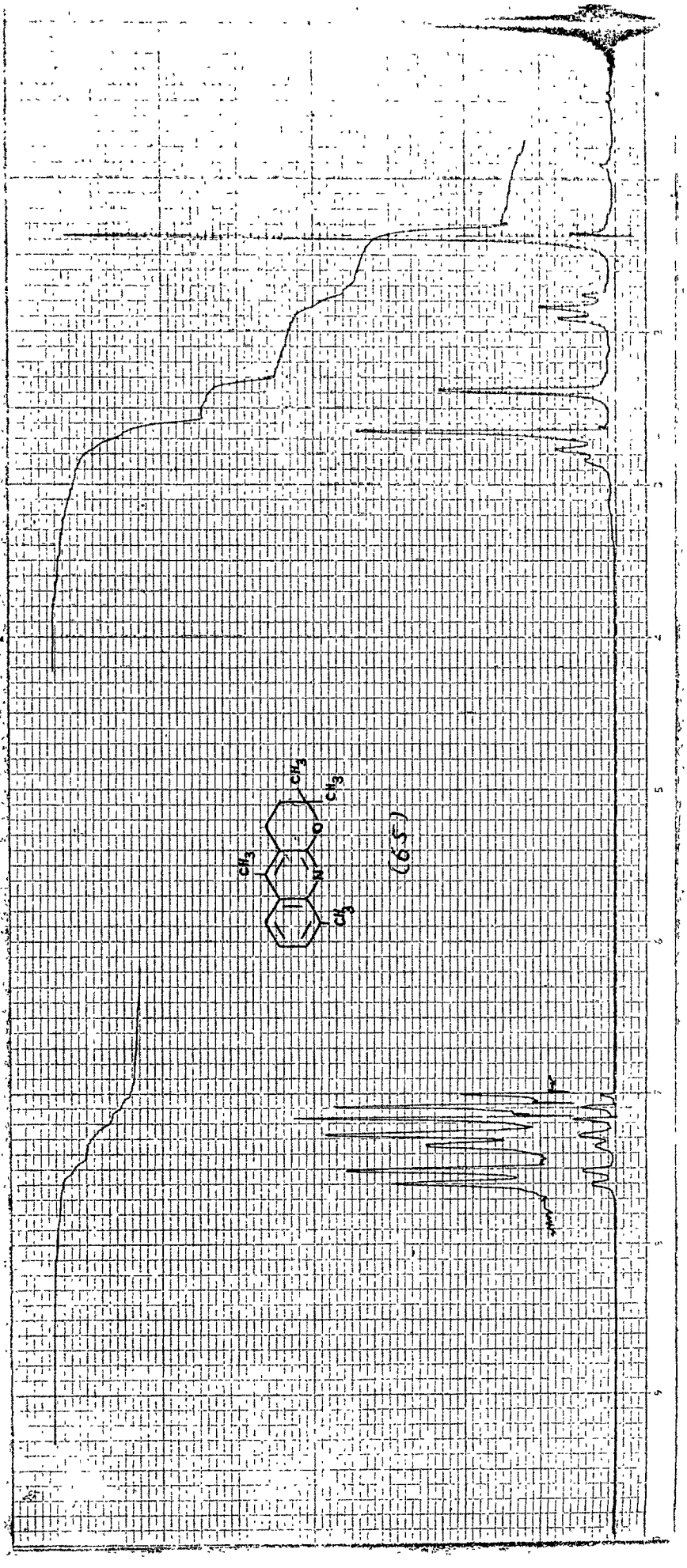
The present work deals with the synthesis of the pyrano (2,3-b)quinoline derivatives from the α-(3-methyl-2-butenyl) acetoacetanilide derivatives which were prepared by the condensation of sodium acetoacetanilide with 3-methyl-1-chloro-but-2-ene. The α-(3-methyl-but-2-enyl) acetoacetanilide derivatives when cyclised with polyphosphoric acid gave corresponding pyrano (2,3-b) quinoline derivatives. The structure of pyrano (2,3-b) quinoline derivatives as well as α-(3-methyl-2-butenyl) acetoacetanilide derivatives were confirmed by IR and NMR spectra.

2,2,5,9-Tetramethyl-3,4-dihydro-pyrano (2,3-b)quinoline (65)

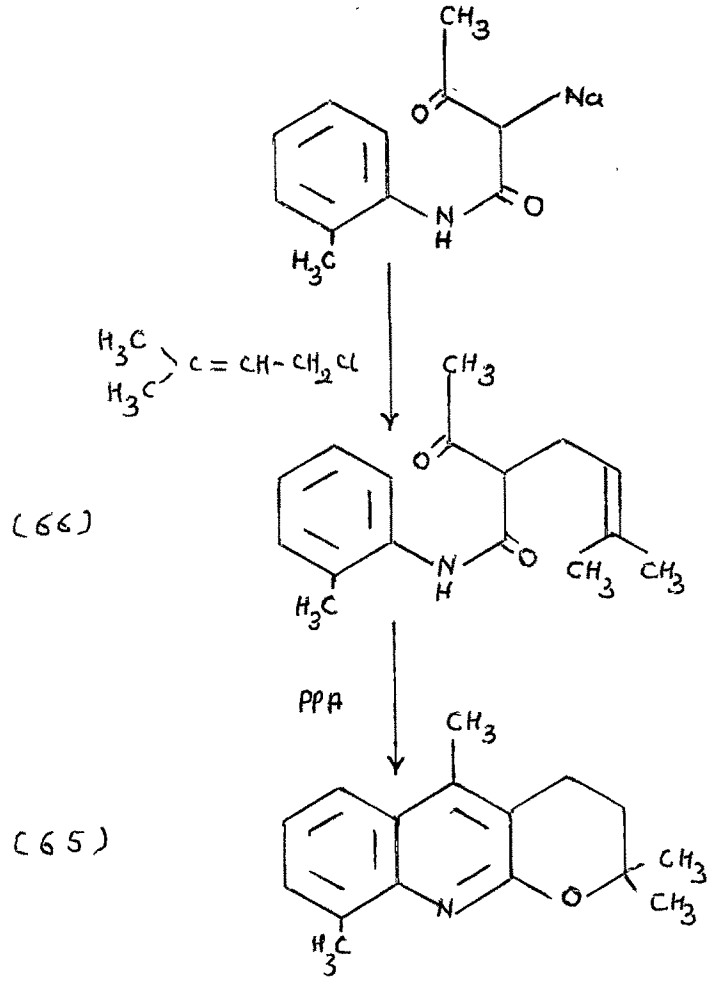
Sodium salt of acetoacet-o-toluidide was condensed with 3-methyl-1-chloro-but-2-ene in dry benzene gave α-(3-methyl-but-2-enyl) acetoacet-o-toluidede (66). IR spectrum (KBr) of (66) showed characteristic bands at 3250 cm^{-1} for -NH group 1725 cm^{-1} for carbonyl group (>C=O) and at 1652 cm^{-1} for >C=C< group. (66), on treatment with polyphosphoric acid at 140° gave 2,2,5,9-tetramethyl-3,4-dihydro-pyrano (2,3-b)quinoline (65). NMR spectrum (C_6Cl_4) of (65) showed signals at δ; 1.38, singlet, 6H, geminal dimethyl group at C_2 ; 1.84, triplet, J = 8Hz, 2H, at C_3 ; 2.79, triplet, J = 8Hz, 2H, at C_4 ; 2.40, singlet, 3H, $-CH_3$ group at C_5 ; 2.65, singlet, 3H, $-CH_3$ group at C_9 and 7.0 - 7.6, multiplet, 3H, aromatic.


3500
3000
2500
1800
1600
1400
1200
1000
800
(66)


CH3
CH3
CH3
N
O
CH3
(65)
00
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
FREQUENCY CM-1


CH3
CH3
O
CH3
N
CH3
(6.5)

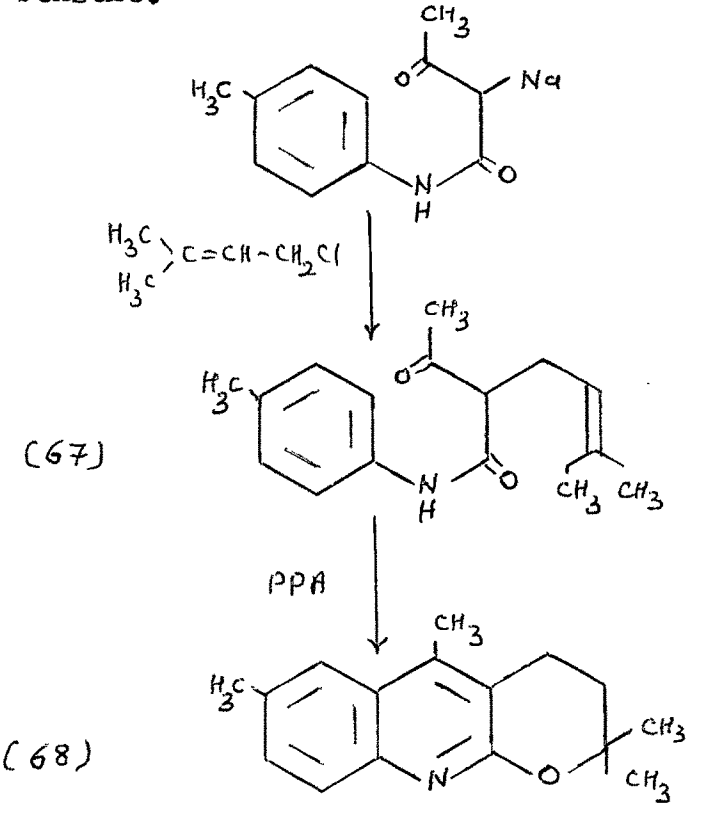
(65) on treatment with DDQ in dry benzene did not give dehydrogenated product.



2,2,5,7-Tetramethyl-3,4-dihydropyrano (2,3-b)quinoline (68) :

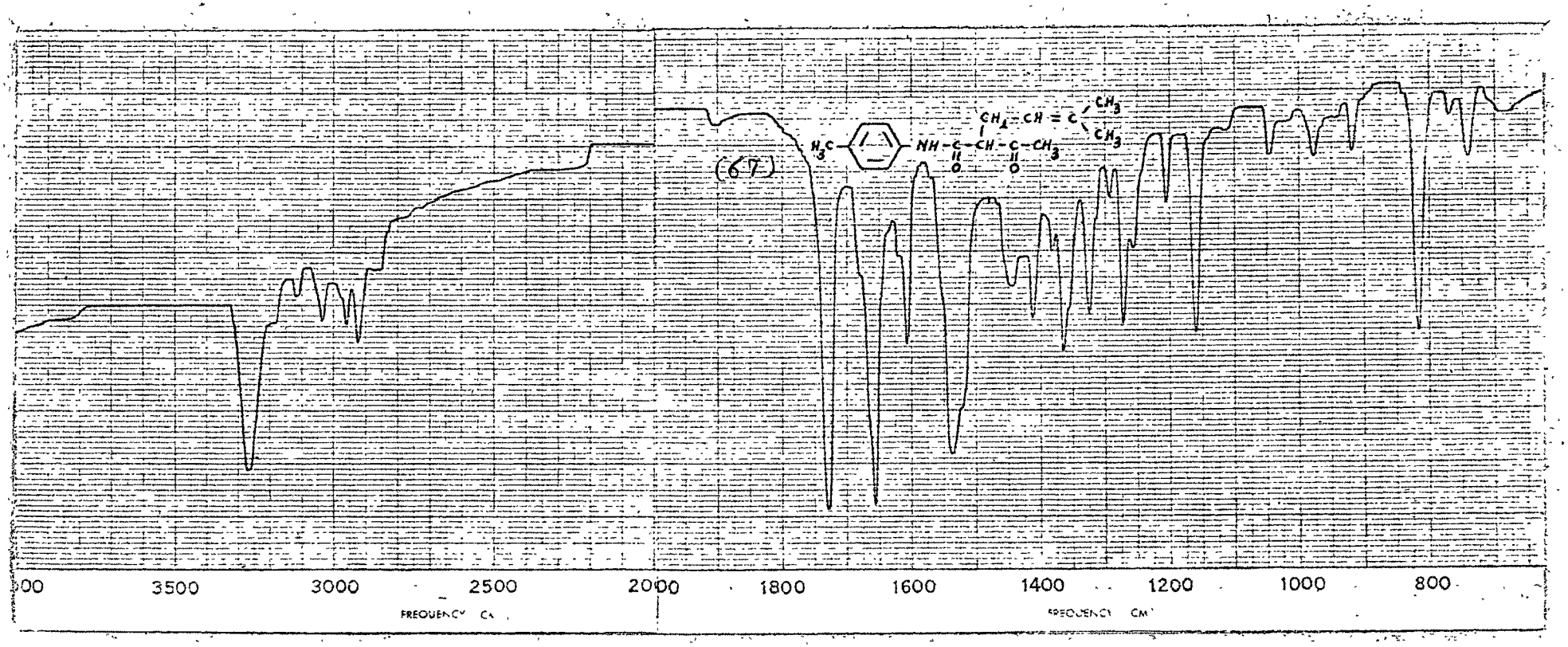
Sodium salt of acetoacet-p-toluidide when condensed with 3-methyl-1-chloro-but-2-ene in dry benzene gave α-(3-methyl-but-2-enyl) acetoacet-p-toluidide (67).

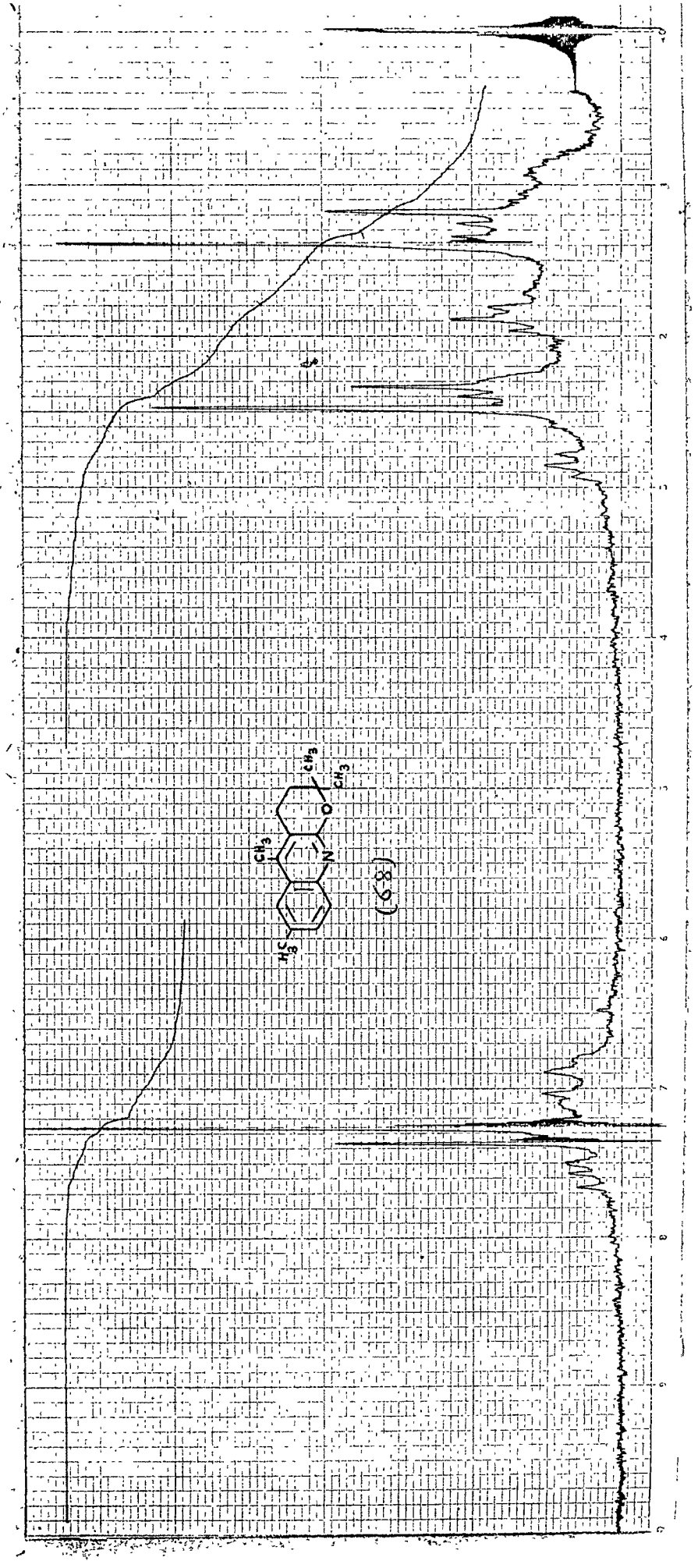
IR spectrum (KBr) of (67) showed characteristic bands at 3260 cm^{-1} for -NH group, 1725 cm^{-1} for carbonyl group (>C=O) and at 1660 cm^{-1} for >C=C< group. The (67) was treated with PPA at 140° gave 2,2,5,7-tetramethyl-3,4-dihydropyrano (2,3b)quinoline (68). NMR spectrum (CCl_4) showed signals at δ; 1.2 and 1.4, two singlets, 6H, geminal dimethyl group at C_2 ; 1.9, triplet, J = 8Hz, 2H, at C_4 ; 2.33, singlet, 3H, $-CH_3$ group at C_7 ; 2.48, singlet, 3H, $-CH_3$ group at C_5 ; 2.85, triplet, J = 8Hz, 2H, at C_3 and 6.9 - 7.7, multiplet, 3H, aromatic. (68) failed to undergo dehydrogenation on treatment with DDQ in dry benzene.



(67)

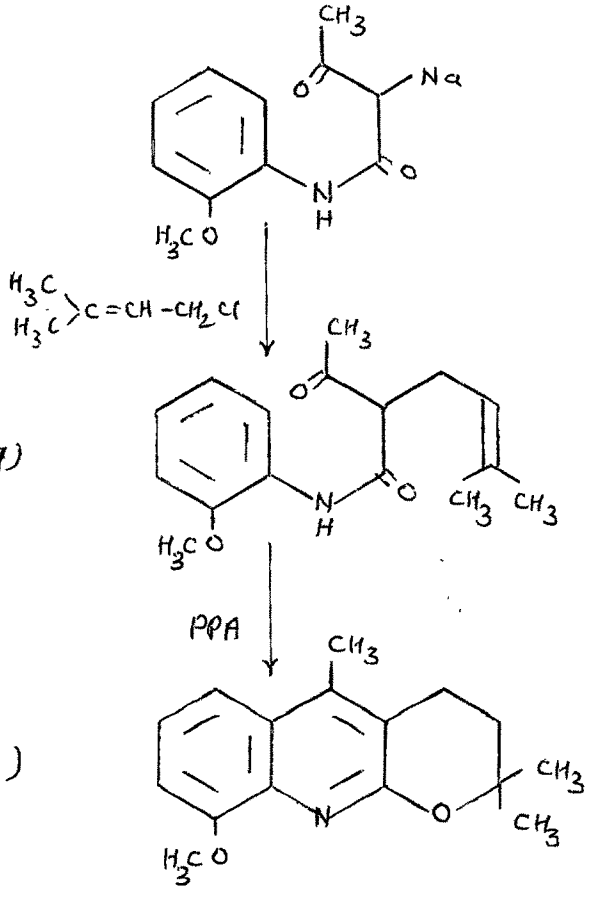
(68)


(67)
H_3C
$NH-C-CH-C-CH_3$
$CH_2=CH-C(CH_3)_2$
00
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY CM


δ
CH3
CH3
CH3
N
O
H3C
(68)

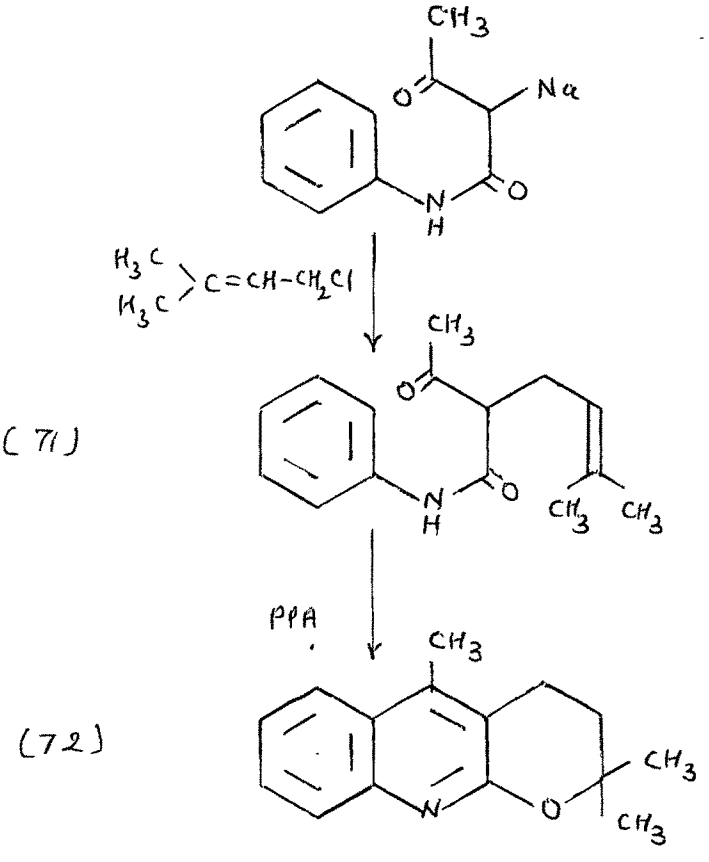
2,2,5-Trimethyl-8-methoxy-3,4-dihydropyrano (2,3-b) quinoline (70) :

Sodium salt acetoacet-o-anisidide was condensed with 3-methyl-1-chloro-but-2-ene in dry benzene gave a-(3-methyl-but-2-enyl) acetoacet-o-anisidide (69) which was cyclised by using PPA to give 2,2,5-trimethyl-8-methoxy-3,4-dihydropyrano (2,3-b)quinoline (70). (70) failed to undergo dehydrogenation with DDQ in dry benzene. The structure of (70) was assigned on the basis of analogy with the above products.



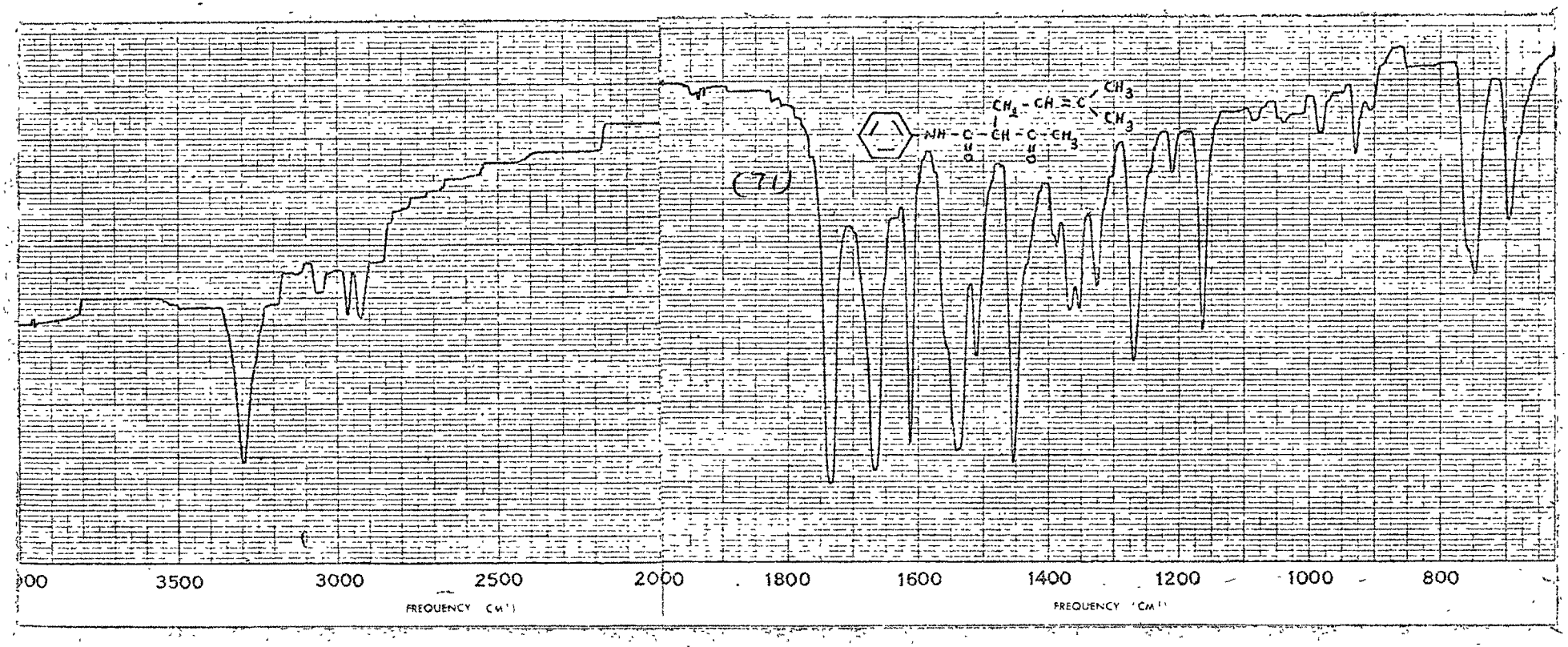
2,2,5-Trimethyl-3,4-dihydropyrano (2,3-b)quinoline (72) :

Sodium salt of acetoacetanilide was condensed with 3-methyl-1-chloro-but-2-ene in dry benzene gave α-(3-methyl-but-2-enyl) acetoacetanilide (71) which was cyclised by using PPA to give 2,2,5-trimethyl-3,4-dihydropyrano (2,3-b)quinoline (72). (72) failed to undergo dehydrogenation with DDQ in dry benzene. The structure of (72) was assigned on the basis of analogy with above products.



(71)

(72)


(71)
NH - C - CH - C - CH3
CH2 - CH = C
CH3
CH3
00
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY (CM⁻¹)

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra (KBr) or (nujol) were recorded on a Perkin-Elmer 457 or Beckmann 20X spectrophotometer. The NMR spectra were recorded on Perkin Elmer 90 MHz spectrophotometer.

2,2,5,7-Tetramethyl-3,4-dihydropyrano (3,2-c)quinoline(50):

2,8-Dimethyl-3-(3-methyl-but-ene-2)-4-hydroxyquinoline(49):

2,8-Dimethyl-4-hydroxyquinoline (1.7 g) was dissolved in ethylmethylketone (250 ml) and was refluxed with 3-methyl-1-chloro-2-butene (1.5 ml) in presence of anhydrous potassium carbonate (5.0 g) and potassium iodide (1.0 g) on steam bath for 15 hrs. The solvent was removed and reaction mixture was poured into water to give an oily product, which was extracted with ether. The ether layer was then washed with water, made dry and solvent was evaporated to give oily product 2,8-dimethyl-4-(3-methyl-but-2-enyloxy)quinoline. The oil was heated at 200° for 30 minutes in an oil bath and then digested with benzene. The benzene insoluble rearranged product 2,8-dimethyl-3-(3-methyl-2-butenyl)-4-hydroxyquinoline (49), crystalised from ethanol, yield 0.7 g, m.p. 224°. (Found : C, 80.07, H, 8.095, N, 5.991 ; $C_{16}H_{19}NO$; required : C, 79.68, H, 7.886, N, 5.81 %).

Attempted cyclo-dehydrogenation of 2,3-dimethyl-3-(3-methyl-but-2-ene)-4-hydroxyquinoline

The above 2,8-dimethyl-3-(3-methyl-but-2-ene)-4-hydroxyquinoline (49) (1.0 g) was dissolved in dry dioxan (25 ml) and DDQ (1.0 g) was added. The reaction mixture was heated on steam bath for 5-6 hrs, which was then worked out. The product was [illegible], found to be original (49).

2,2,5,7-Tetramethyl-3,4-dihydropyrano (3,2-c)quinoline (50) :

2,8-Dimethyl-3-(3-methyl-but-2-enyl)-4-hydroxy-quinoline (1.0 g) was dissolved in PPA (10.0 g) and was heated in an oilbath at 140° for 3-5 hrs. The reaction mixture was poured over crushed ice and then neutralised by 10 % Na_2CO_3 solution. The crude product was chromatographed over Silica gel and eluted with benzene-petroleum ether (1:3) mixture gave 2,2,5,7-tetramethyl-3,4-dihydropyrano (3,2-c)quinoline, which crystallised from petroleum ether, yield 0.4 g, m.p. 69-70°. (Found : C, 79.68, H, 7.934, N, 6.272 ; $C_{16}H_{19}NO$: Required : C, 79.68, H, 7.886 N, 5.81 %).

Attempted dehydrogenation reaction on 2,2,5,7-tetramethyl-3,4-dihydro pyrano (3,2-c)quinoline

A mixture of 2,2,5,7-tetramethyl-3,4-dihydro pyrano

(3,2-c)quinoline (1.0 g), DDQ (1.0 g) in dry benzene (25 ml) was refluxed on water bath for 6-7 hrs. The reaction mixture was worked out as usual. The product was found to be original unreacted (50).

2,2,5-Trimethyl-3,4-dihydro pyrano (3,2-c)quinoline (47):

2-Methyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline (46):

2-Methyl-4-hydroxy quinoline (1.7 g), 3-methyl-1-chloro-but-2-ene (1.5 ml), potassium carbonate (5.0 g) and potassium iodide (1.0 g) were refluxed in ethylmethyl-ketone (400 ml) as a solvent for 15 hrs. on steam bath. The solvent was removed and reaction mixture was decomposed into water. The separated product was extracted with ether and organic layer was washed with water. After removal of solvent the oily product 2-methyl-4-(3-methyl-but-2-enyloxy) quinoline was collected. The oil was pyrolysed at 200° for 30 min. and then digested with benzene. The benzene insoluble fraction was collected and washed with benzene as rearranged 2-methyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline (46). It was crystallised from ethanol, yield 1.0 gm, m.p. 256°. (Found ; C, 79.12 H, 7.43 N, 6.11 ; $C_{15}H_{17}NO$; required ; C, 79.30 H, 7.49 N, 6.17 %).

Attempted cyclo-dehydrogenation of 2-methyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline :

The above product (1.C g) and DDQ (1.0 g) were refluxed in dry dioxan (25 ml) for 6 hrs. on steam bath. It was worked out as before and found to be original one (46) as unreacted.

2,2,5-Trimethyl-3,4-dihydro pyrano (3,2-c)quinoline (47):

2-Methyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline (1.0 g) was dissolved in PPA (10 ml) and heated in an oil-bath for 5 hrs. at 140°. The reaction mixture was decomposed over crushed ice and neutralised with Na_2CO_3 solution (10 %). The crude product was chromatographed over silica gel, and eluted with benzene-petroleum ether (1:3) mixture. It crystallised from petroleum ether, yield 0.5 gm, b.p. 222°. (Found ; C, 79.56 H, 7.50 N, 5.89 ; $C_{15}H_{17}NO$; required ; C, 79.30 H, 7.49 N, 6.17 %).

Attempted dehydrogenation reaction on 2,2,5-trimethyl-3,4-dihydro pyrano (3,2-c)quinoline :

A mixture of above product (1.0 g) and DDQ (1.0g) in dry benzene (25 ml) was refluxed on steam bath for 5 hrs. The reaction mixture was worked out as above, the product obtained was found to be original,unreacted (47).

2,2,5,9-Tetramethyl-3,4-dihydro pyrano (3,2-c)quinoline (53) :

2,6-Dimethyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline(52):

A mixture of 2,6-dimethyl-4-hydroxy quinoline (2.0 g), 3-methyl-1-chloro-but-2-ene (1.5 ml), potassium carbonate (5 g), potassium iodide (1.0 g) and ethylmethyl-ketone (500 ml) was refluxed on steam bath for 20 hrs. The solvent was removed and it was decomposed into water. The separated product was extracted with ether and the organic layer was washed with water. After removal of solvent, the oily product 2,6-dimethyl-4-(3-methyl-but-2-enyloxy)quinoline was collected, which was pyrolysed at 200° for 30 min. without solvent. The reaction mixture was then digested with benzene and benzene insoluble fraction was collected as rearranged 2,6-dimethyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline (52). It crystallised from ethanol, yield 1.2 gm, m.p. 294°. (Found ; C, 79.47 H, 7.76 N, 5.97 ; $C_{16}H_{19}NO$; required ; C, 79.68 H, 7.89 N, 5.81 %).

Attempted cyclo-dehydrogenation of 2,6-dimethyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline :

A mixture of above product (1.0 g) and DDQ (1.0 g) in dry dioxan (25 ml) was refluxed for 6 hrs. on steam bath It was worked out as above and the product obtained was found to be original, unreacted (52).

2,2,5,9-Tetramethyl-3,4-dihydro pyrano (3,2-c) quinoline (53) :

2,6-Dimethyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline (1.0 g) was dissolved in PPA and heated in an oil-bath for 5 hrs. at 140°. The reaction mixture was decomposed over crushed ice and neutralised with Na_2CO_3 solution (10 %). The crude product was chromatographed over silica gel, and eluted with benzene-petroleum ether (1:2) mixture. It was crystallised from petroleum ether, yield 0.6 gm, m.p. 73°. (Found ; C, 80.12 H, 7.88 N, 5.55 ; $C_{16}H_{19}NO$; required ; C, 79.68 H, 7.89 N, 5.81 %).

Attempted dehydrogenation reaction on 2,2,5,9-tetramethyl-3,4-dihydro pyrano (3,2-c)quinoline :

A mixture of above product (1.0 g) and DDQ (1.0 g) in dry benzene (25 ml) was refluxed on steam bath for 5 hrs. The reaction mixture was worked out as above, the product obtained was found to be original, unreacted (53).

2,2,5-Trimethyl pyrano (3,2-c) quinoline (48) :

2-Methyl-4-hydroxyquinoline (1.6 g) was dissolved in ethylmethylketone (250 ml) and was refluxed with 3-methyl-3-chloro-but-1-yne (1.5 g) in the presence of potassium carbonate (5.0 g) and potassium iodide (1.0 g) on water bath for 50 hrs. The solvent was then removed by distillation and the residue was poured into water to give crude product, which was chromatographed over silica gel using benzene-petroleum ether (1:2) as eluent. It crystallised from petroleum ether, yield 0.5 gm, m.p. 99° (Found : C, 79.89 H, 6.480, N, 6.558 ; $C_{15}H_{15}NO$; required ; C, 80.00 H, 6.666 N, 6.221 %).

2,2,5,7-Tetramethyl pyrano (3,2-c) quinoline (51) :

A mixture of 2,8-dimethyl-4-hydroxy quinoline (1.9 g) 3-methyl-3-chloro-but-1-yne (1.5 g), potassium carbonate (5.0 g), potassium iodide (1.0 g) and ethylmethylketone (250 ml) was refluxed in water bath for 50 hrs. The solvent was removed by distillation and [illegible] was decomposed into water. The obtained product was filtered, washed with water and dried. It was chromatographed over silica gel, using benzene-petroleum ether (1:2) mixture as eluent. It was crystallised from petroleum ether, yield 0.3 gm, m.p. 100°. (Found ; C, 80.50 H, 7.08 N, 5.55 ; $C_{16}H_{17}NO$; required ; C, 80.34 H, 7.11 N, 5.86 %).

2,2,5,9-Tetramethyl pyrano (3,2-c) quinoline (54) :

A mixture of 2,6-dimethyl-4-hydroxy quinoline (1.9 g) 3-methyl-3-chloro-but-1-yne (1.5 g), potassium carbonate (5.0 g), potassium iodide (1.0 g) and ethylmethylketone (250 ml) was refluxed in water bath for 50 hrs. The solvent was removed by distillation and [illegible] was decomposed into water. The obtained product was filtered, washed with water and dried. It was chromatographed over silica gel, using benzene-petroleum ether (1:2) mixture as eluent. It was crystallised from petroleum ether, yield 0.3 gm, m.p. 93°. (Found ; C, 79.92 H, 6.94 N, 5.86 ; $C_{16}H_{17}NO$; required ; C, 80.34 H, 7.11 N, 5.86 %).

2,2,5,-Trimethyl-9-methoxy pyrano (3,2-c) quinoline (59) :

A mixture of 2-methyl-4-hydroxy-6-methoxy quinoline (2.2 g) 3-methyl-3-chloro-but-1-yne (1.5 g), potassium carbonate (5.0 g), potassium iodide (1.0 g) and ethyl-methylketone (250 ml) was refluxed in water bath for 50 hr. The solvent was removed by distillation and [illegible] was decomposed into water. The obtained product was filtered, washed with water and dried. It was chromatographed over silica gel, using benzene-petroleum ether (1:2) mixture as eluent. It was crystallised from petroleum ether, yield 0.5 gm, m.p. 60°. (Found ; C, 75.48 H, 6.52 N, 5.37 ; $C_{16}H_{17}NO_2$; required ; C, 75.30 H, 6.67 N, 5.49 %).

2,2,5,9-Tetramethyl-3,4-dihydropyrano (2,3-b)quinoline(65) :

α-(3-Methyl-but-2-enyl)acetoacet-o-toluidide (66) :

Acetoacet-o-toluidide (2.0 g) was refluxed with 0.25 gm. of pulverised sodium in dry benzene in waterbath for 5 hr. To this reaction mixture, 3-methyl-1-chloro-but-2-ene (1.5 ml) was added and then the reaction mixture was further refluxed for 20 hrs. It was then poured into water and the organic (benzene) layer was separated. The solvent was removed and the product crystallised from petroleum ether, yield 2.5 gm, m.p. 87° (Found : C, 74.06 H, 8.316 N, 5.714 ; $C_{16}H_{21}NO_2$; required ; C, 74.14 H, 8.107, N, 5.404 %).

2,2,5,9-Tetramethyl-3,4-dihydropyrano (2,3-b)quinoline(65):

α-(3-Methyl-but-2-enyl)acetoacet-o-toluidide (2.0 g) was dissolved in PPA (20 g) and heated, the reaction mixture was then poured over crushed ice and neutralised with 10 % Na_2CO_3 solution. The product was chromatographed over silica gel using benzene-petroleum ether (1:3) mixture as eluent. It crystallised from petroleum ether, yield, 0.8 gm, m.p. 112° (Found : C, 79.86 H, 7.8 N, 5.95 ; $C_{16}H_{19}NO$; required ; C, 79.68, H, 7.88 N, 5.81 %).

Attempted dehydrogenation reaction on 2,2,5,9-tetramethyl-3,4-dihydro pyrano (2,3-b)quinoline

A mixture of 2,2,5,9-tetramethyl-3,4-dihydro pyrano (2,3-b)quinoline (1.0 g), DDQ (1.0 g) and dry benzene (25 ml) was refluxed for 6 hrs. on waterbath. The reaction mixture was worked out as before but the product was found to be original,unreacted (65).

2,2,5,7-Tetramethyl-3,4-dihydro pyrano (2,3-b)quinoline (68) :

α-(3-Methyl-but-2-enyl)acetoacet-p-toluidide (67) :

Acetoacet-p-toluidide (2.0 g) was refluxed with pulverised sodium (0.23 g) in dry benzene in waterbath for 5 hrs. To this reaction mixture, 3-methyl-1-chloro-but-2-ene (1.5 ml) was added and then the reaction mixture was refluxed for 20 hrs. It was decomposed into water and organic layer was separated. After removal of solvent, it was crystallised from petroleum ether, yield 2.0 gm, m.p. 83°. (Found ; C, 74.26 H, 8.70 N, 5.72 ; $C_{16}H_{21}NO_2$; required ; C, 74.14 H, 8.11 N, 5.41 %).

2,2,5,7-Tetramethyl-3,4-dihydro pyrano (2,3-b)quinoline (68) :

The above product (2.0 g) was dissolved in PPA (20 ml) and heated the reaction mixture at 140° for 3 hrs. in an oil-bath. It was decomposed over crushed ice and

neutralised with 10 % Na_2CO_3 solution. The product was chromatographed over silica gel, using benzene-petroleum ether (1:3) mixture as eluent. It was crystallised from petroleum ether, yield 0.5 gm, b.p. 205°. (Found ; C, 79.58 H, 7.90 N, 5.77 ; $C_{16}H_{19}NO$; required ; C, 79.68 H, 7.89 N, 5.81 %).

Attempted dehydrogenation reaction on 2,2,5,7-tetramethyl-3,4-dihydro pyrano (2,3-b)quinoline :

A mixture of 2,2,5,7-tetramethyl-3,4-dihydro pyrano (2,3-b)quinoline (1.0 g), DDQ (1.0 g) and dry benzene (25 ml) was refluxed for 6 hrs. on waterbath. The reaction mixture was worked out as before but the product was found to be original,unreacted (68).

2,2,5-Trimethyl-8-methoxy-3,4-dihydropyrano (2,3-b) quinoline (70) :

α-(3-Methyl-but-2-enyl)acetoacet-o-anisidide (69) :

Acetoacet-o-anisidide (2.2 g) was refluxed with pulverised sodium (0.23 g) in dry benzene in waterbath for 5 hrs. To this reaction mixture, 3-methyl-1-chloro-but-2-ene (1.5 ml) was added and then the reaction mixture was refluxed for 20 hrs. It was decomposed into water and organic layer was separated. After removal of solvent it was crystallised from petroleum ether, yield 1.8 gm, m.p. 100°. (Found ; C, 70.12 H, 7.5 N, 4.00 ; $C_{16}H_{21}NO_3$; required ; C, 69.81 H, 7.63 N, 4.07 %).

2,2,5-Trimethyl-8-methoxy-3,4-dihydropyrano (2,3-b) quinoline (70) :

The above product (1.0 g) and PPA (10 ml) were heated at 140° for 3 hrs. in an oil-bath. It was decomposed over crushed ice and neutralised with sodium carbonate solution (10 %). The product was chromatographed over silica gel, using benzene-petroleum ether (1:3) mixture as eluent, yield 0.7 gm, b.p. 225°. (Found ; C, 74.70 H, 7.09 N, 5.55 ; $C_{16}H_{19}NO_2$; required ; C, 74.72 H, 7.39 N, 5.45 %).

Attempted dehydrogenation reaction on 2,2,5-trimethyl-8-methoxy-3,4-dihydro pyrano (2,3-b)quinoline :

A mixture of above product, (1.0 g), DDQ (1.0 g) and dry benzene (25 ml) was refluxed for 6 hrs. in water bath. The reaction mixture was worked out as before but the product was found to be original,unreacted (70).:

2,2,5-Trimethyl-3,4-dihydro pyrano (2,3-b)quinoline (72):

α-(3-Methyl-but-2-enyl)acetoacetanilide (71) :

Acetoacetanilide (1.7 g) was refluxed with pulverised sodium (0.23 g) in dry benzene in waterbath for 5 hrs. To this reaction mixture 3-methyl-1-chloro-but-2-ene (1.5 g) was added and the reaction mixture was refluxed for 20 hrs. It was decomposed into water and

the organic layer was separated. After removal of solvent it was crystallised from petroleum ether, yield 1.0 gm, m.p. 68°. (Found ; C, 73.03 H, 7.37 N, 5.92 ; $C_{15}H_{19}NO_2$; required ; C, 73.46 H, 7.76 N, 5.72 %).

2,2,5-Trimethyl-3,4-dihydro pyrano (2,3-b)quinoline (72):

The above product (1.0 g) was heated with PPA (10 ml) in an oil-bath at 140° for 3 hrs. It was decomposed over crushed ice and neutralised with Na_2CO_3 (10 %) solution. The product was chromatographed over silica gel, using benzene-petroleum ether (1:4) mixture as eluent, yield 0.9 gm, b.p. 218°. (Found ; C, 79.00 H, 7.55 N, 6.26 ; $C_{15}H_{17}NO$; required ; C, 79.30 H, 7.49 N, 6.16 %).

Attempted dehydrogenation reaction on 2,2,5-trimethyl-3,4-dihydro pyrano (2,3-b)quinoline :

A mixture of above product, (1.0 g) and DDQ (1.0 g) in dry benzene (25 ml) was refluxed for 6 hrs. in water bath. The reaction mixture was worked out as before and the product was found to be original, unreacted (72).

REFERENCES

1. B.B.Dey, I.Sarkar and T.R.Seshadri ; J.Indian Chem. Soc., 3, 187, 1926.

2. D.P.Ahuja, K.K.Chakravarti and S.Siddiqui ; J.Sci. Ind.Res.(India), 9B No.7, 165, 1950.

3. B.B.Dey, and V.Ammalukutti ; Proc.Natl.Inst.Sci., (Indian) 6, 641, 1940.

4. B.Borbranski and L.Kochanska ; Roczniki Chem., 17, 30, 1937. C.A., 31, 3048, 1937.

5. H.Fiedler, Arch.Pharm. 297(2), 108, 1964. C.A., 60, 10645, 1964.

6. R.F.C.Brown, G.K.Hughes and E.Ritchie ; Australian J.Chem., 9, 277, 1955. C.A., 50, 12085, 1956.

7. K.Elliott and E.Tittenson ; J.Chem.Soc., 484, 1959. ibid, 2796, 1961.

8. Yashuiko Asahina and Mototuro Inubuse ; Ber., 65(B), 61-3, 1932. C.A., 26, 2196, 1932.

9. E.A. Clarke and M.F.Grundon ; J.Chem.Soc., 4190-6, 1964. C.A., 62, 1697, 1965.

10. E.A. Clarke and M.F.Grundon ; J.Chem.Soc., 4196-4200, 1964. C.A., 62, 1699, 1965.

11. Franco Piozzi, Pietro Venturella and Aurora Bellino ; Gazz.Chim.(Ital) ; 99(1), 711-4, 1969. C.A., 71, 91707 t, 1969.

12. J.W.Huffman, T.M.Hsu ; Tetrahedron lett., 2, 141-3, 1972. C.A., 76, 85978 s, 1972.

13. De Groot Ae, Jansen B.J.M. ; Tetrahedron lett., 39, 3407-10, 1975.

14. P.Venturella, A.Bellino and Franco Piozzi ; Heterocycles, 3(5), 367-70, 1975. C.A., 83, 43554 q, 1975.

15. J.Zsindely and H.Schmid., Helv. Chim.Acta., 51, 1510, 1968.

16. R.D.H.Murrary, M.M.Ballantyne and K.P.Mathai, Tetrahedron, 27, 1247, 1971.

17. N.Kornblum, R.Seltzer and P.Harbfield ; J.Amer. Chem.Soc.,85, 1148, 1963.

18. S.J.Rhoads and R.W.Holder ; Tetrahedron, 25, 5543, 1969.

19. A.Jefferson and E.Scheinmann ; Quat.Rev.(London), 22, 391, 1968.

20. A.Habich, R.Barner, R.M.Roberts and H.Schmid ; Helv.Chem.Acta., 45, 1943, 1962.

21. G.Frater and H.Schmid ; Helv.Chim.Acta, 49,1957, 1963.

22. E.N.Marvell and B.Schatz ; Tetrahedron Lett., 67, 1967.

23. E.N.Marvel, D.R.Anderson and Josephine Ong; J.Org. Chem., 27, 1109, 1962.

24. A.Habich, R.Barner, W.Von.Philipsborn, H.Schmid, H.J.Hansen and H.J.Rosenkranz ; Helv.Chim.Acta., 48, 1297, 1955.

25. R.M.Roberts and R.G.Londolt ; J.Org.Chem., 31, 2699, 1966.

26. R.M.Roberts, R.G.Landolt, R.N.Greene and E.W.Heyer ; J.Amer.Chem.Soc., 89, 1404, 1967.

27. Yasuo Makisumi ; Chem.Pharm.Bull.(Tokyo) ; 12(12), 1424-32, 1964(Eng). C.A., 62, 10407, 1965.

28. P.Shanmugam and V.T.Ramkrishnan ; Proc.Indian Acad., Sci., Sec.A, 75(2) 96-101, 1972. C.A., 77, 139848 r, 1972.

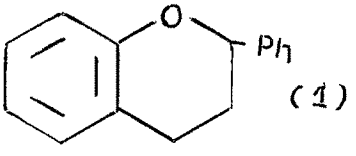
29. L.V.Gyul'budagyan and V.G.Durgaryan ; Khim.Getero. tsikl Soedin., 7, 975-7, 1972. C.A., 77, 151850 t, 1972.

SECTION - II

Cinnamylation of 4-hydroxyquinoline derivatives

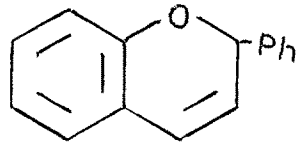
Synthesis of 2,4-dimethyl-3-dimethyl-3-phenyl-2,3-dihydrofuro (2,3-b)quinoline derivatives.

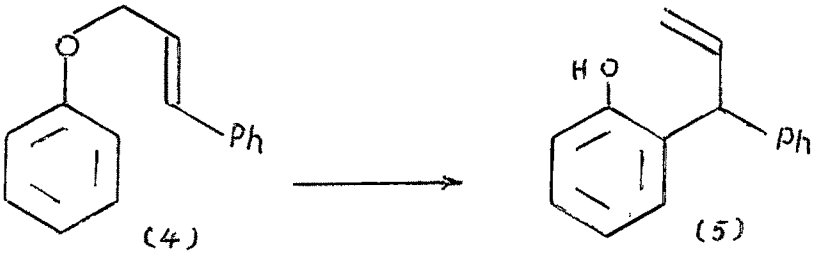
Benzopyrans containing phenyl group at C_2 position are generally known as flavans (I) and (2). Many naturally occuring alkaloids and flavanoides contain this nucleus. Many routes are known to synthesise flavans. In recent years Claisen rearrangement of cinnamyl ether of phenols, followed by cyclisation is a common route for the synthesis of flavan. Claisen rearrangement of cinnamyl ethers gave both normal and abnormal migration products. White and Fife[1] observed that Claisen rearrangement of cinnamyl p-substituted phenyl ethers (4) gave normal rearranged product (5).



(1)

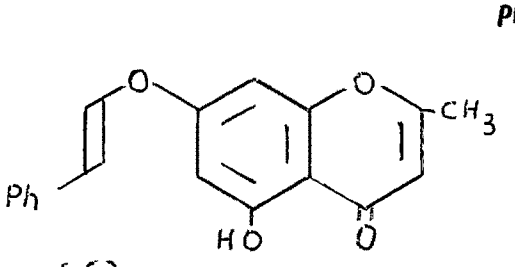
(2)



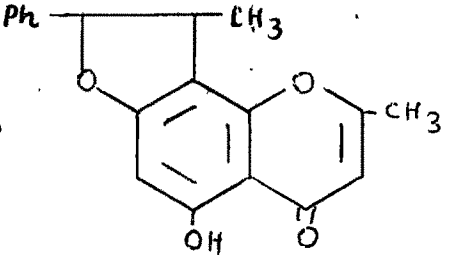


(4) (5)

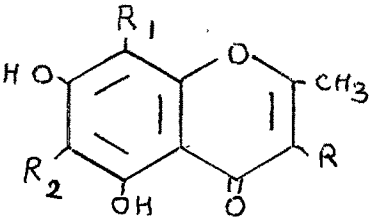
Jain et at[2] carried out the Claisen migration of 5-hydroxy-7-cinnamyloxy-2-methyl chromone (6) and obtained (7) through the abnormal migration. The same authors in their further studies[3] in C-cinnamylation of 5,7-dihydroxy-2-methyl isoflavone and chromone observed that when 5,7-dihydroxy-2-methyl-isoflavone (8-a) was condensed with cinnamyl alcohol and acetic acid gave 6,8-dicinnamyl derivative (8-b) along with 8-cinnamyl derivative (8-c). It was pointed out by them that when same isoflavone (8-a) was condensed with cinnamyl bromide in methanol-sodium methoxide gave (8-b) and 6-cinnamyl derivative (8-d). They obtained pyrano isoflavone (9) and pyrano chromone(10) from (8-c) and (8-d) by cyclodehydrogenation.



(6)



(7)



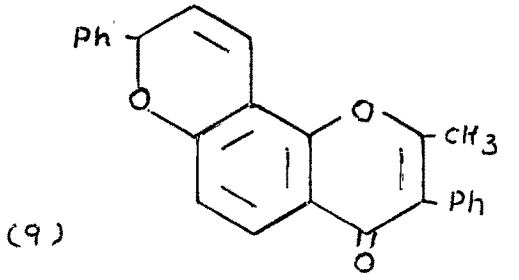
(8-a) $R_1 = R_2 = H$, R = Ph

(8-b) $R_1 = R_2 = -CH_2-CH=CH-Ph$, R = Ph.

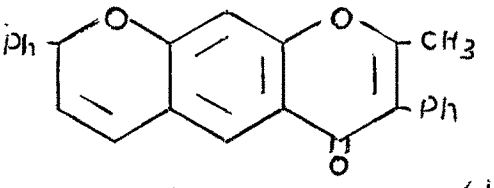
(8-c) $R_1 = -CH_2-CH=CH-Ph$, $R_2 = H$, R = Ph.

(8-d) $R_1 = H$, $R_2 =$ [illegible] $-CH_2-CH=CH-Ph$, R = Ph.

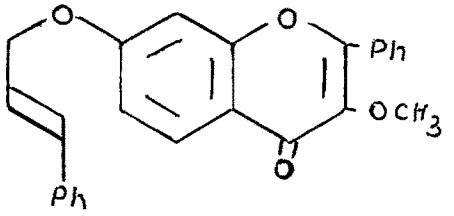
Jain and Tuli[4] have reported the rearrangement of 7-cinnamyloxy derivative of 3-hydroxyflavone (11) and 4-methyl coumarin (12). They obtained normal rearranged product (13) from (11) and abnormal rearranged product (14) from (12).



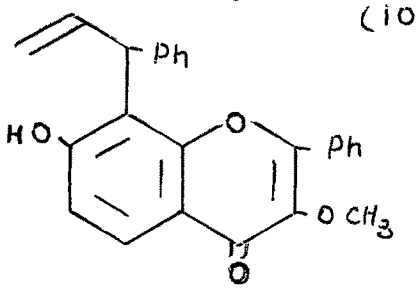
(9)



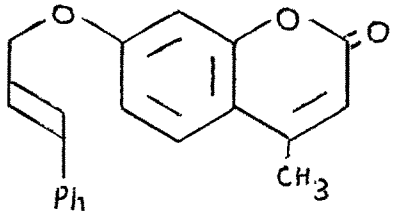
(10)



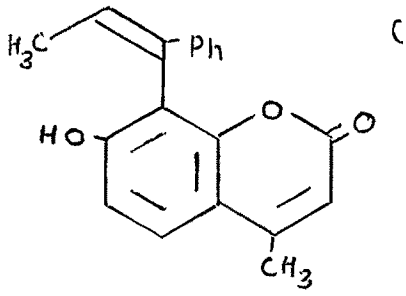
(11)



(13)

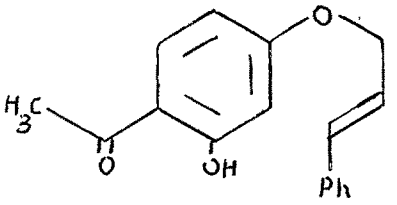


(12)

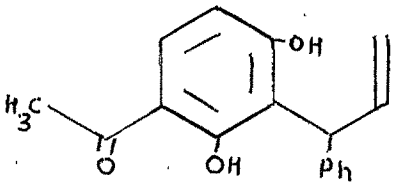


(14)

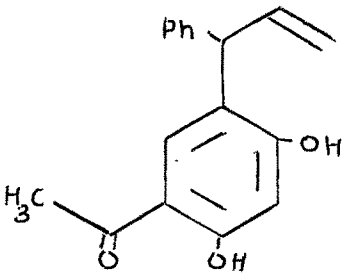
The same authors[5] have further reported that Claisen rearrangement of (15) gave normal products (16), (17) along with further rearranged but uncyclised product(18).



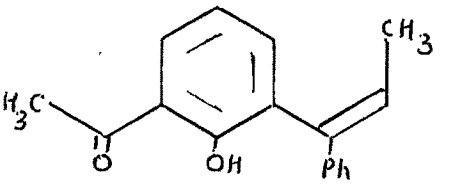
(15)



(16)

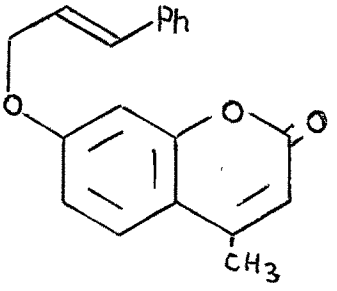


(17)

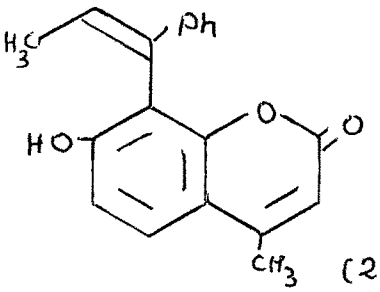


(18)

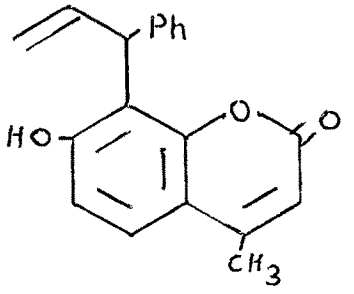
Ahluwalia and Devendrakumar[6] have reported that 7-cinnamyloxy-4-methyl coumarin (19) on Claisen rearrangement by refluxing in N,N-dimethylaniline yields 4,4'-dimethyl--5'-phenylfuro (2'.3'-6,7) coumarin (20) and 7-hydroxy-4-methyl-8-(1'-phenylprop-1'ene)coumarin (21). While in vacuo, the products obtained are the coumarin (21) and 7-hydroxy-8-(1'-phenylprop-2'-ene)coumarin (22). The structure of these compounds have been established by NMR spectra.



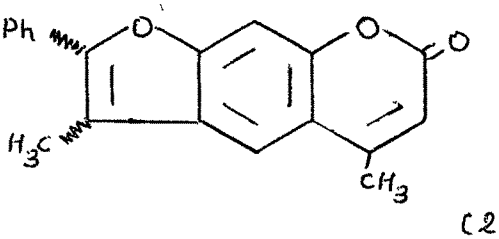
(19)



(21)

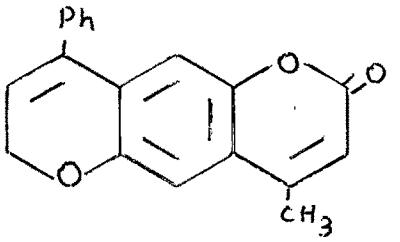


(22)

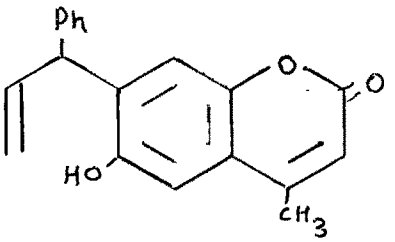


(20)

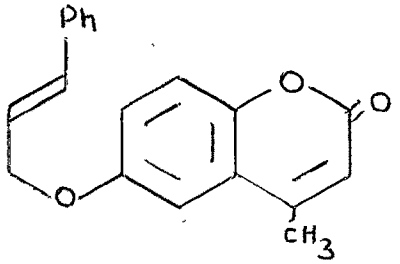
Jain and A.Kumar[7] showed a novel product (23) along with (24) as a normal rearranged product, in the Claisen rearrangement of 6-cinnamyloxy-4-methyl coumarin (25). Jain and Tuli[8] have reported their observation on Claisen rearrangement of 7-cinnamyloxy derivatives of 3-methoxyflavone, 4-methylcoumarin and isoflavone. During Claisen rearrangement they obtained (26), (27) and (28), respectively.



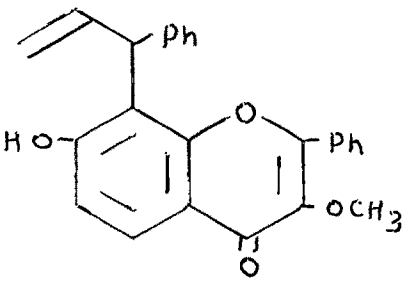
(23)



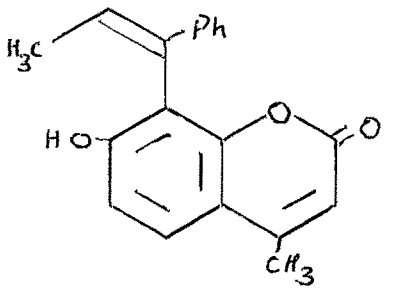
(24)



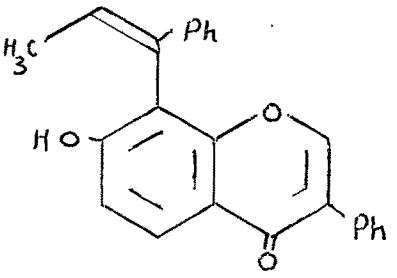
(25)



(26)

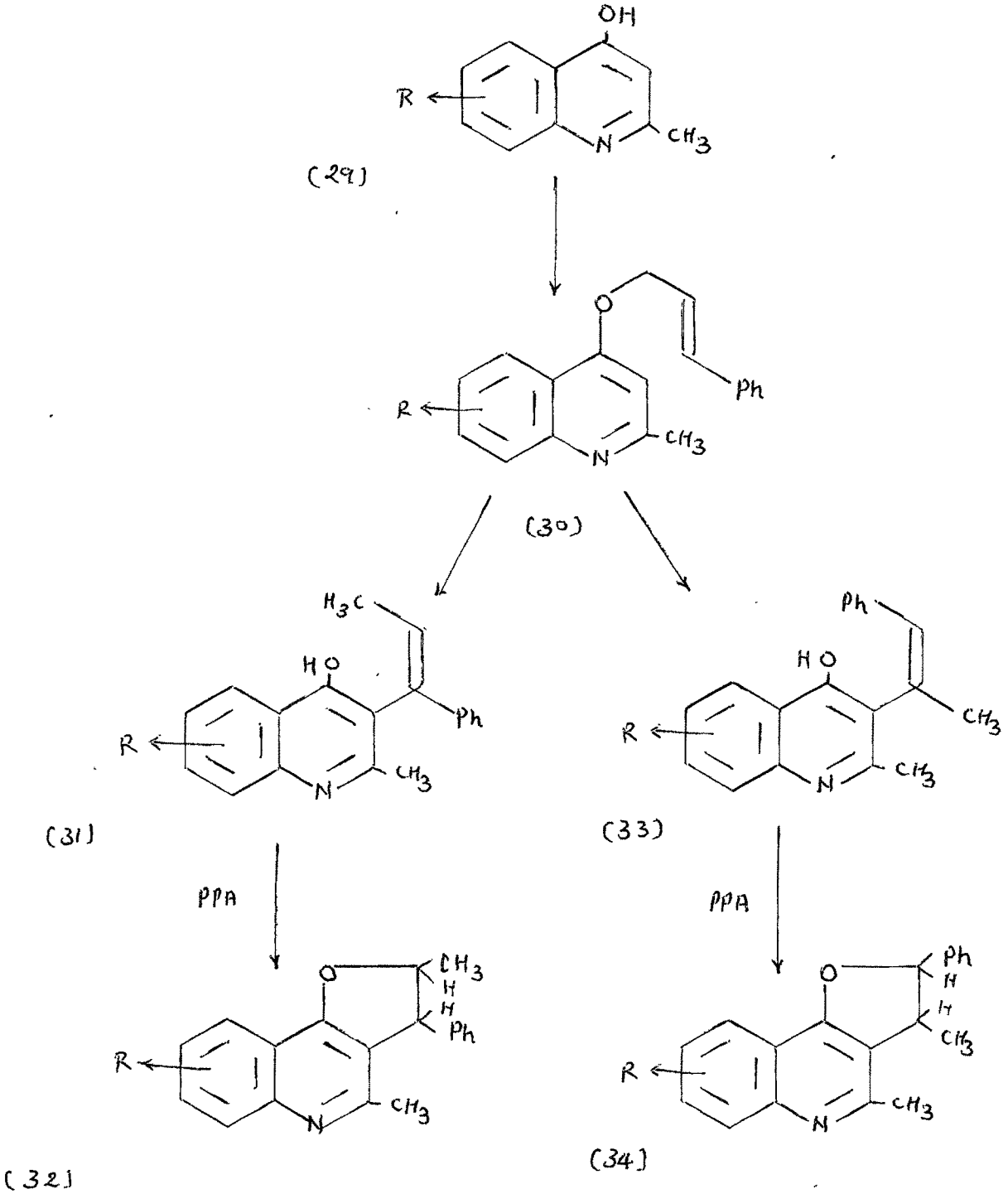


(27)

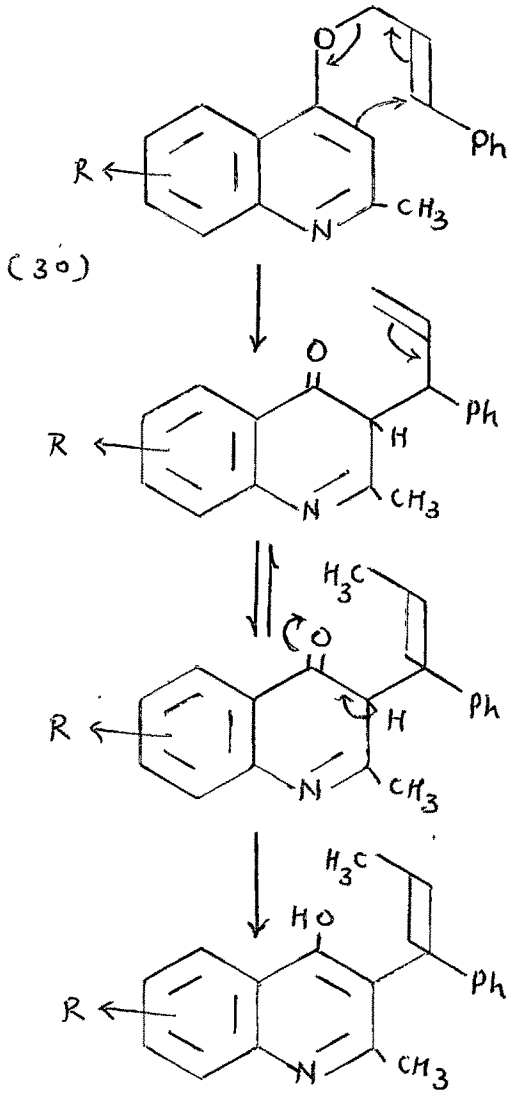


(28)

On reviewing the literature, it was observed that most of the studies on cinnamylation were carried out on the Oxygen Heterocyclic compounds and almost no work has been carried out on Nitrogen Heterocycles. As different types of rearranged products were obtained in the Claisen rearrangement of Oxygen heterocycles, it was thought of interest to study the cinnamylation of the quinoline derivatives. In the present work, 4-cinnamyloxy-2-methyl quinoline was prepared by reacting cinnamyl chloride with 4-hydroxy-2-methylquinoline and then subjected to Claisen rearrangement by heating it at 200° for 30 min. without any solvent. The reaction mixture was digested with benzene. The benzene-insoluble fraction gave the mixture of two rearranged products, which were difficult to separate by chromatographic methods and so the mixture was subjected to further cyclisation with polyphosphoric acid. The cyclised products could not be separated through column chromatography but could be separated by preparative thin-layer-chromatography. The structure of cyclised products were confirmed by NMR spectra. The above reactions series are represented as follows :-

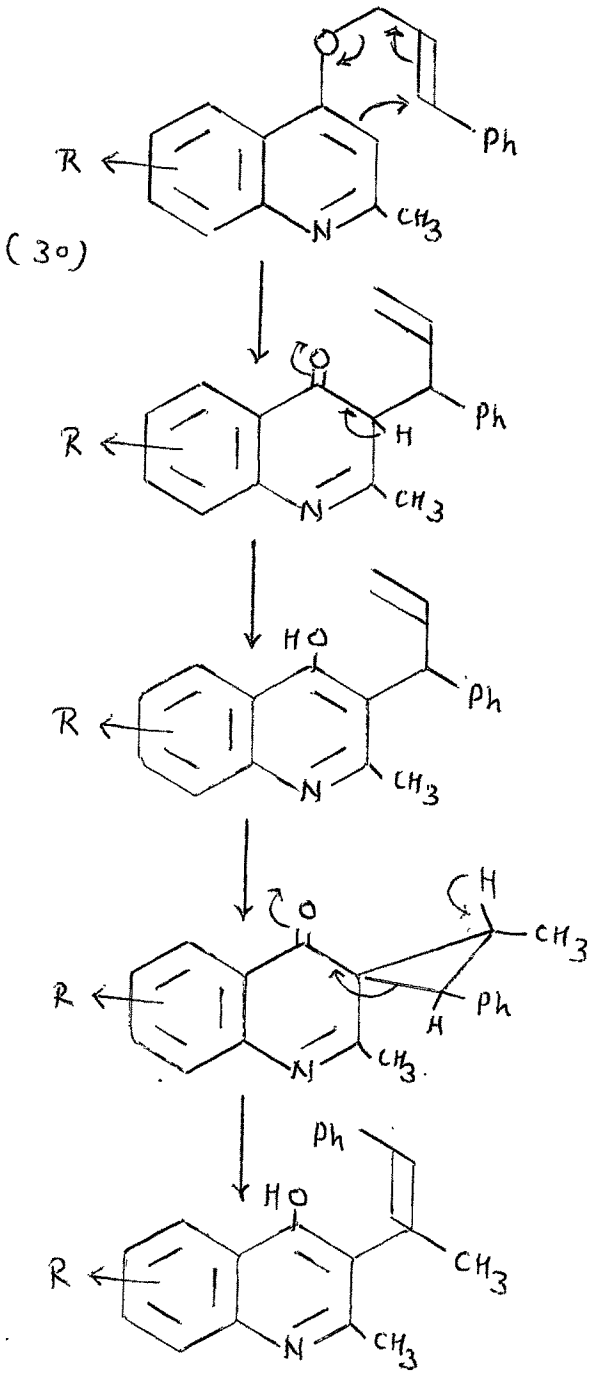

OH
R
N
CH3
(29)
O
Ph
(30)
H3C
HO
(31)
PPA
(32)
(33)
(34)
H

The formation of two isomeric migrated products can be explained by following reaction mechanism. The rearranged product (31) was obtained by normal rearrangement of cinnamyl group during Claisen rearrangement, which underwent further double bond migration as follows :-



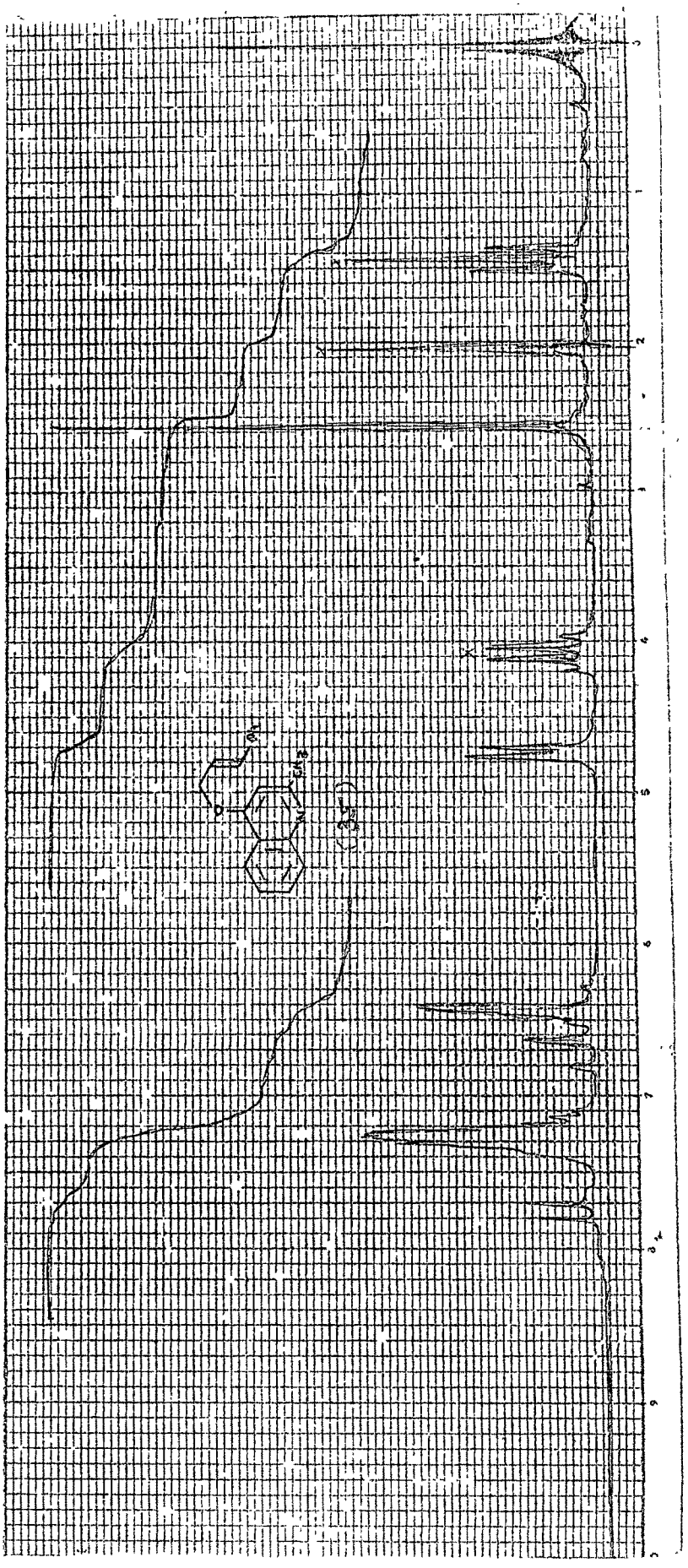
(31)

The formation of (33) is explained on the basis of abnormal Claisen rearrangement. The mechanism for the formation of (33) is proposed as follows :-



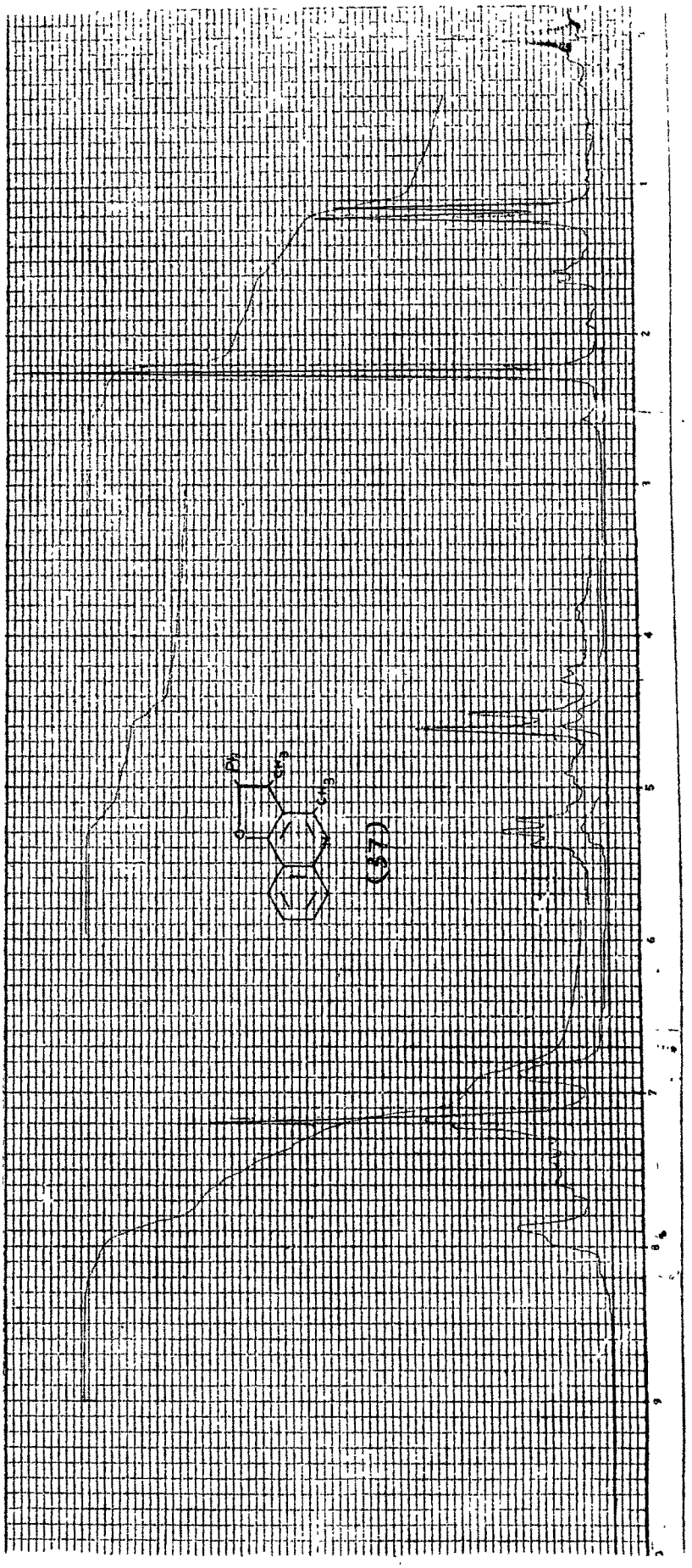
Synthesis of 2,4-dimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (37) and 3,4-dimethyl-2-phenyl-2,3-dihydro furo (3,2-c)quinoline (39) :

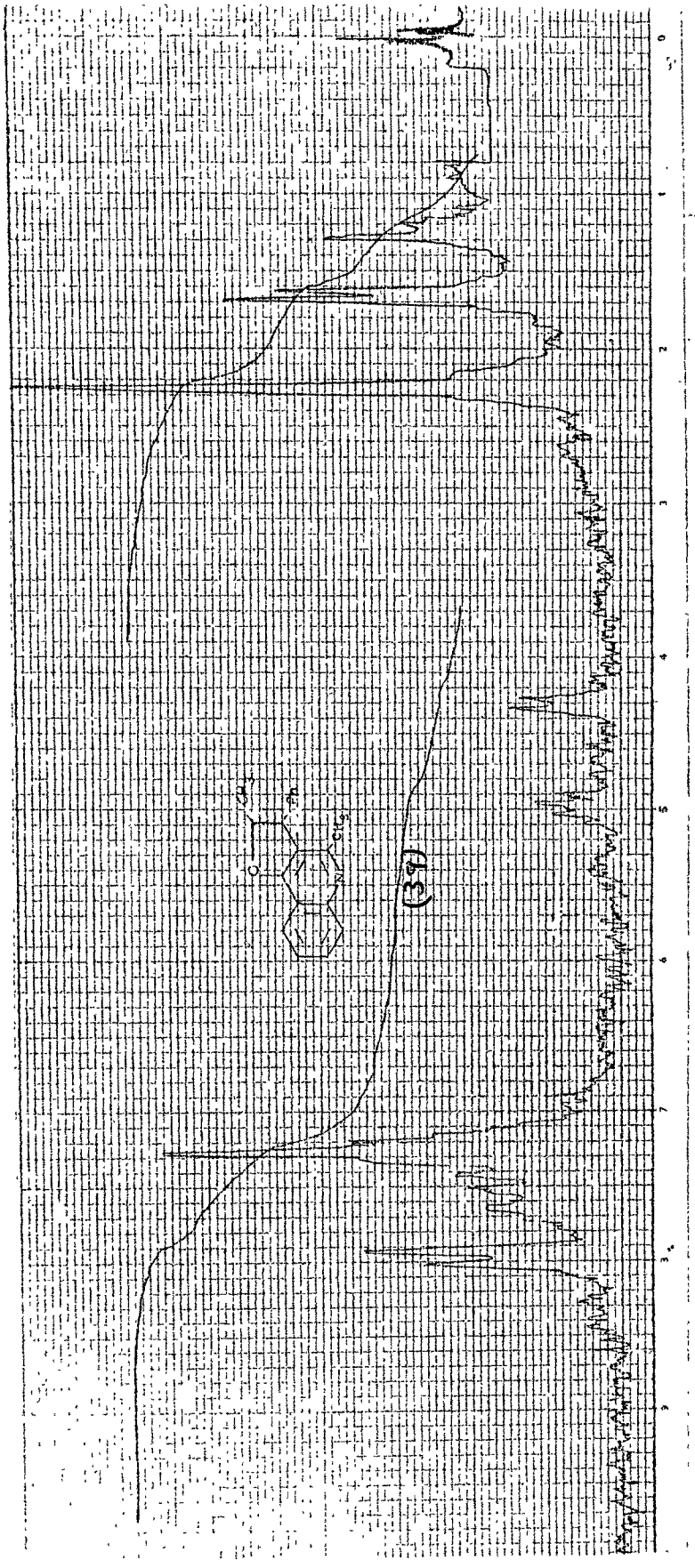
2-Methyl-4-hydroxyquinoline was refluxed with cinnamyl chloride in presence of potassium carbonate and potassium iodide in ethylmethylketone to give 2-methyl-4-cinnamyloxy quinoline (35). The structure of (35) was confirmed by NMR spectrum (CCl_4) which showed signals at δ; 2.58, singlet, 3H, $-CH_3$ group at C_2 ; 4.75, doublet, J = 7Hz, 2H, $-O-\underline{CH_2}-$ group ; 6.30 to 6.80, multiplet, 2H, $-\underline{CH}=\underline{CH}-$ group ; 7.1 to 7.8, multiplet, 10H, aromatic. The ether (35) was subjected to Claisen rearrangement by heating at 200° without any solvent. The rearranged product was digested with benzene and benzene insoluble fraction was collected as Claisen rearranged product, which was found to be a mixture of (36) and (37). On the basis of NMR spectrum of the migrated product containing mixture of (36) and (37), their structures are assigned. The NMR spectrum of migrated product (CF_3COOH) showed one doublet, at δ ; 1.85 with coupling constant J = 8Hz, for the $C=\underline{CH}-\underline{CH_3}$ group, indicating presence of isomers (36) in the mixture. Also the spectrum showed a singlet at δ; 2.25 for $-C(\underline{CH_3})=CHPh$ group indicating the presence of isomers (38). Also the spectrum showed singlet at 2.68 for CH_3 group at C_2 position. On elementry analysis of mixture,



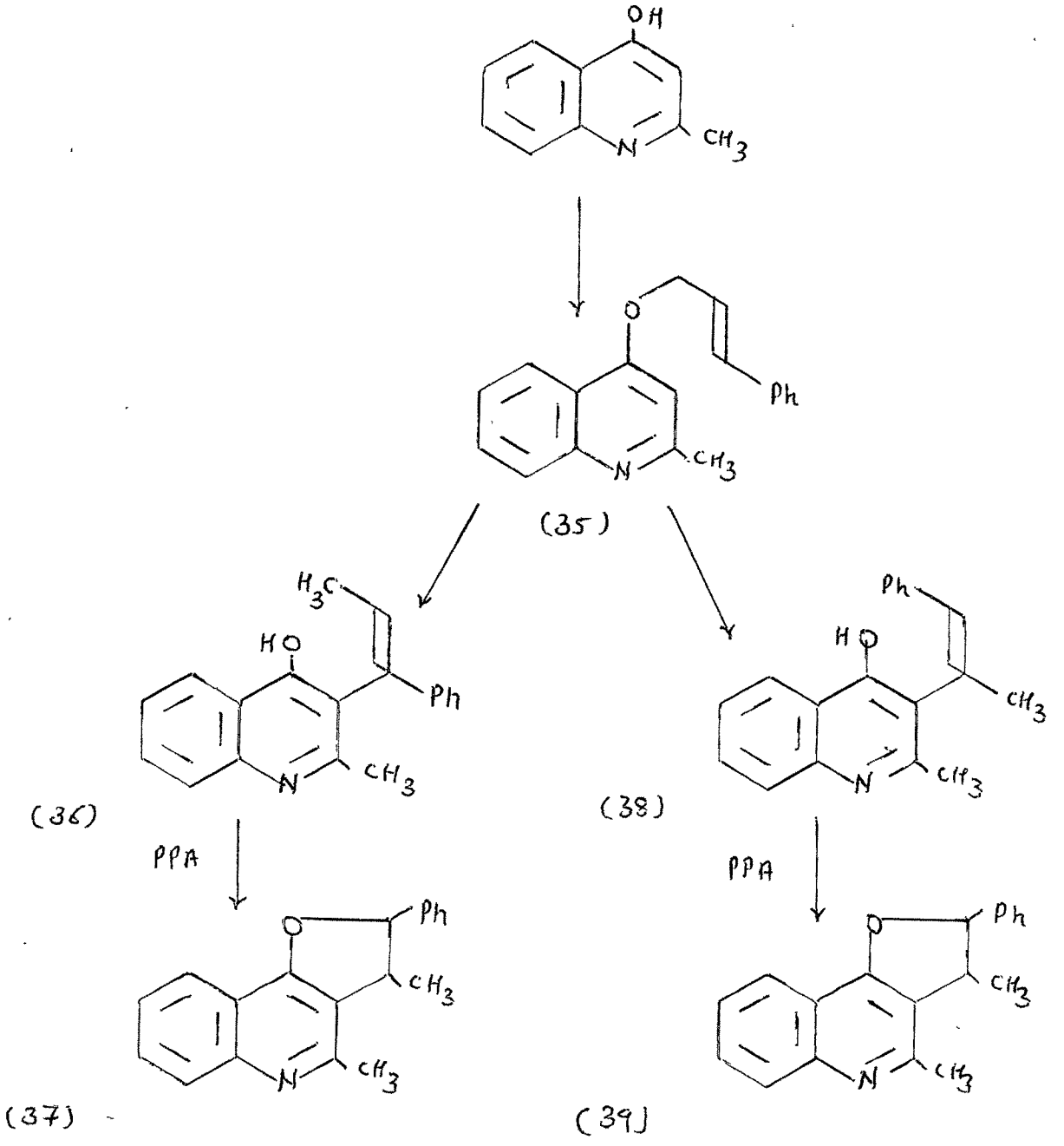
(36)
(38)

obtained results were found to be satisfactory with the required. All attempts to separate these isomers failed and hence the mixture was cyclised with polyphosphoric acid. The separation of the cyclic products could not be affected by column chromatography using silica gel but, they were separated by preparative thin-layer chromatography (silicagel). The structure of the separated isomers 2,4-dimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (37) and 3,4-dimethyl-2-phenyl-2,3-dihydro furo(3,2-c)quinoline (39) were assigned on the basis of their NMR spectra. The NMR (CCl_4) of (39) showed signals at δ; 1.20, doublet, J = 7Hz, 3H, $-CH_3$ group at C_3 ; 2.25, singlet, 3H, $-CH_3$ group at C_4 ; 4.45, doublet, J = 8Hz, 1H, -O-CH-Ph ; 5.30, multiplet, 1H, $-CH-CH_3$; 6.9 to 7.9, multiplet, 9H, aromat: The NMR (CCl_4) of (37) showed signals at δ; 1.65, doublet, J = 7Hz, 3H, $-CH_3$ at C_2 ; 2.25, singlet, 3H, CH_3 group at C_4 ; 4.3, doublet, J = 8Hz, 1H, -CH-Ph ; 4.96, multiplet, 1H, $-O-CH-CH_3$; 7.2 to 8.1, multiplet, 9H, aromatic. The NMR spectra of the two isomers suggest that each isomer is not completely separated but is contaminated with the other isomer to the extent of 10 % because the methyl signals are much predominent for other isomer in each spectrum. The structure of two isomers (37) and (39), 2,3-dimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline, respectively, were assigned on the basis of the $-CH_3$, $-CH-CH_3$, -CH-Ph signals appeared in their NMR spectra. $-CH_3$ protons of (37) were appeared in down field at δ; 1.65, that of (39) appeared at


Br
CH3
CH3
O
(37)

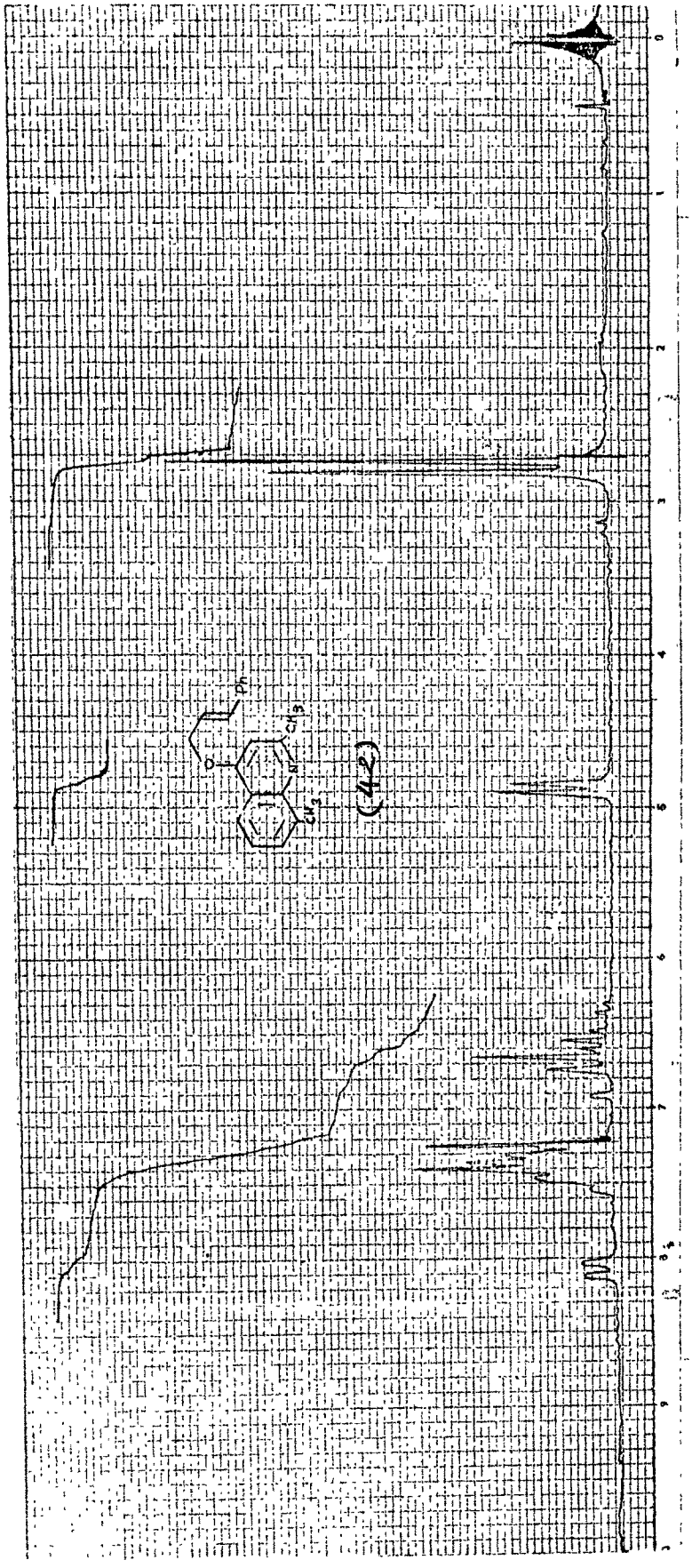

(3f)

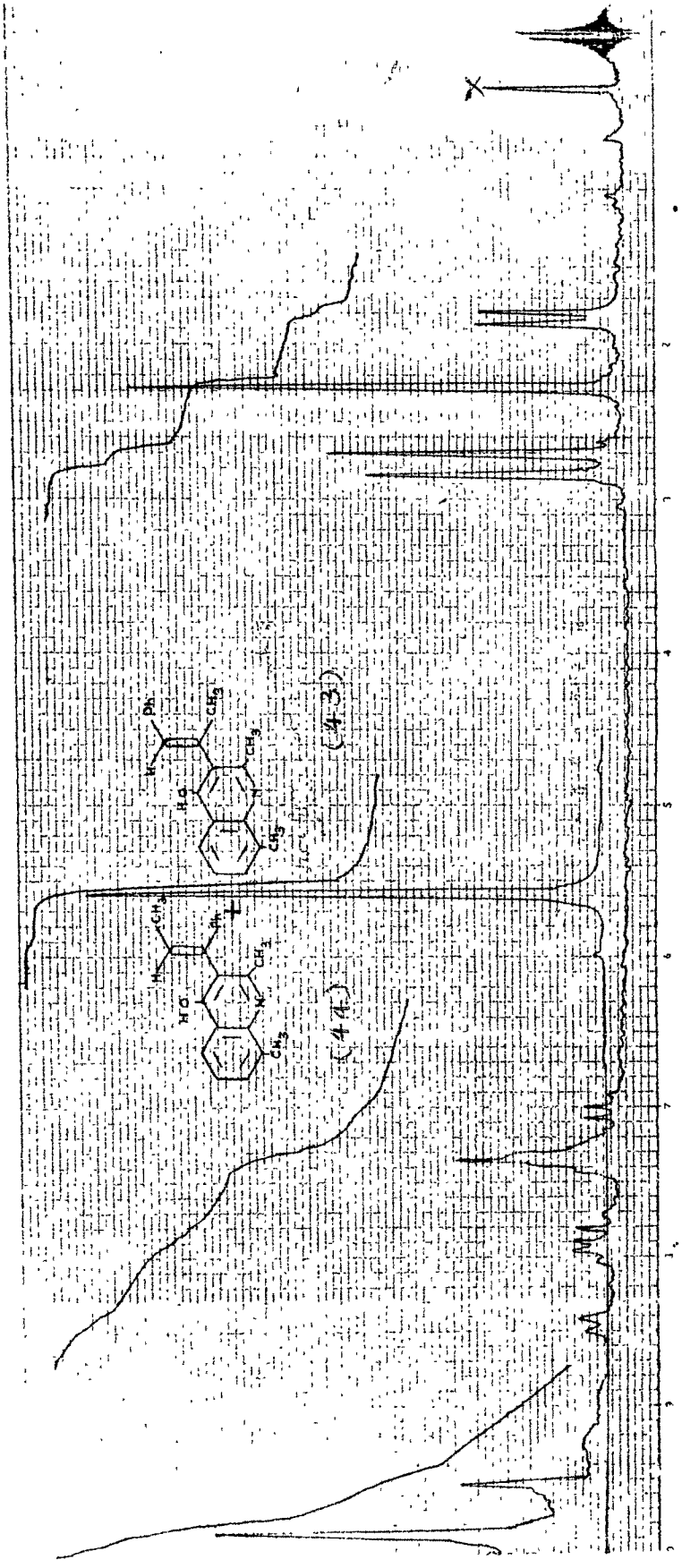
δ, 1.2, -CH-CH_3 proton for (37) appeared δ, 4.96 and that of (39) at δ, 5.3 in the down field and -CH-Ph proton for (37) at δ, 4.3 and for (39) at δ, 4.55 in the down field.



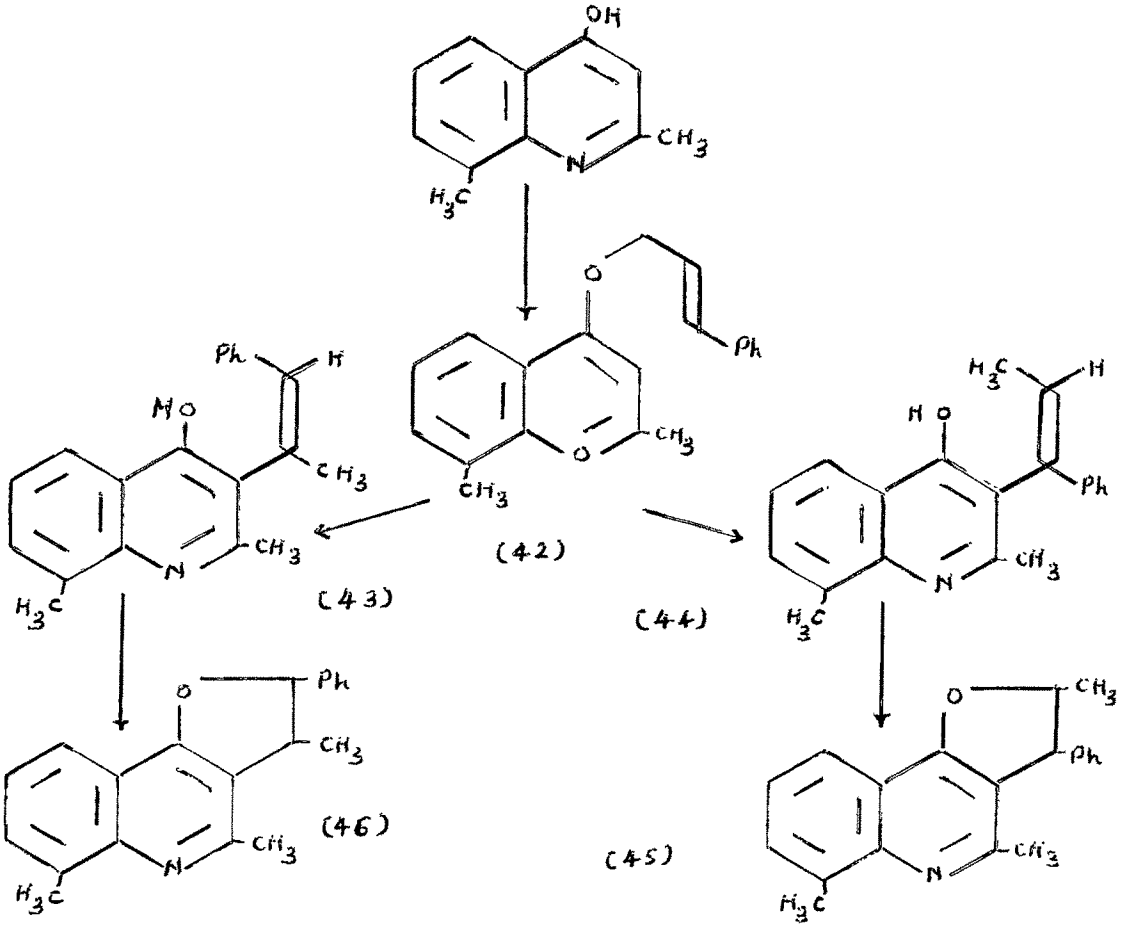
Synthesis of 2,4,6-trimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (45) and 2-phenyl-3,4,6-trimethyl-2,3-dihydro furo (3,2-c)quinoline (46) :

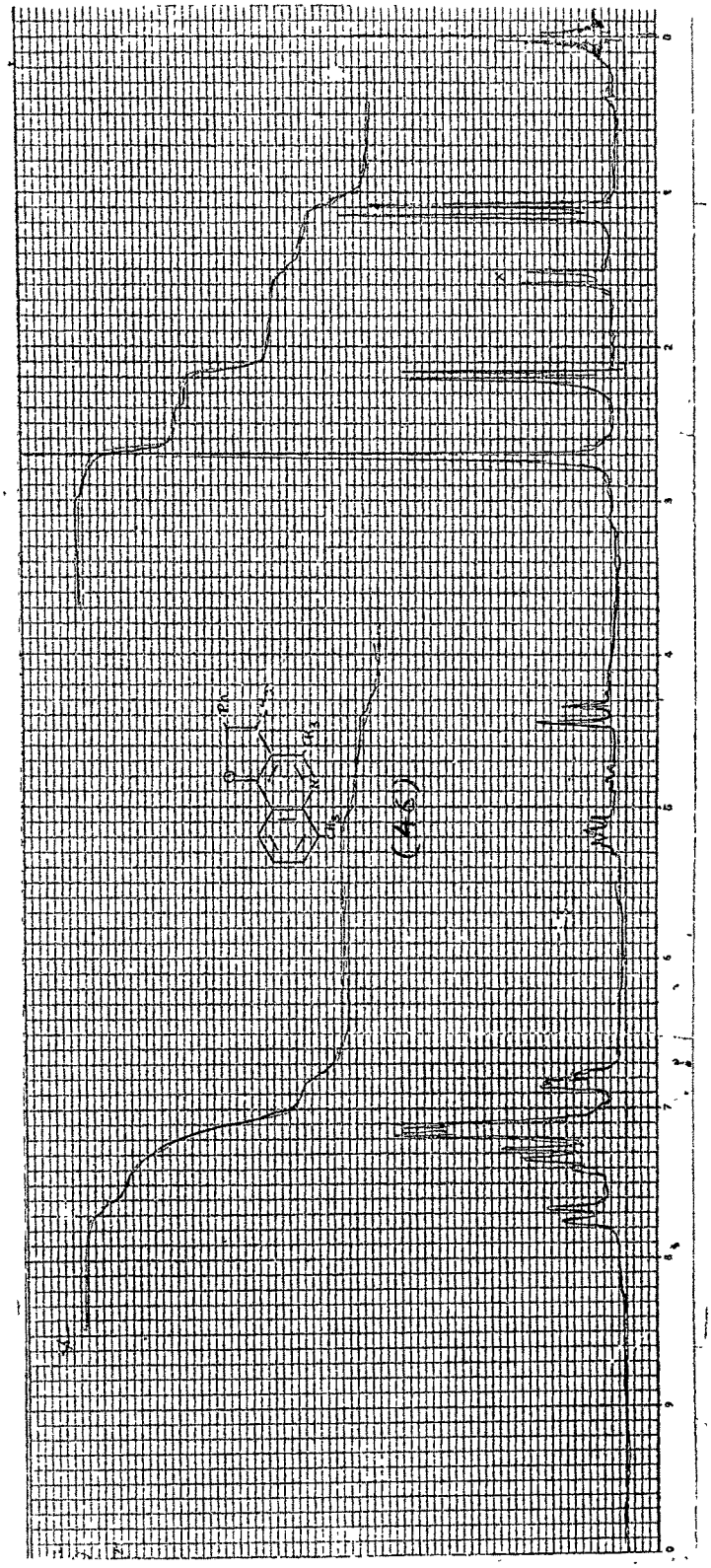
2,8-Dimethyl-4-hydroxyquinoline was condensed with cinnamyl chloride as above to give 2,8-dimethyl-4-cinnamyloxy quinoline (42). The structure of (42) was confirmed by NMR spectrum ($CDCl_3$) which showed signals at δ; 2.75, singlet, 3H, $-CH_3$ group at C_2 ; 2.80, singlet, 3H, $-CH_3$ group at C_8 ; 4.88, doublet, J = 7Hz, 2H, $-O-\underline{CH_2}-$ group ; 6.3 to 6.9, multiplet, 2H, $-\underline{CH}=\underline{CH}-$ group ; 7.25 to 8.12, multiplet, 9H, aromatic. The ether (42) was subjected to Claisen rearrangement by heating it at 200° without solvent, the reaction mixture was digested with benzene and benzene-insoluble fraction was collected as rearranged product, which was found to be a mixture of (43) and (44). The NMR of migrated mixture showed a doublet at δ; 1.8 for $C=CH-\underline{CH_3}$, indicating the presence of (44), and also a singlet appears at δ ; 2.28 for $-C(\underline{CH_3})=CHPh$, indicating presence of (43). All attempts to separate them failed, and hence the mixture was cyclised with PPA. The separation of the cyclic products could not be effected by column chromatography using silica gel, therefore, they were separated by preparative thin-layer chromatrography (silicagel). The structure of separated isomers (45) and (46) were assigned on the basis of NMR spectrum. The NMR

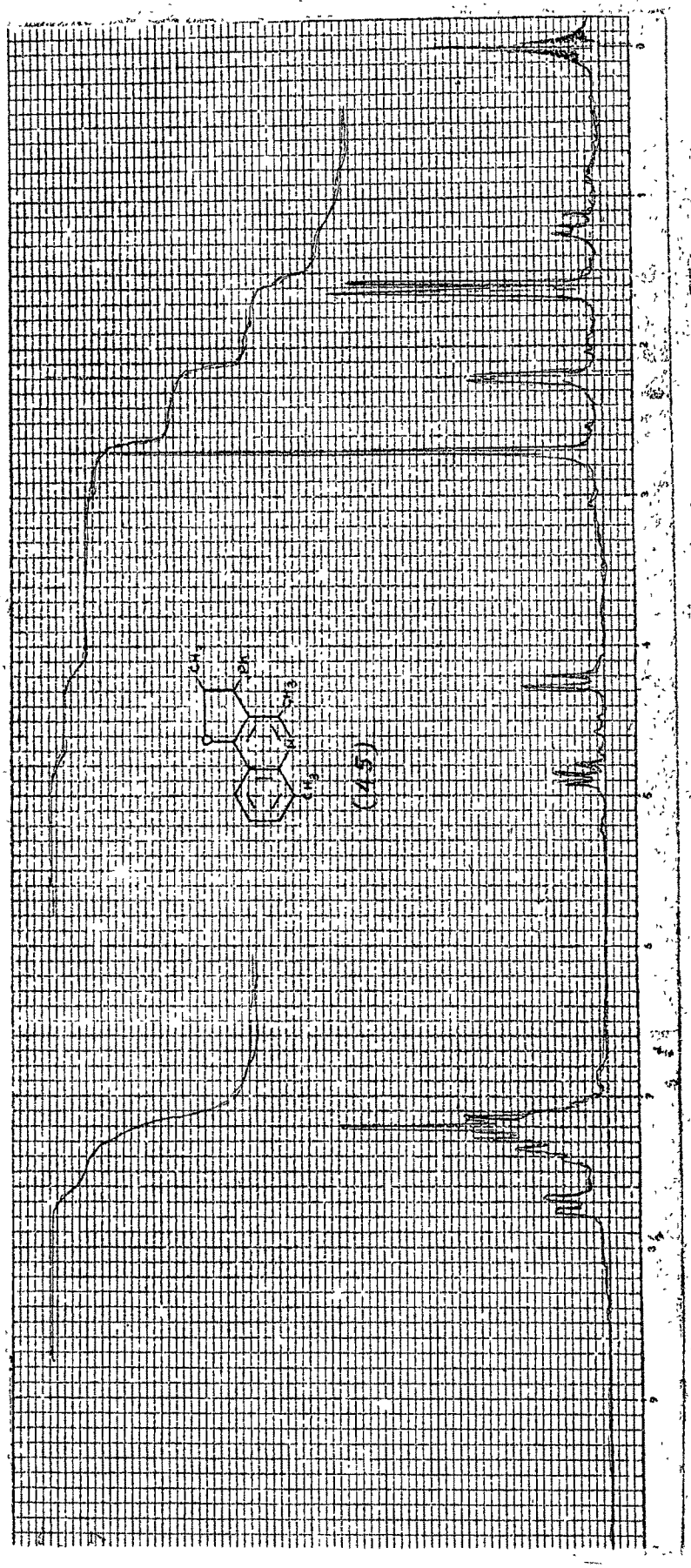

Ph
CH3
O
CH3
(42)


(43)
(44)

($C Cl_4$) of (45) showed signals at δ ; 1.6, doublet, J = 7Hz, 3H, $-CH_3$ group at C_2 ; 2.2, singlet, 3H, $-CH_3$ at C_4 ; 2.7, singlet, 3H, $-CH_3$ at C_6 ; 4.25, doublet, J = 7Hz, 1H, -CH-Ph ; 4.85, multiplet, -CH-CH_3 ; 7.05 to 7.8, multiplet, 8H, aromatic. The NMR of (46) showed signals at δ ; 1.12, doublet, J = 7Hz, 3H, $-CH_3$ at C_3 ; 2.2, singlet, 3H, $-CH_3$ at C_4 ; 2.7, singlet, 3H, $-CH_3$ at C_6 ; 4.4, doublet, J = 10Hz, 1H, -CH-Ph ; 5.15, multiplet, 1H, -CH-CH_3 and 6.8 to 7.75, multiplet, 8H, aromatic. The NMR specta of the two isomers suggest that each isomer is not completely separated but is contaminated with the other isomer to the extent of 10 % because the methyl signals are much predominent for other isomer in each spectrum.

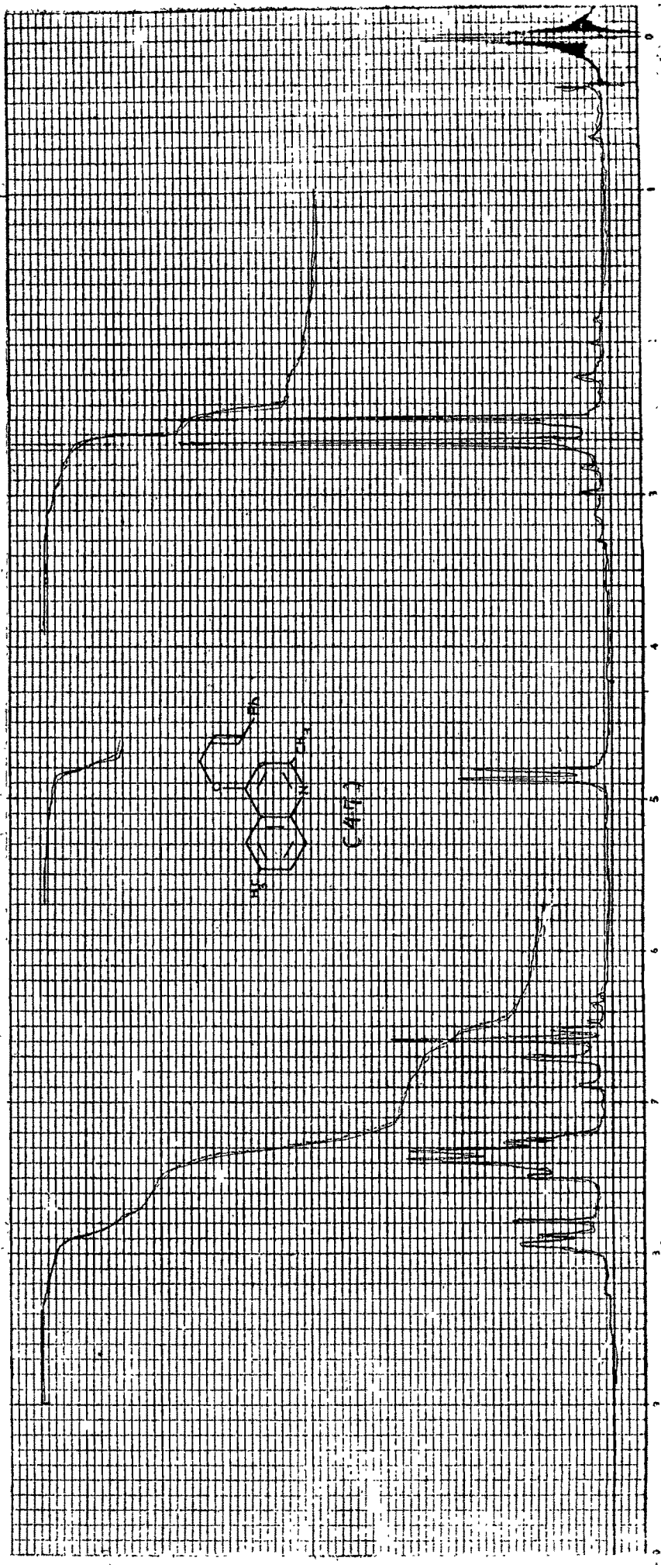


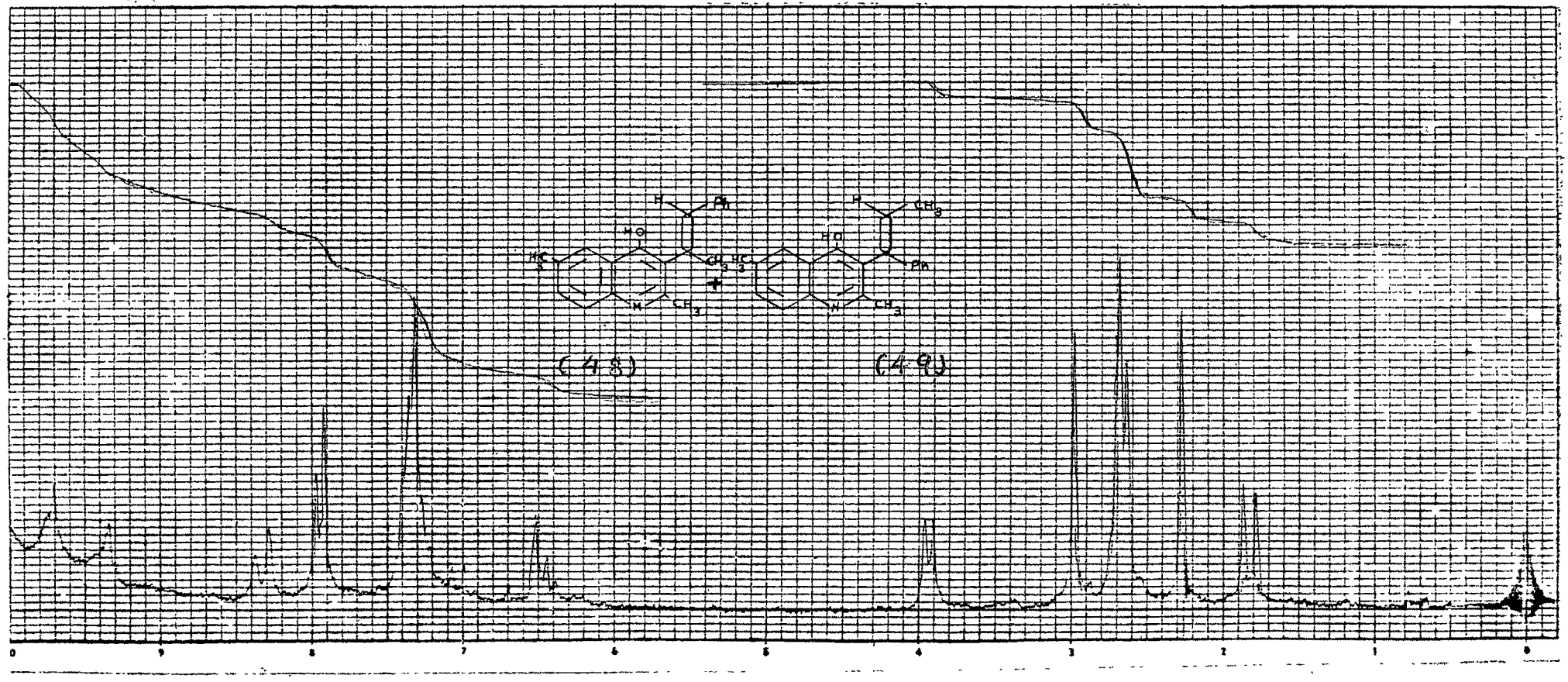



(4.5)

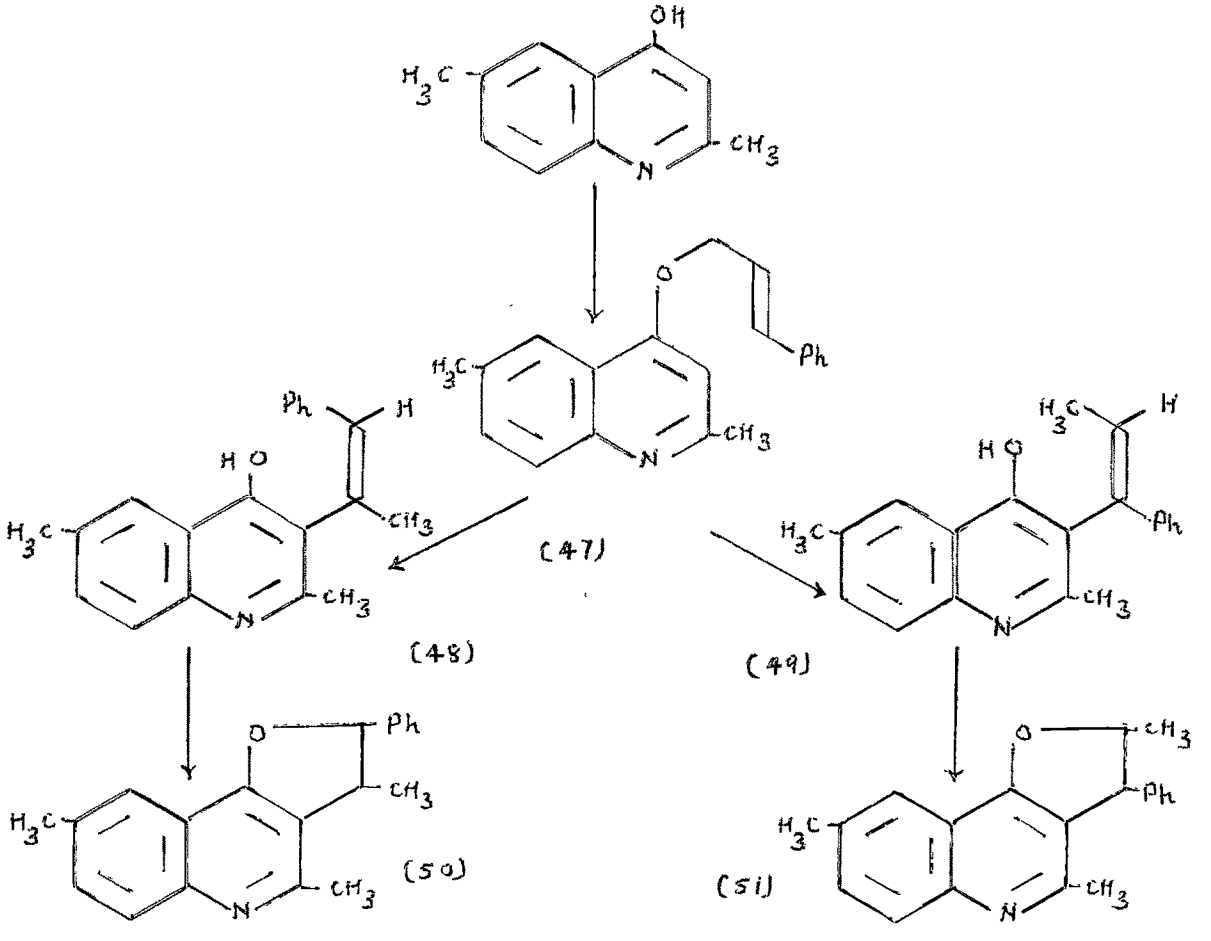
Synthesis of 2,4,8-trimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (50) and 2-phenyl-3,4-8-trimethyl-2,3-dihydro furo (3,2-c)quinoline (51) :

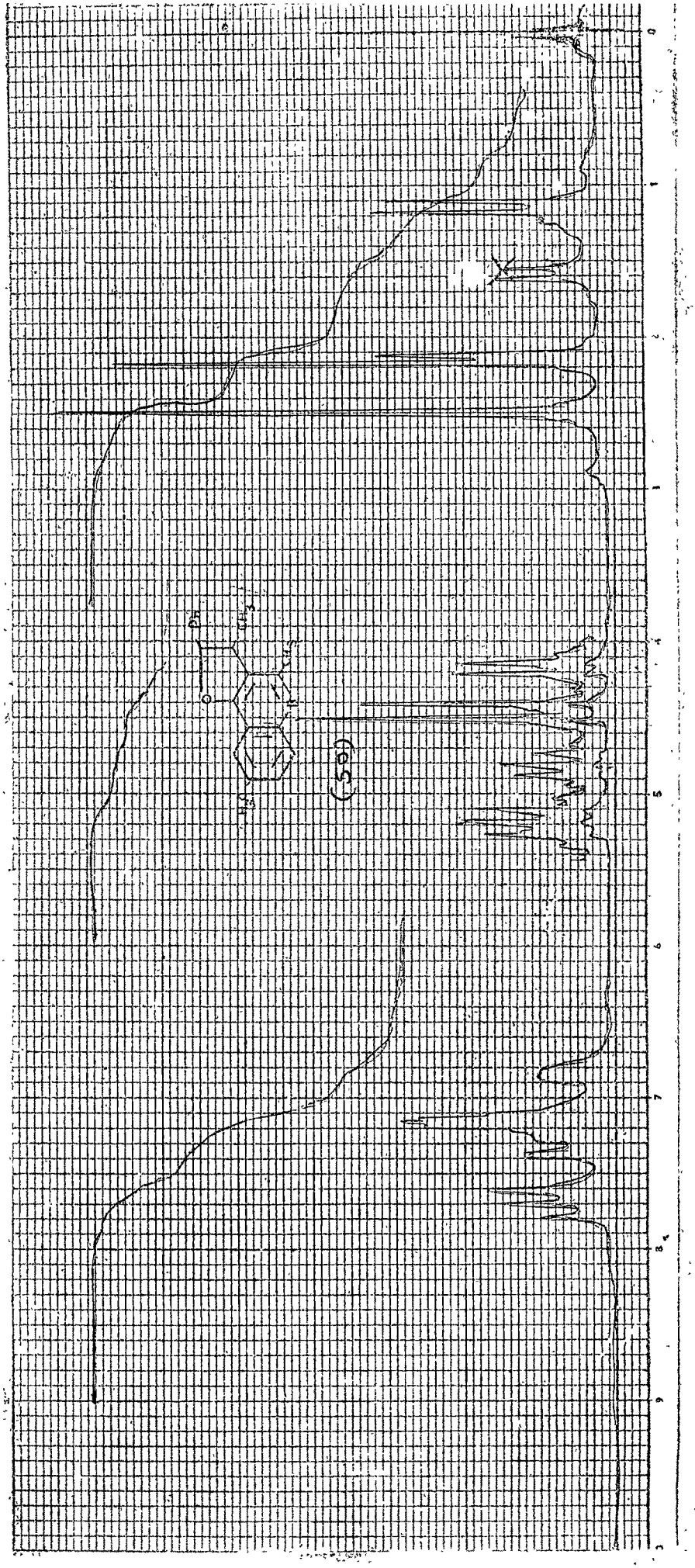
2,6-Dimethyl-4-hydroxyquinoline was condensed with cinnamyl chloride as above to give 2,6-dimethyl-4-cinnamyloxy quinoline (47). The structure of (47) was confirmed by NMR spectrum ($CDCl_3$) which showed signals at δ; 2.5, singlet, 3H, $-CH_3$ at C_2 ; 2.65, singlet, 3H, $-CH_3$ at C_6 ; 4.85, doublet, J = 7Hz, 2H, $-O-CH_2-$ group ; 6.3 to 6.9, multiplet, 2H, -CH=CH- group and 7.2 to 7.9, multiplet, 9H, aromatic. The ether (47) was subjected to Claisen rearrangement by heating it at 200° without solvent, the reaction mixture was digested with benzene and benzene-insoluble fraction was collected as rearranged product, which was found to be a mixture of (48) and (49). The NMR spectrum of migrated mixture product showed a doublet at δ; 1.85 with the coupling constant J = 7Hz for $C=CH-\underline{CH_3}$, indicating the presence of (49) and a singlet appeared at δ, 2.28 for $-C(CH_3)=CHPh$, indicating presence of (48). All attempts to separate them failed, and hence the mixture was cyclised with PPA. The separation of the cyclic products could not be effected by column chromatography using silica gel, therefore, they were separated by preparative thin-layer chromatography (silicagel). The structure of separated isomers (50) and (51) were assigned on the basis of NMR spectra. NMR spectrum (C_6Cl_4) of

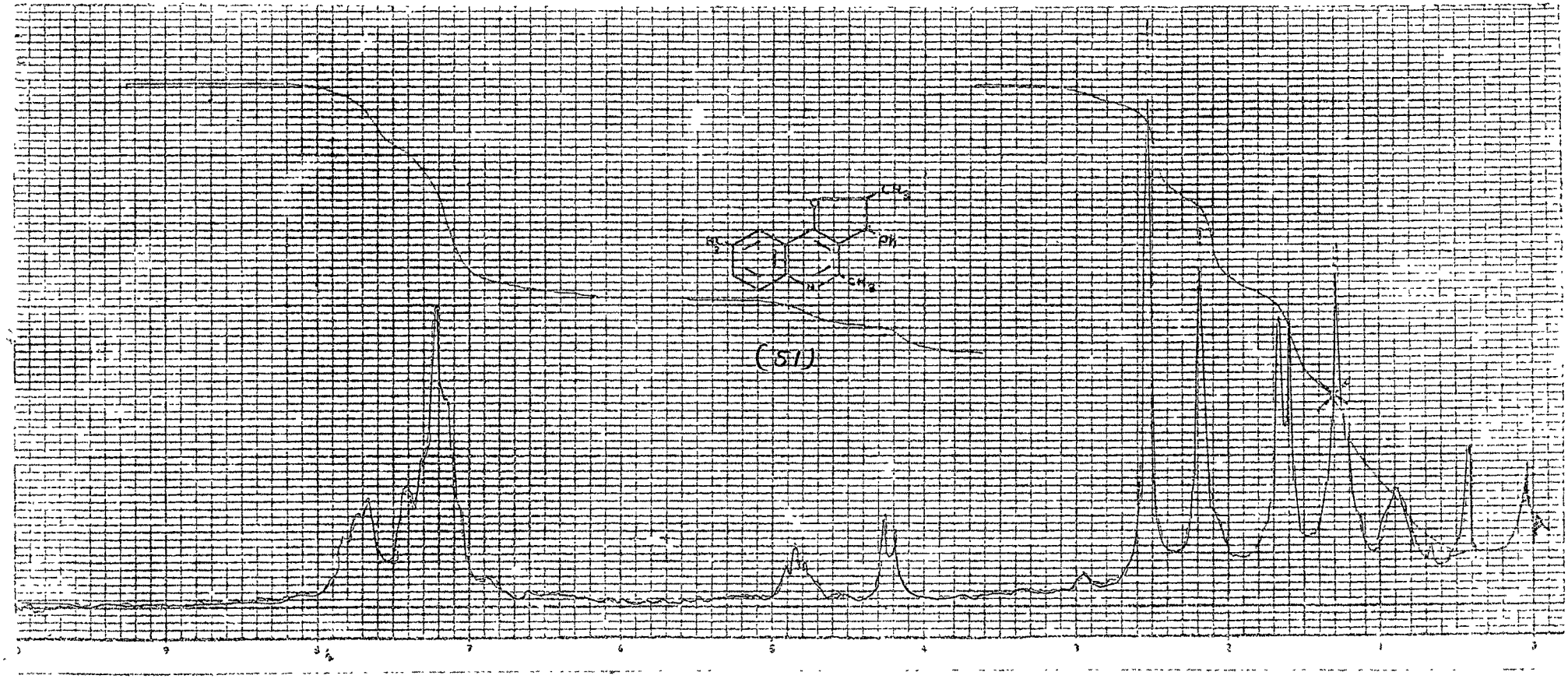



(48)
(49)

(51) showed signals at δ; 1.65, doublet, J = 7Hz, 3H, CH_3 at C_2 ; 2.2, singlet, 3H, $-CH_3$ at C_4 ; 2.52, singlet, 3H, $-CH_3$ at C_8 ; 4.25, doublet, J = 7Hz, 1H, -CH-Ph ; 4.85, multiplet, $-CH-CH_3$; 7.12 to 7.85, multiplet, 8H, aromatic. The NMR of (50) showed signals at δ; 1.15, doublet, J = 7Hz, 3H, $-CH_3$ at C_3 ; 2.18, singlet, 3H, $-CH_3$ at C_4 ; 2.5, singlet, 3H, CH_3 at C_8 ; 4.45, doublet, J = 10Hz, 1H, -CH-Ph ; 5.15, multiplet, 1H, $-CH-CH_3$ and 7.1 to 7.8, multiplet, 8H, aromatic. The NMR spectra of the two isomers suggest that each isomer is not completely separated but is contaminated with the other isomer to the extent of 10 % because the methyl signals are much predominent for other isomer in each spectrum.

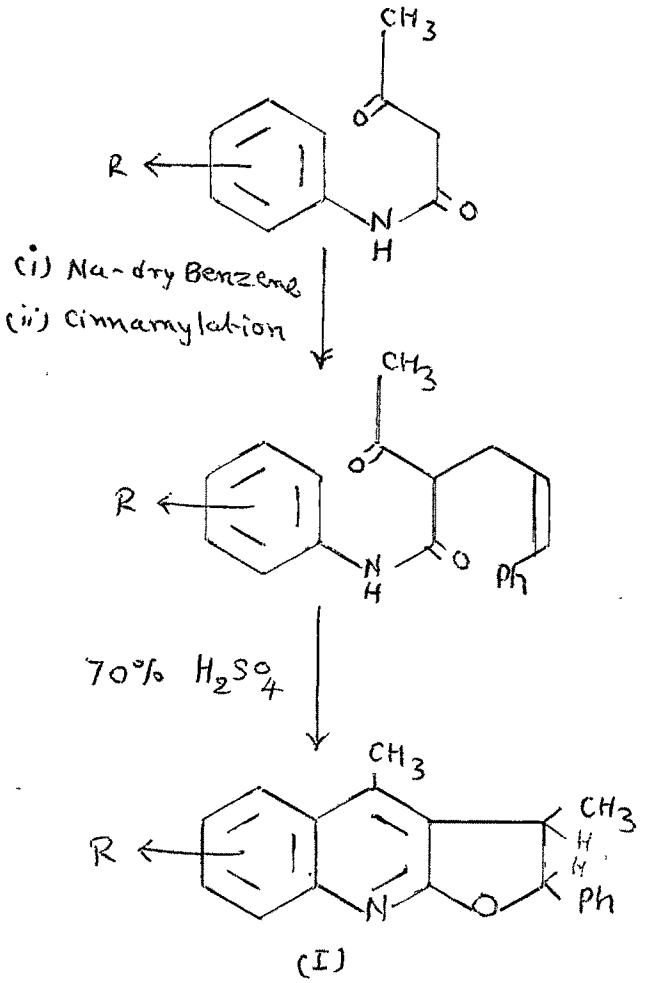



(CDCl3)


(5.1)

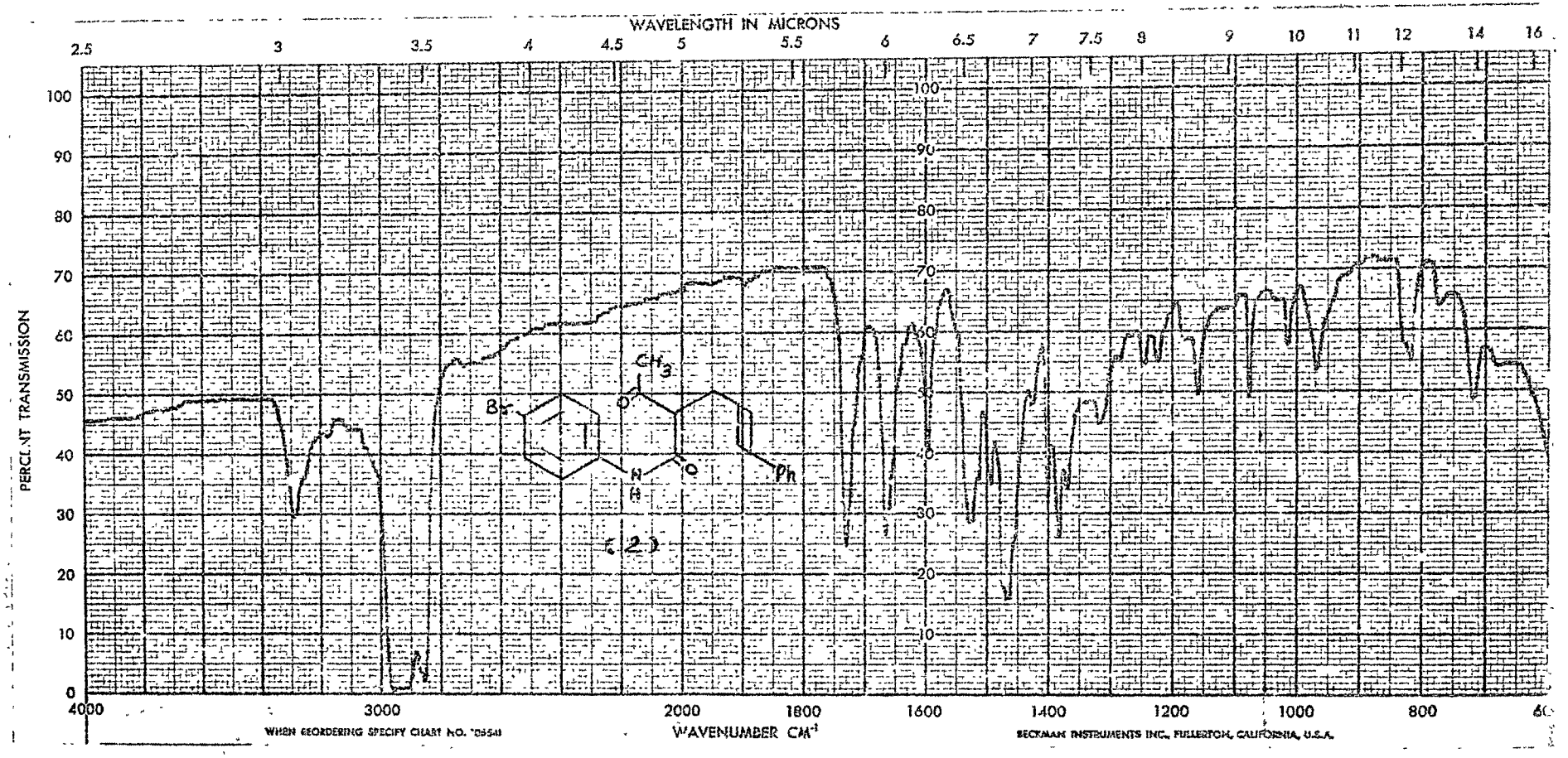
Cinnamylation of Acetoacetanilide derivative and cyclisation to N-(phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine derivatives :

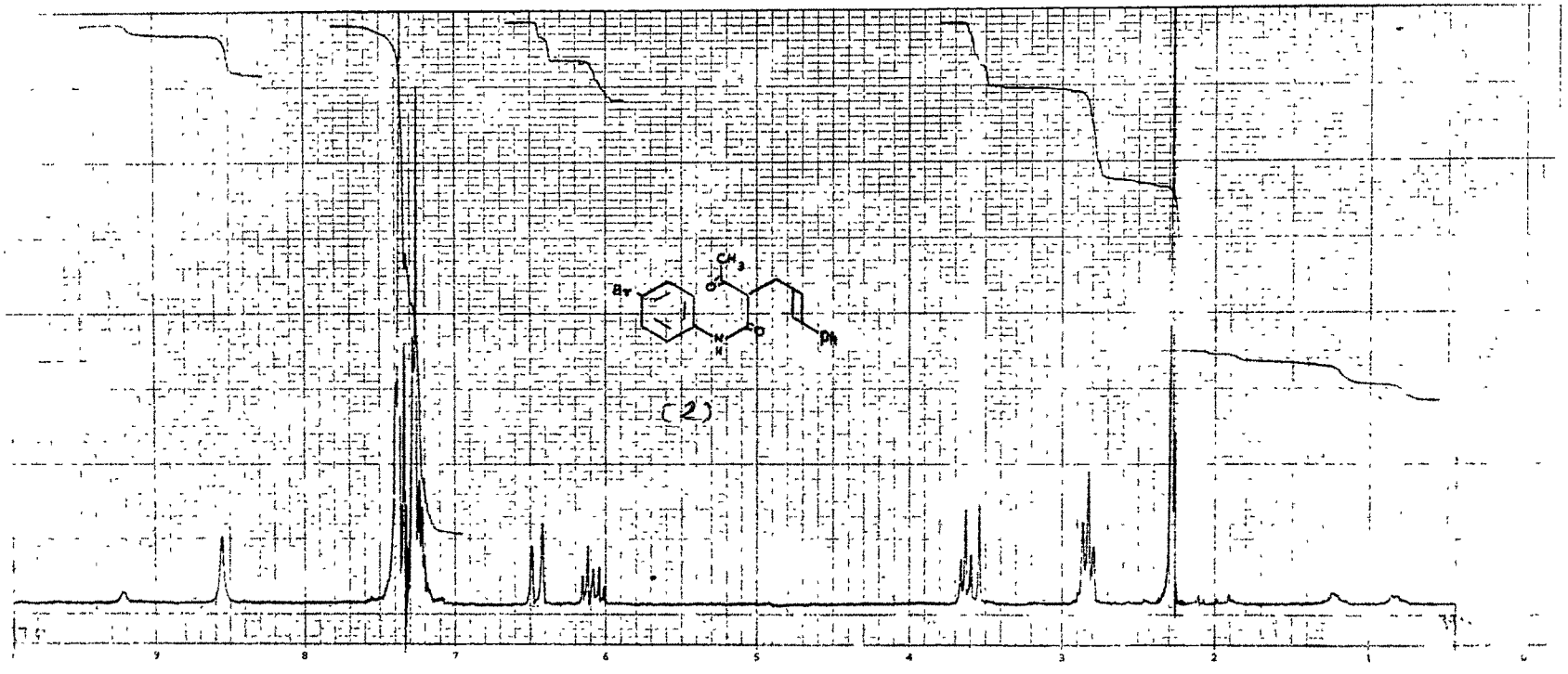
In view of the interesting results of the cinnamylation of 4-hydroxy-2-methylquinoline derivatives, the cinnamylation of acetoacetanilide derivatives were next tried to synthesise 3,4-dimethyl-2,3-dihydro-2-phenyl furo (2,3-b)quinoline derivatives (1) according to the following scheme.



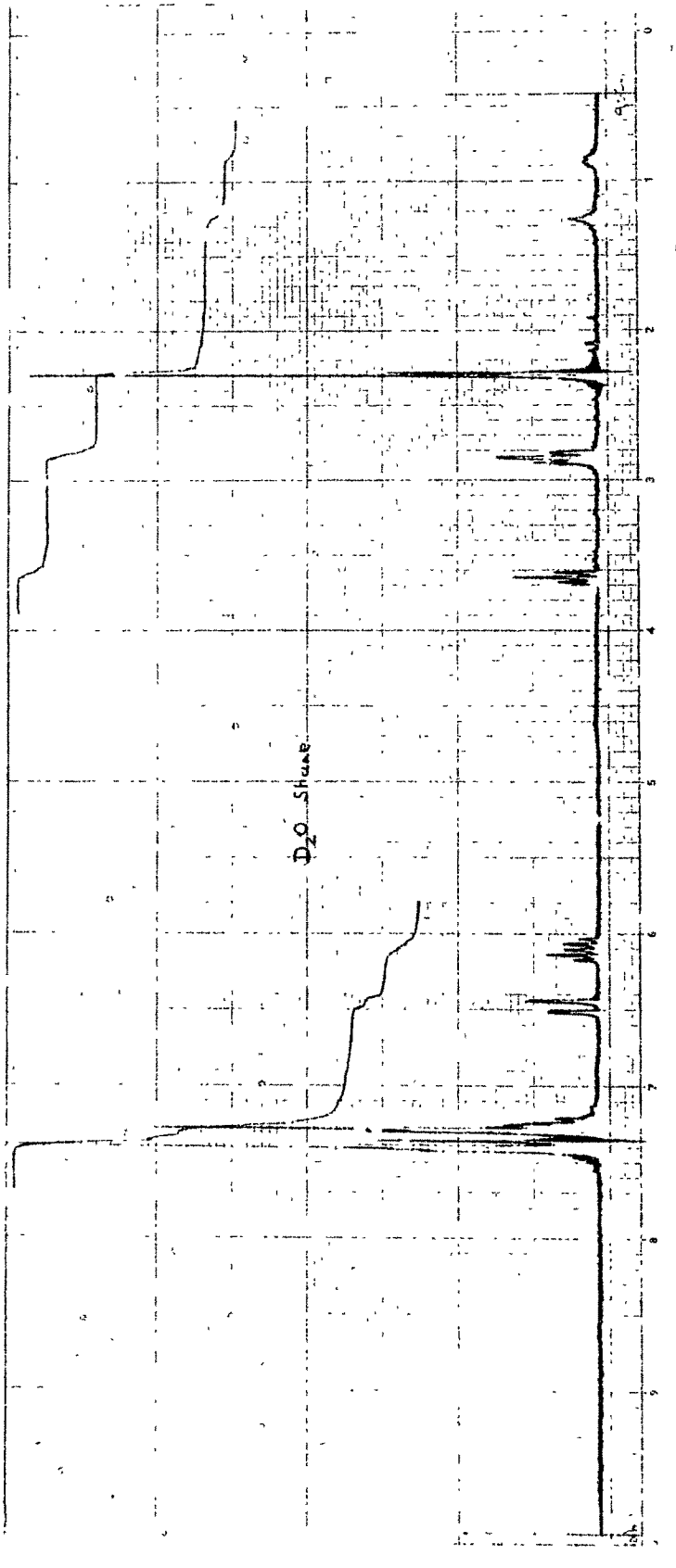
(I)

Acetoacet-p-bromoanilide was first subjected to cinnamylation by reacting the sodium salt of acetoacet-p-bromoanilide with cinnamyl chloride in dry benzene. This gave α-cinnamyl-acetoacet-p-anilide (2), thestructure of which was confirmed by IR and NMR spectra. IR spectrum (nujol) showed band at 3300 cm^{-1}, -CO-NH- group. The 230 MHz NMR spectrum ($CDCl_3$) showed signals at δ; 2.28, singlet, 3H, $-COCH_3$; 2.82, triplet, J = 7Hz, 2H, $-\underline{CH_2}-CH=CH-Ph$; 3.62, triplet, J = 7Hz, 1H, $-\underset{\underset{O}{\|}}{C}-\underset{\underset{C=O}{|}}{CH}-CH_2-CH=$; 6.15, multiplet J = 16 + 7Hz, 1H, $-CH_2-\underline{CH}=CH-Ph$; 6.5, doublet, J = 16Hz, 1H, $-CH=\underline{CH}-Ph$; 7.25 to 7.4, multiplet, 9H, aromatic and 8.55, singlet, 1H, -NH. The signal at δ; 8.55 slowly disappeared by D_2O suggesting -NH group. The two ethylenic protons are trans to one another. indicated by their high coupling constant of J = 16Hz. The compound is partially ketonic form (3) but it also developed ink-blue colour with ferric chloride in ethanol, which is the indication for small amount of enolic form (4). This is also indicated in the NMR spectrum which showed a small neighbouring $-CH_3$ signal at δ, 2.25 along with the original $-CH_3$ signal. The decoupling experiment was also performed by double irradiation the signal at δ, 2.82 for methylene protons. This resulted in the collapse of the triplet at δ, 3.62 to a singlet and multiplet at δ, 6.15 also collapse to a doublet. This experiment also confirmed the ketonic structure (3).

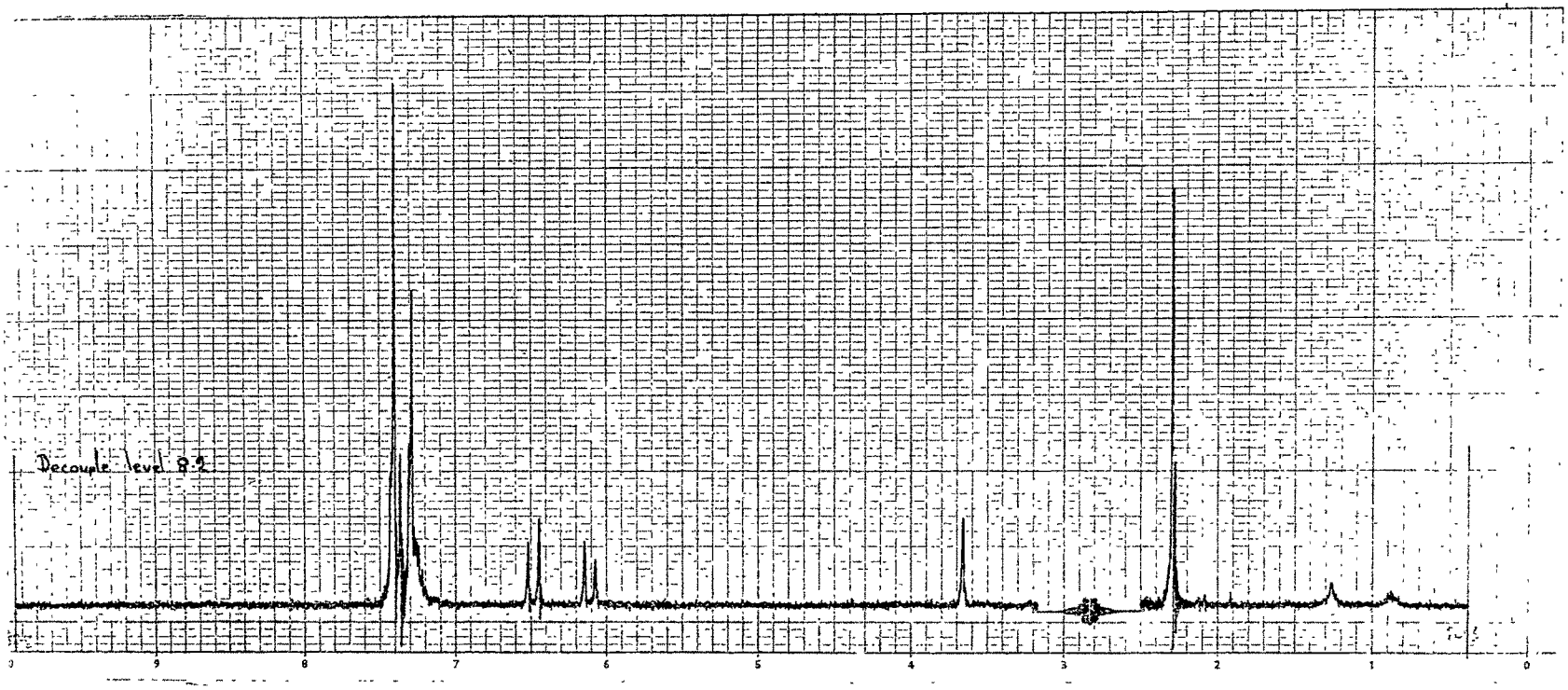

WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
WHEN REORDERING SPECIFY CHART NO. 0854
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.
CH3
O
Br
H
N
O
Ph
(2)



(2)



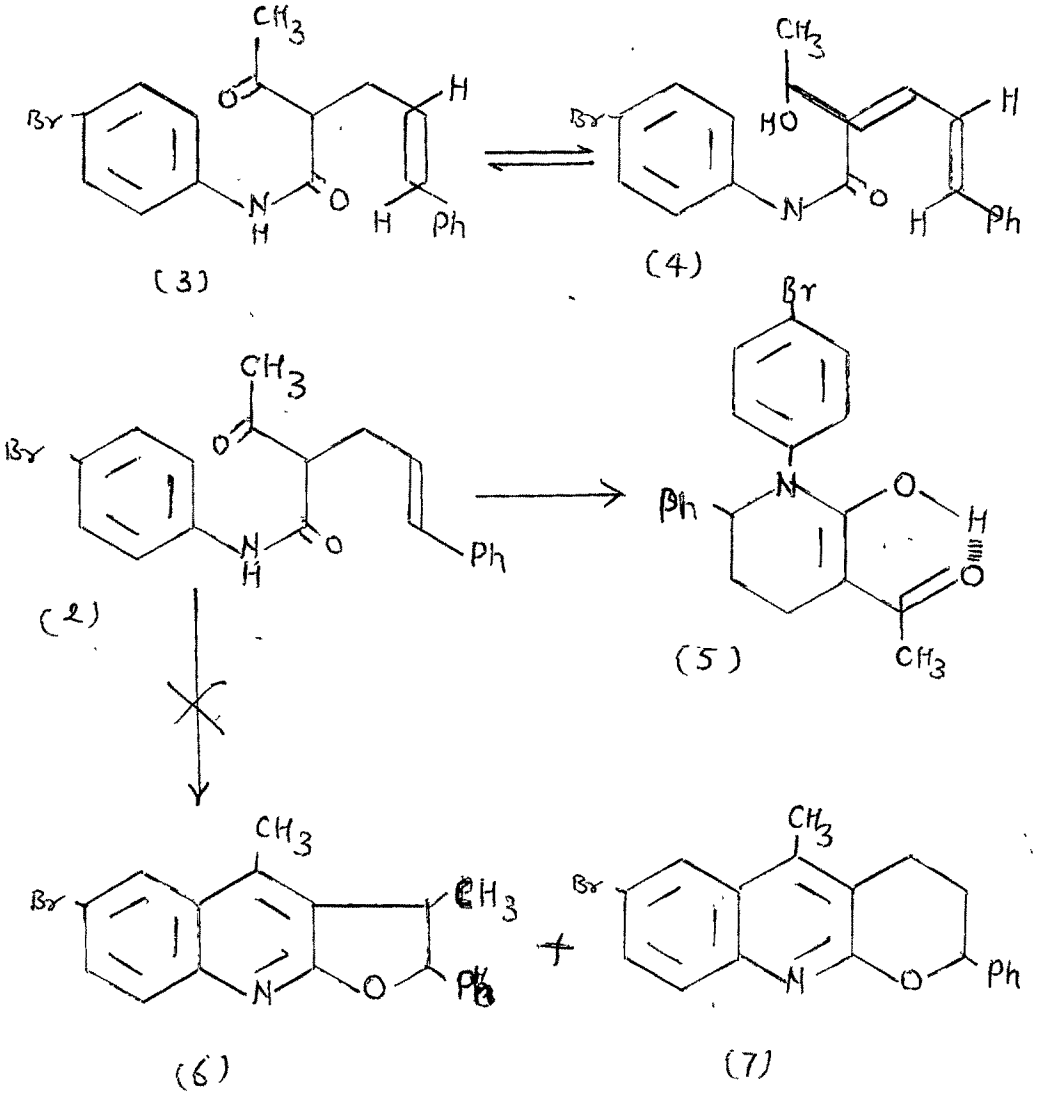
D_2O - shake in (2) compound

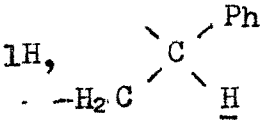


Decoupling Experiment

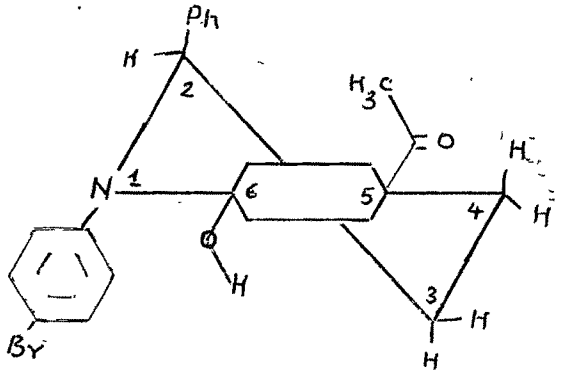
compound No. 2

The above compound (2) on treatment with sulphuric acid (70 %) gave N-(p-bromophenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (5) instead of 3,4-dimethyl-2-phenyl-6-bromo-2,3-dihydro furo(2,3-b)quinoline (6) or 2-phenyl-4-methyl-3,4-dihydro pyrano (2,3-b) quinoline (7).

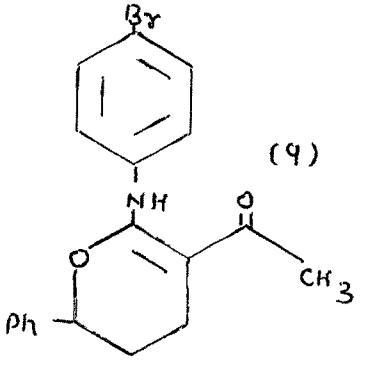


The structure of (5) was confirmed by IR and NMR spectra. IR(nujol) spectrum showed band at 1630 cm^{-1} for the chelated >C=O group. The NMR ($CDCl_3$) (220 MHz) showed signals at δ; 1.96, singlet, 3H, $-COCH_3$; 2.05, multiplet, 1H, ; 2.30, multiplet, 3H ; 4.93, triplet, 1H,  ; 6.9 to 7.4, multiplet, 9H, aromatic and 15.0, singlet, 1H, chelated OH group. The signal at δ, 15.0 was also reduced by D_2O exchange. The presence of chelated hydroxy group was further confirmed by the development of deep bluish green colour with alcoholic ferric chloride solution. The signals at δ; 2.05 for 1H and δ, at 2.3 for 3H are for the two methylene groups in the tetrahydro pyridine nucleus. One proton has separated from the other three protons due to the cis-trans effect of the phenyl ring (8).

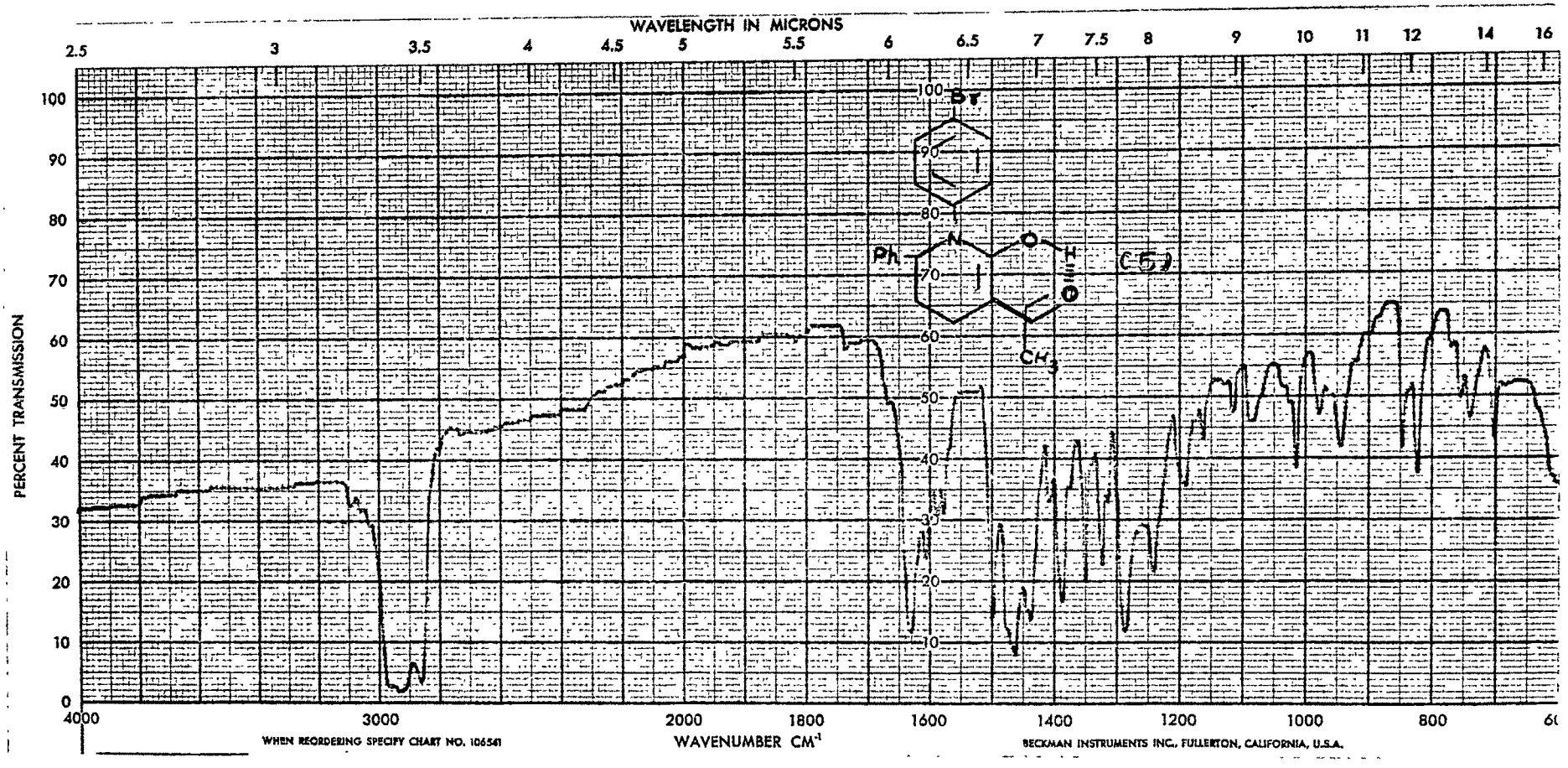
(8)

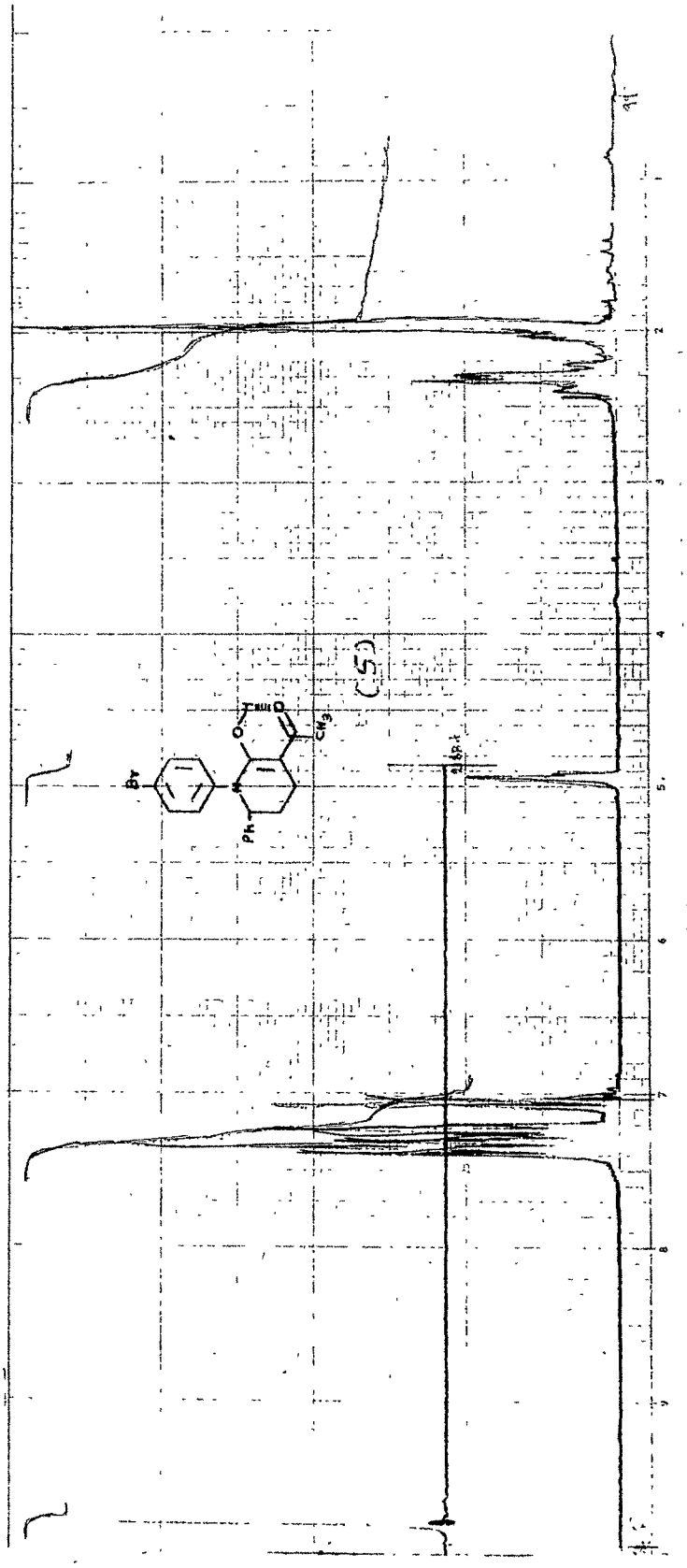


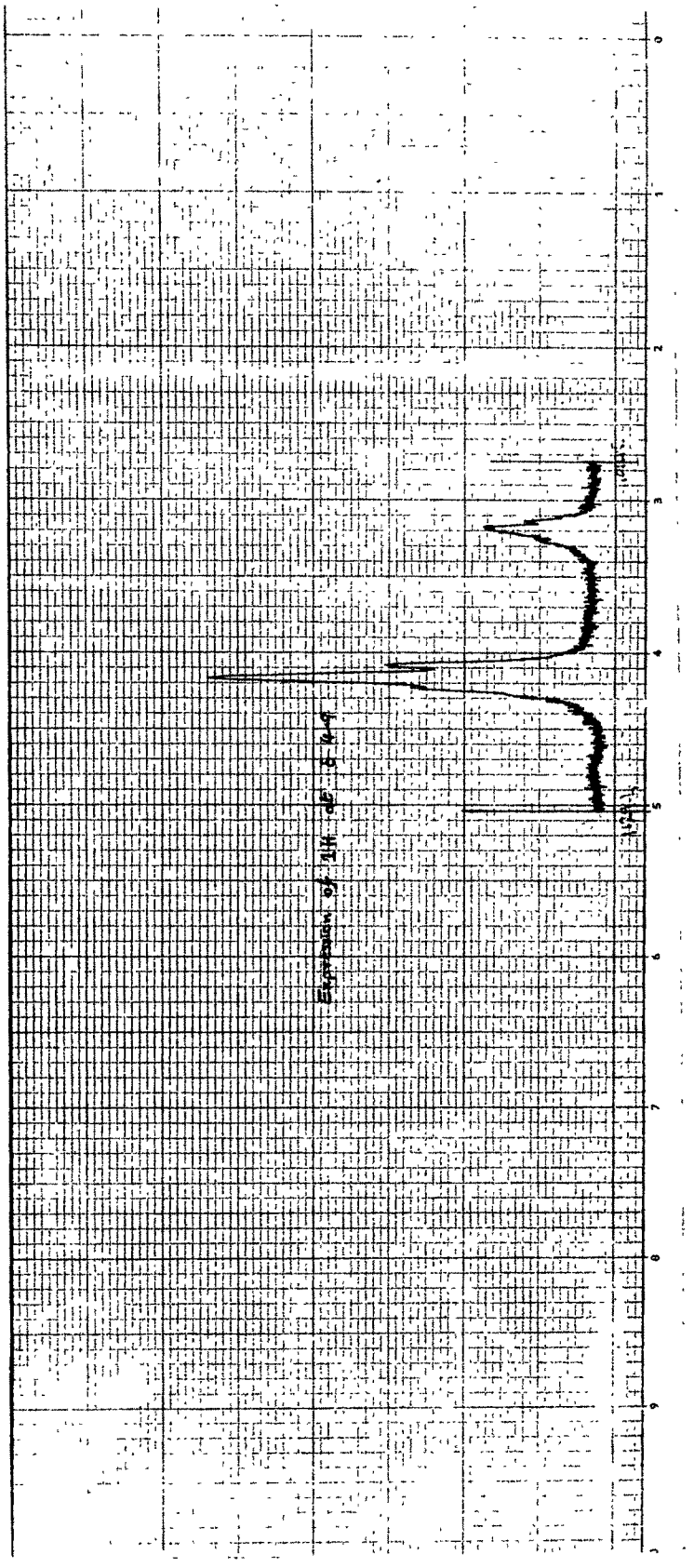
(9)

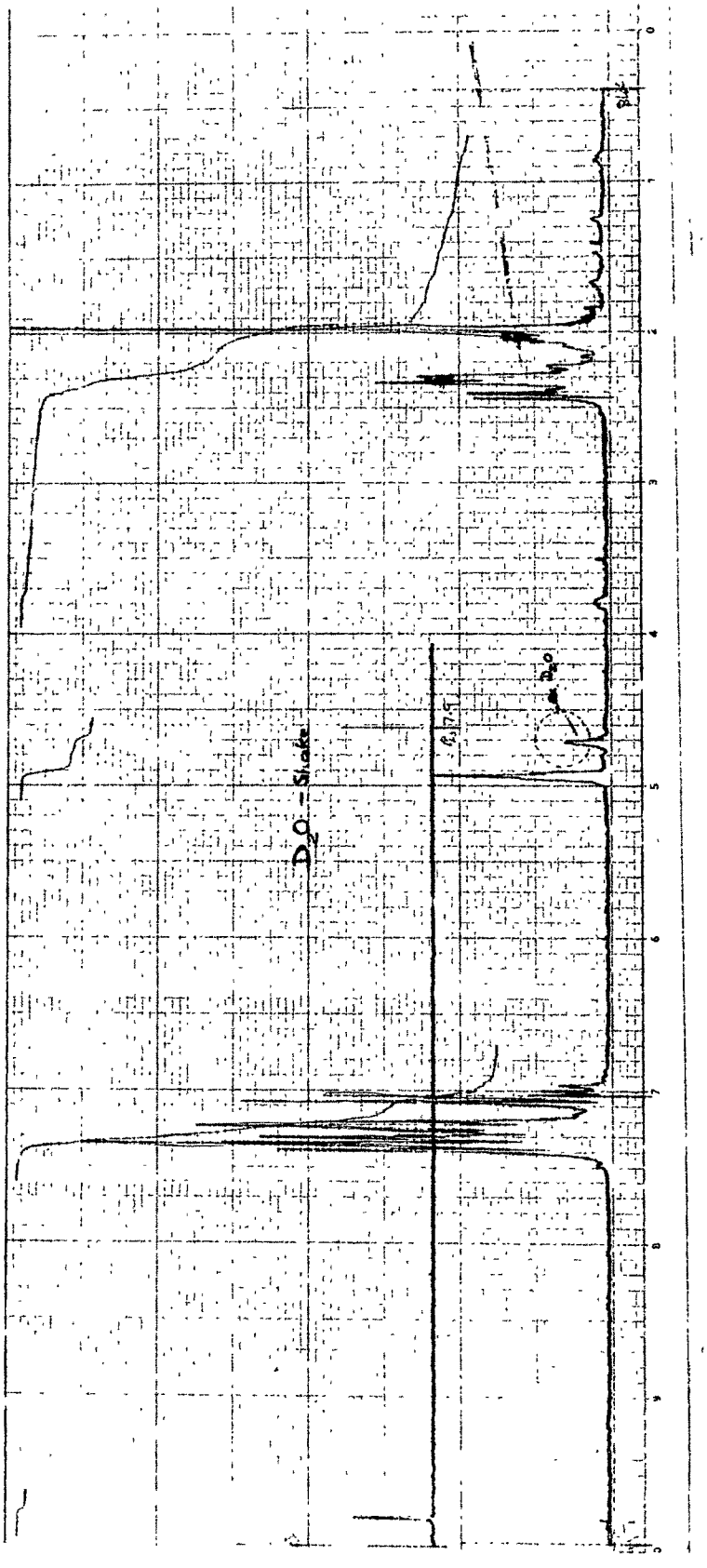


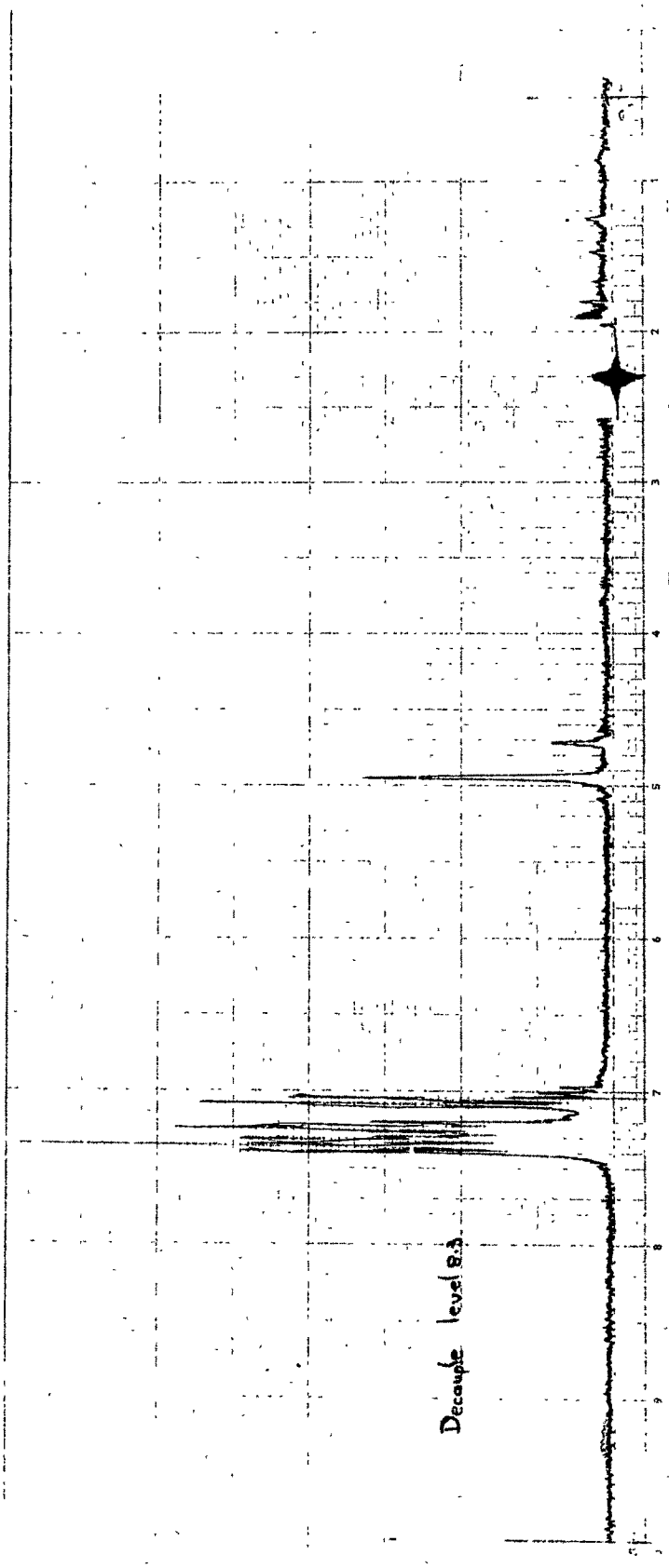
The decoupling experiment was performed by double irradiation the signal at δ, 2.3. This resulted into the collapse for triplet at δ, 4.93 to a singlet with greater intensity (NOE).


WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
Br
Ph
N
O
H
O
CH3
(5)
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM-1
WHEN REORDERING SPECIFY CHART NO. 106541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.


(5d)
Br
Ph
O
O
CH3


Expansion of 1H

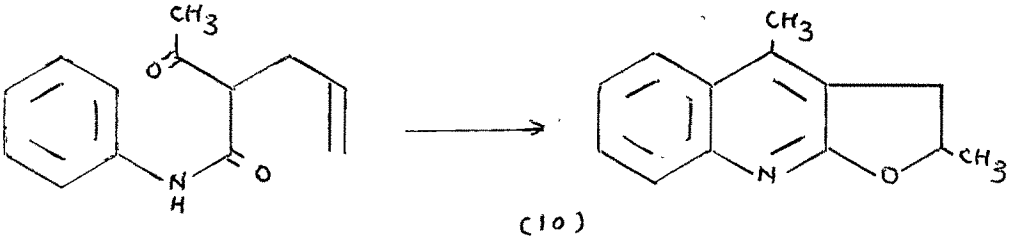

D2O - Shake
H2O



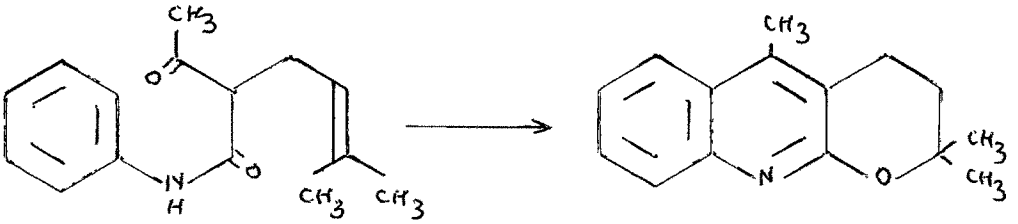
Decoupling experiment

Compound No. 5

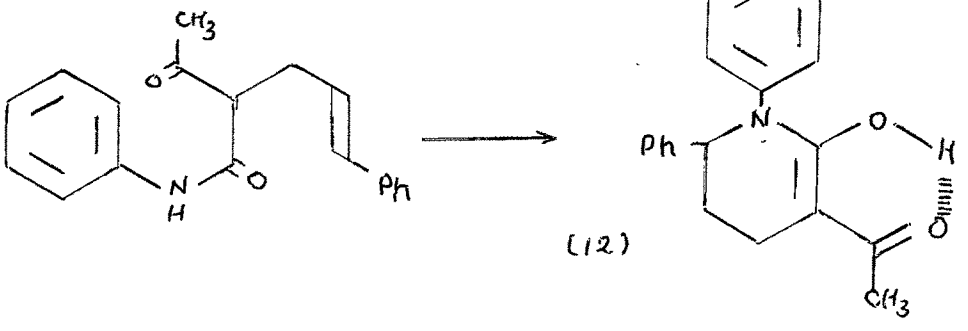
The possibility of the formation of 2-phenyl-5-acetyl-6-(p-bromophenyl)-amino-3,4-dihydro pyran (9) during cyclisation of α-cinnamyl-acetoacet-p-bromo anilide (4) was ruled out on the basis of IR and NMR spectra. The IR spectrum of cyclised product did not show any band for -NH group at 3300 cm^{-1} and also signal at δ, 8-9 for the -NH proton did not appear in NMR spectrum. It was reported that cyclisation of α-allyl acetoacetanilide gave 2,4-dimethyl-2,3-dihydro furo(2,3-b)quinoline (10), α-prenyl acetoacetanilide gave 2,2,5-trimethyl-3,4-dihydropyrano (2,3-b)quinoline (11). While cyclisation of α-cinnamyl-acetoacetanilide gave N-(Phenyl)-2-phenyl--5-acetyl-6-hydroxy-1,2,3,4-tetrahydropyridine (12) a novel compound.



(10)



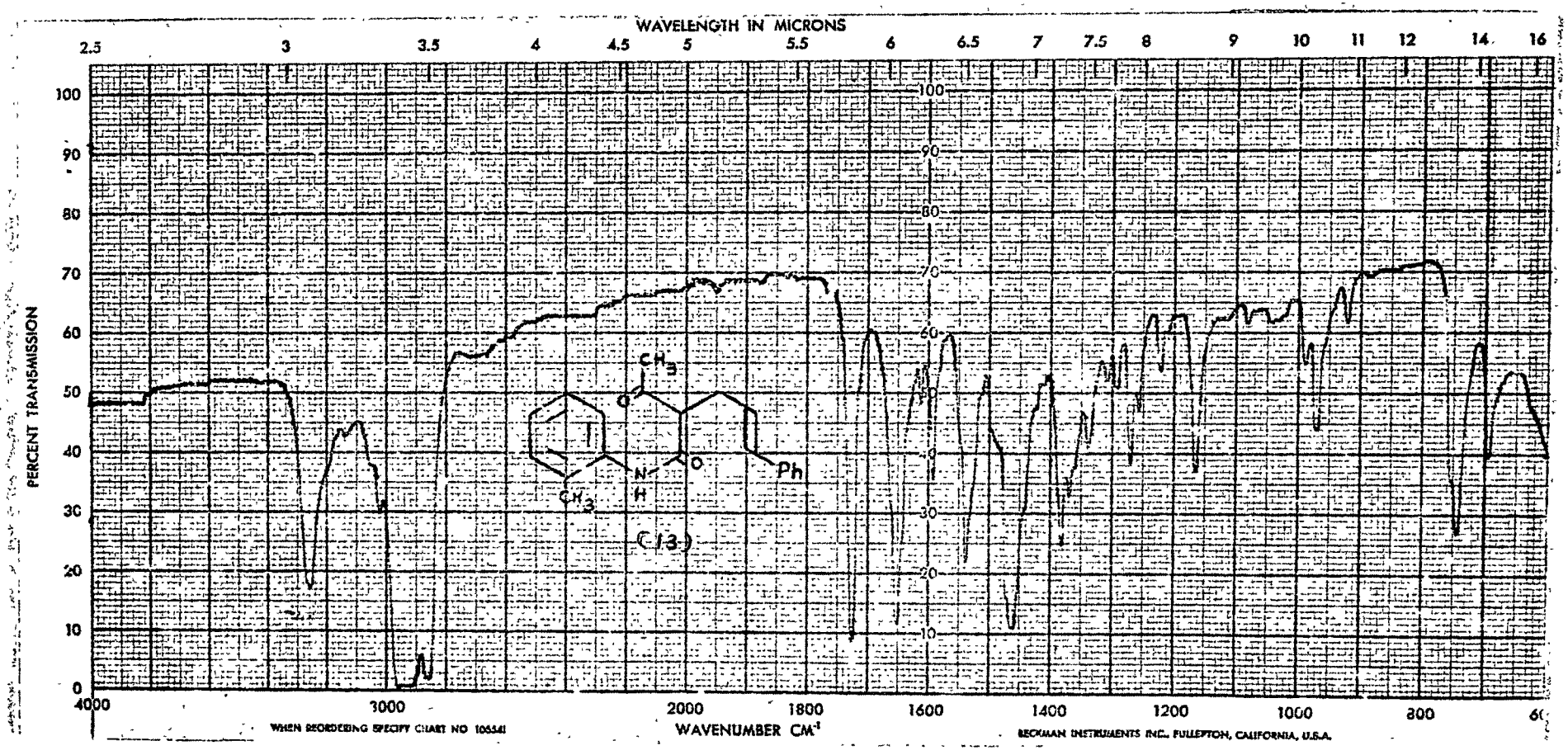
(11)

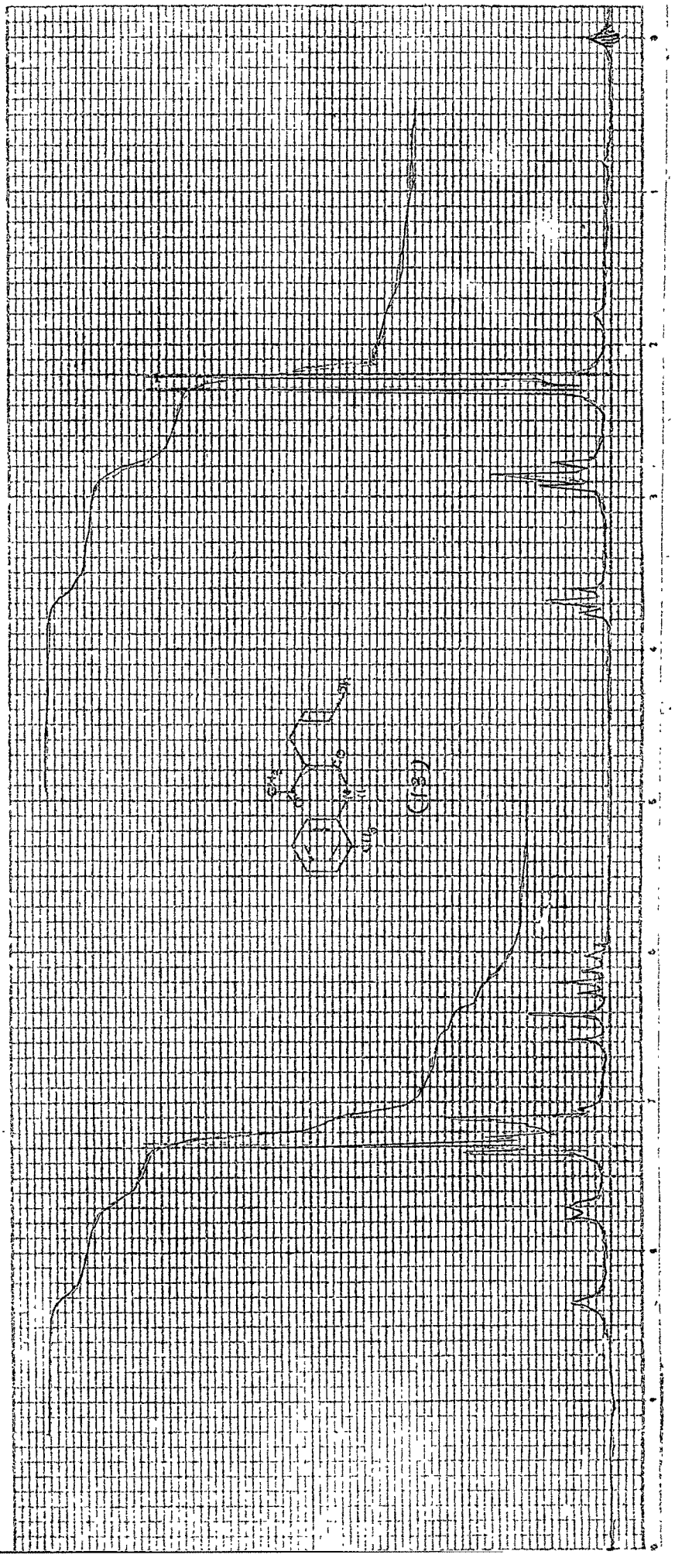


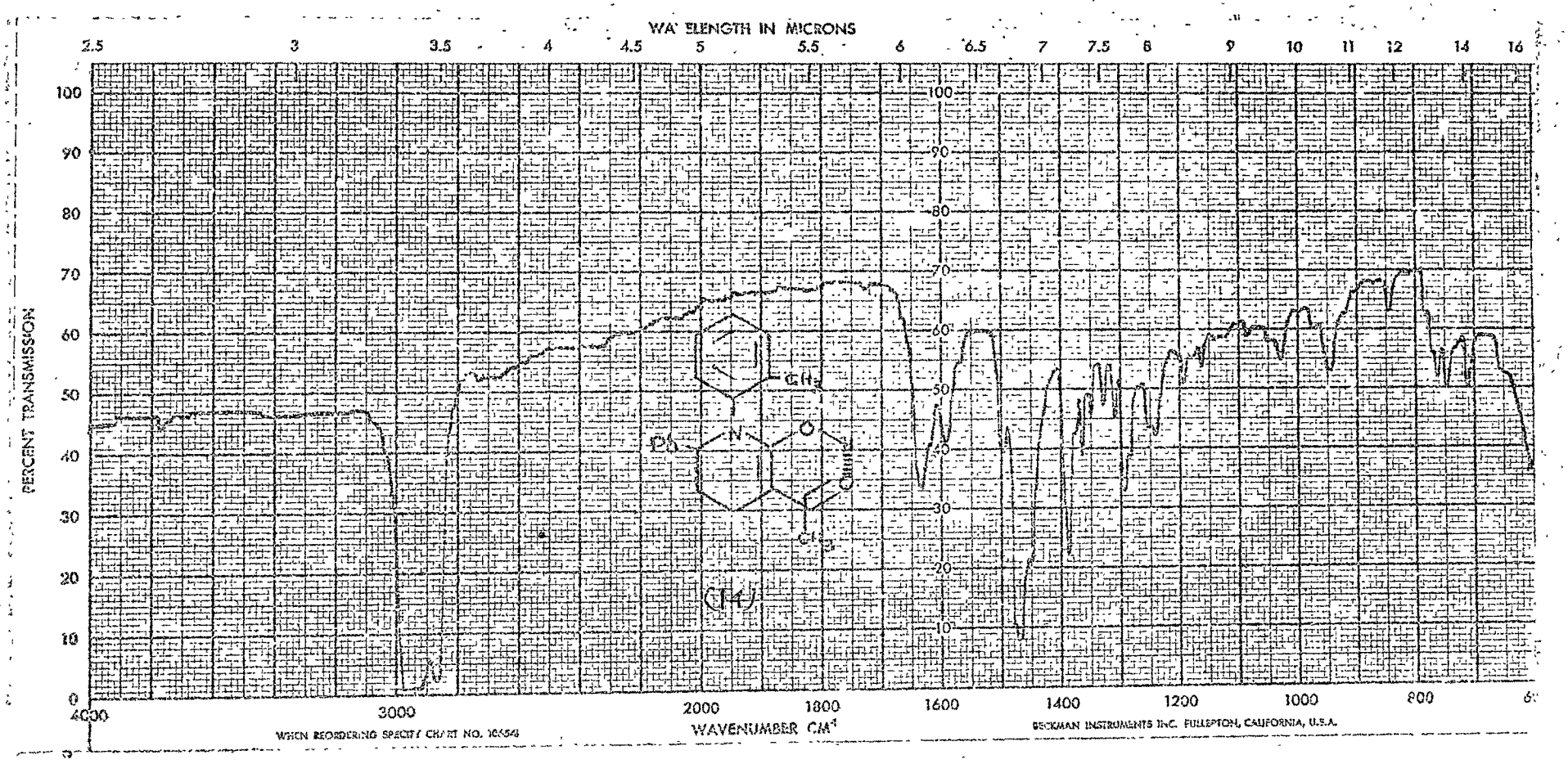
(12)

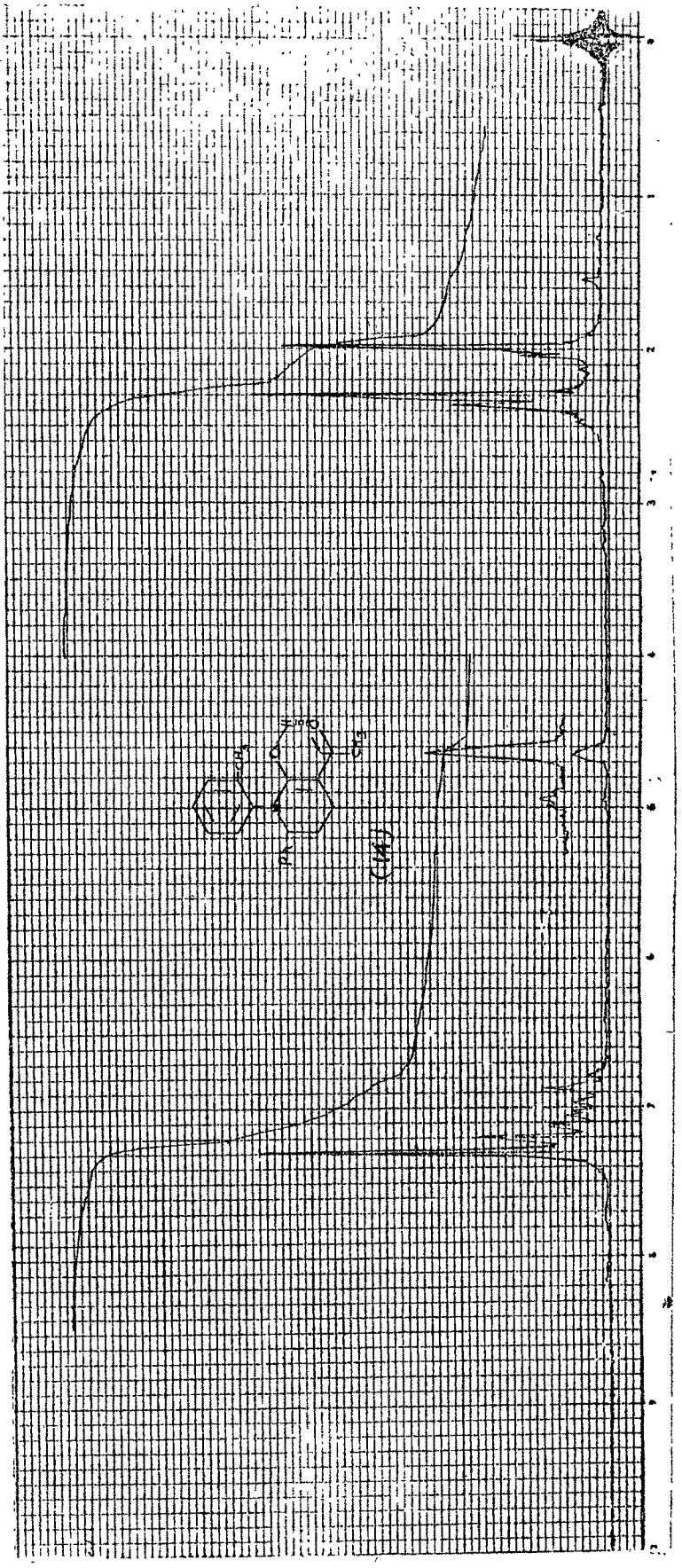
Synthesis of N-(O-methyl phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (14) :

α-sodium salt of acetoacet-o-toluidide was condensed with cinnamyl chloride in dry benzene to give α-cinnamyl acetoacet-o-toludide (13). The structure of (13) was confirmed on the basis of IR and NMR spectra. The IR spectrum(nujol) showed 3260 cm^{-1} for -NH group, at 1730 cm^{-1} for $-CO-CH_3$ and at 1650 cm^{-1} for C=O NH group. The NMR ($CDCl_3$) showed signals at δ ; 2.31, singlet, 3H, $-CO-CH_3$ group ; 2.30, singlet, 3H, $-CH_3$ group on aromatic ring ; 2.85, triplet, J = 8Hz, 2H, $-\underline{CH_2}-CH=CH-Ph$; 3.65, triplet, J = 8Hz, 1H, $-CO-\underset{\underset{CH_2}{|}}{\underline{CH}}-CO$; 6.2, quartate, J = 8Hz, 1H, $-CH_2-\underline{CH}=CH-Ph$; 6.5, doublet, J = 16Hz, 1H, $=\underline{CH}-Ph$; 7.1 to 7.8, multiplet, 9H, aromatic and 8.38, singlet, 1H, $-\underline{NH}-CO$. The (13) on cyclisation with 70 % sulphuric acid gave pyridine derivative (14). The structure of (14) was confirmed on the basis of its IR and NMR spectra. IR spectrum of (14) (nujol) was not showing -NH band at 3260 cm^{-1} which had been shown by (13). Also -NH-C=O band was absent at 1650 cm^{-1} which was shown by (13).

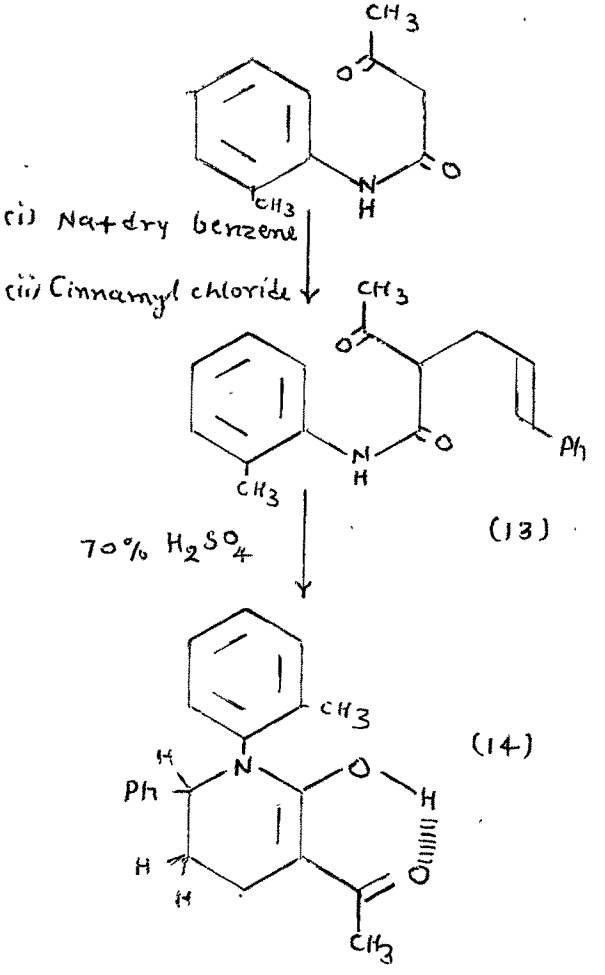

WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM-1
WHEN REORDERING SPECIFY CHART NO 105541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.
CH3
O
N
H
O
Ph
CH3
(13)




WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
WHEN REORDERING SPECIFY CHART NO. 10554
BECKMAN INSTRUMENTS INC. FULLERTON, CALIFORNIA, U.S.A.
(14)

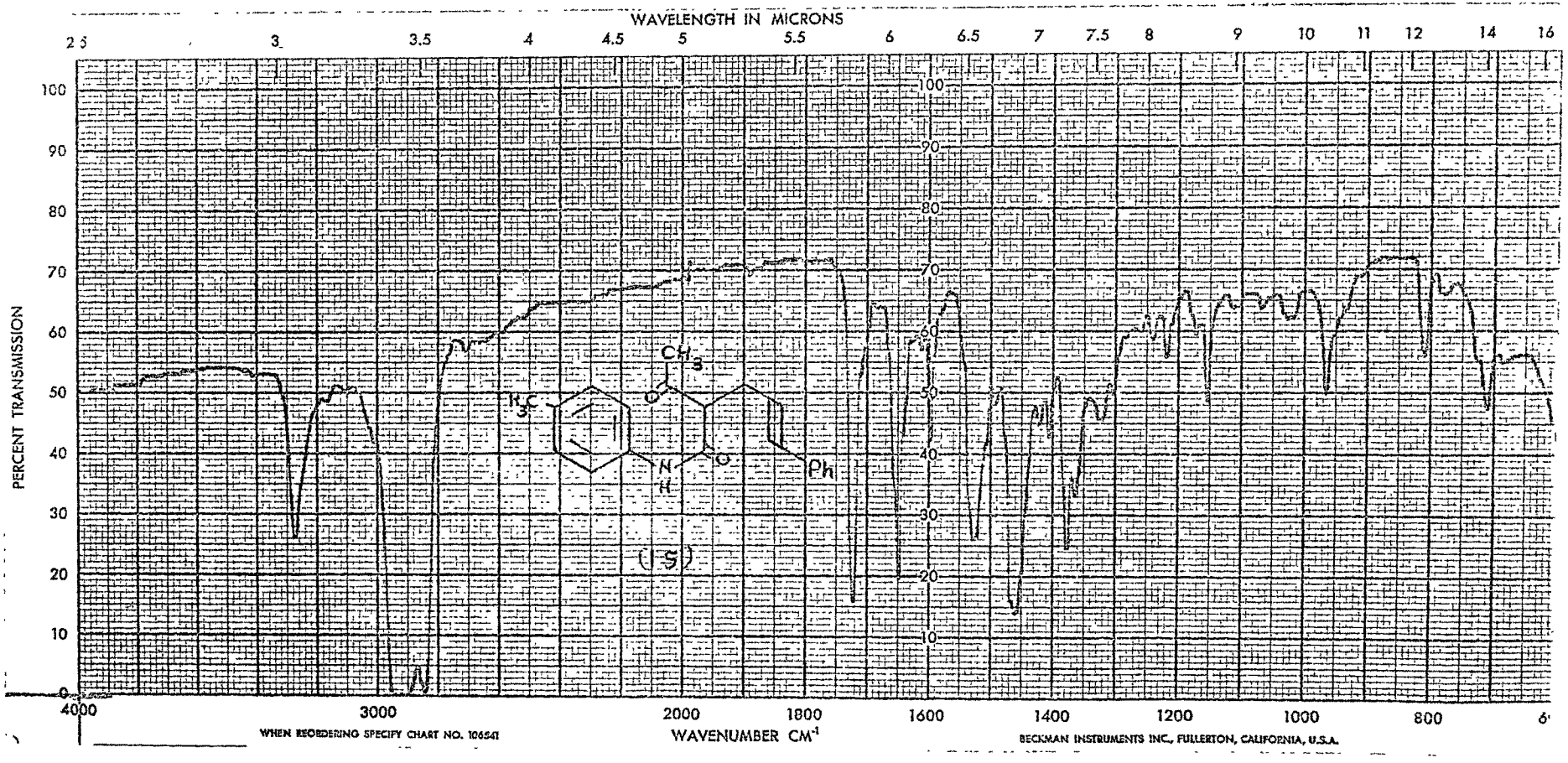


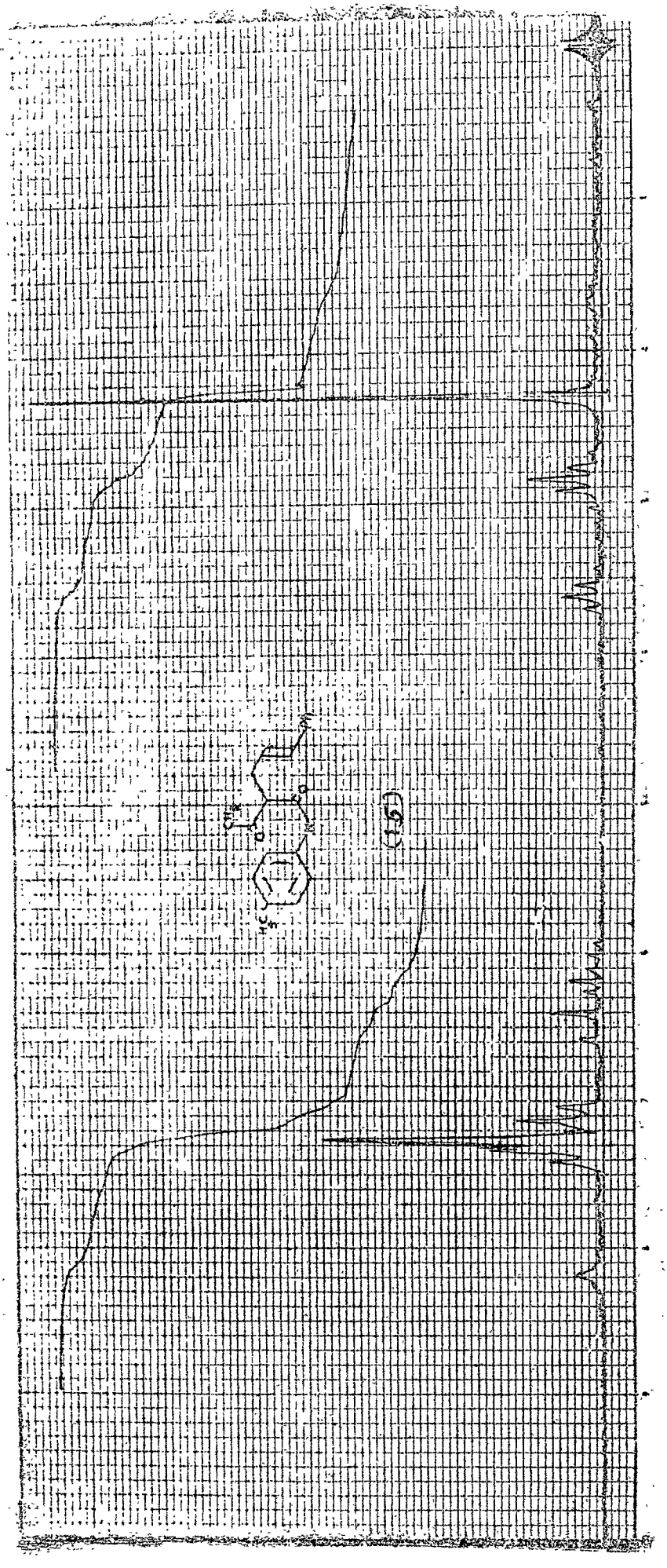
This comparision showed that on treatment with 70 % sulphuric acid, nitrogen atom of anilide is linked with carbon atom of cinnamyl group to give pyridine nucleus. The NMR spectrum ($CDCl_3$) showed signals at δ; 1.98, singlet, 3H, $-CO-CH_3$; 2.02, singlet, 1H, $-CH_2-\underset{H}{C}H-CH-Ph$; 2.3, singlet, 3H, $-CH_3$ group on aromatic ring ; 2.36, triplet, J = 8Hz, 3H, $-\underline{CH_2}-CH_2-\underline{CH}-Ph$; 4.65, singlet, (broad) 1H, $-\underset{H}{N}-CH-Ph$ and 6.8 to 7.3, multiplet, 9H, aromatic.

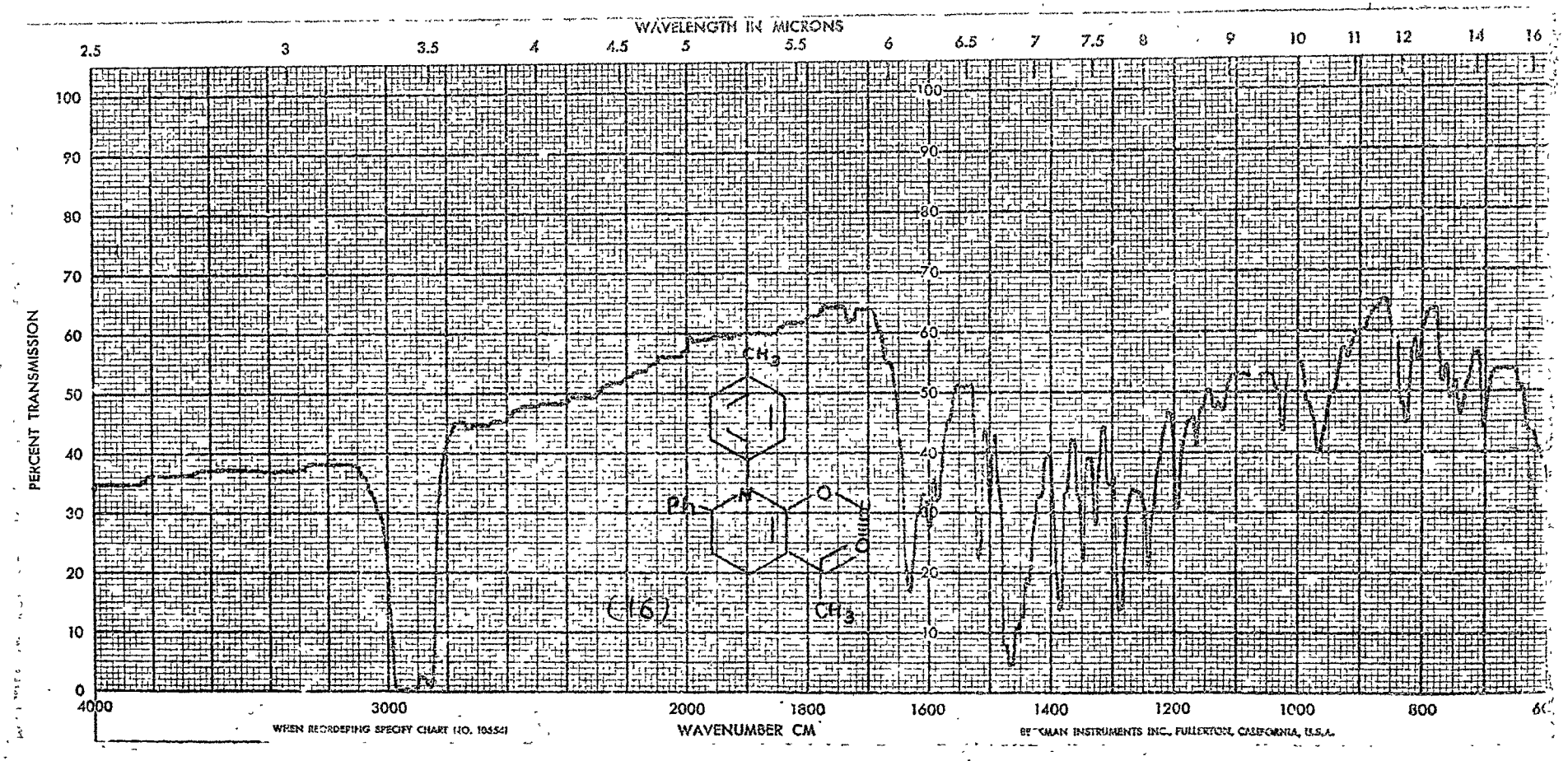


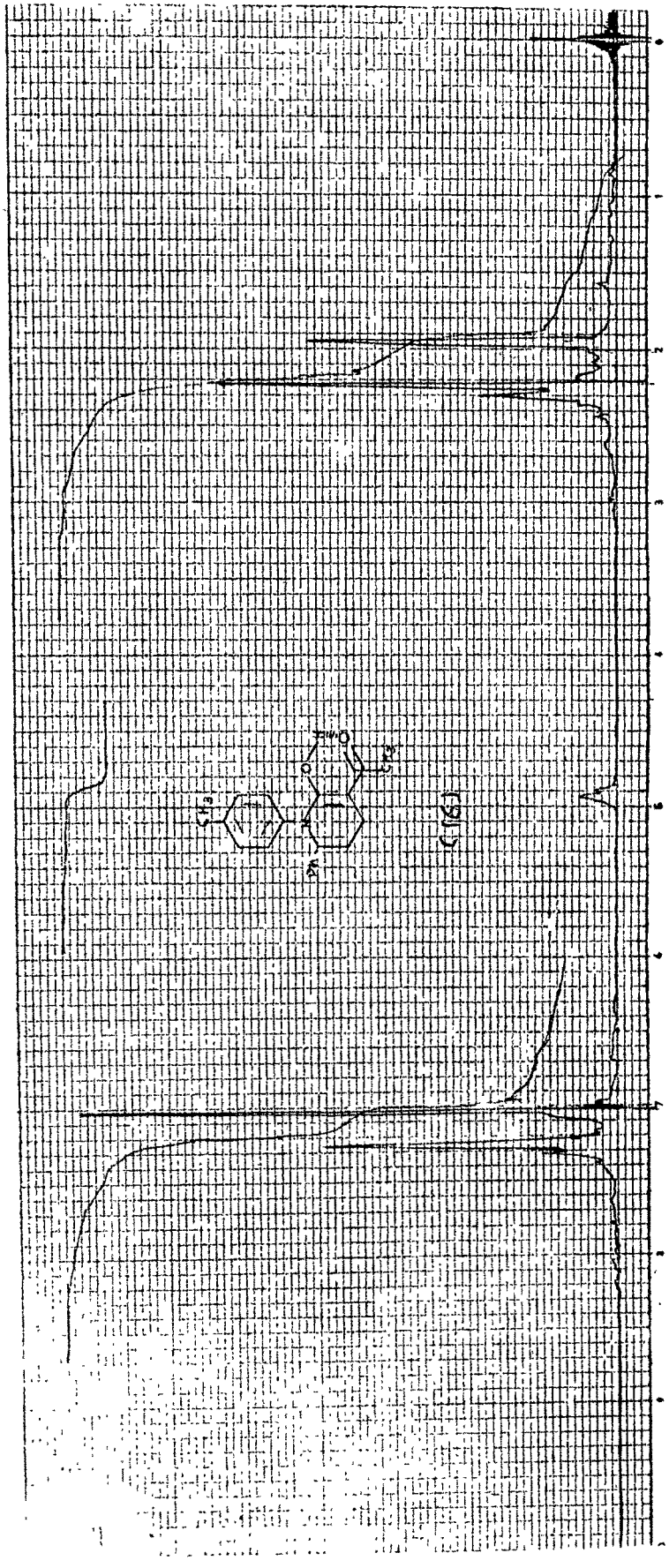
Synthesis of N-(p-methyl phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (16) :

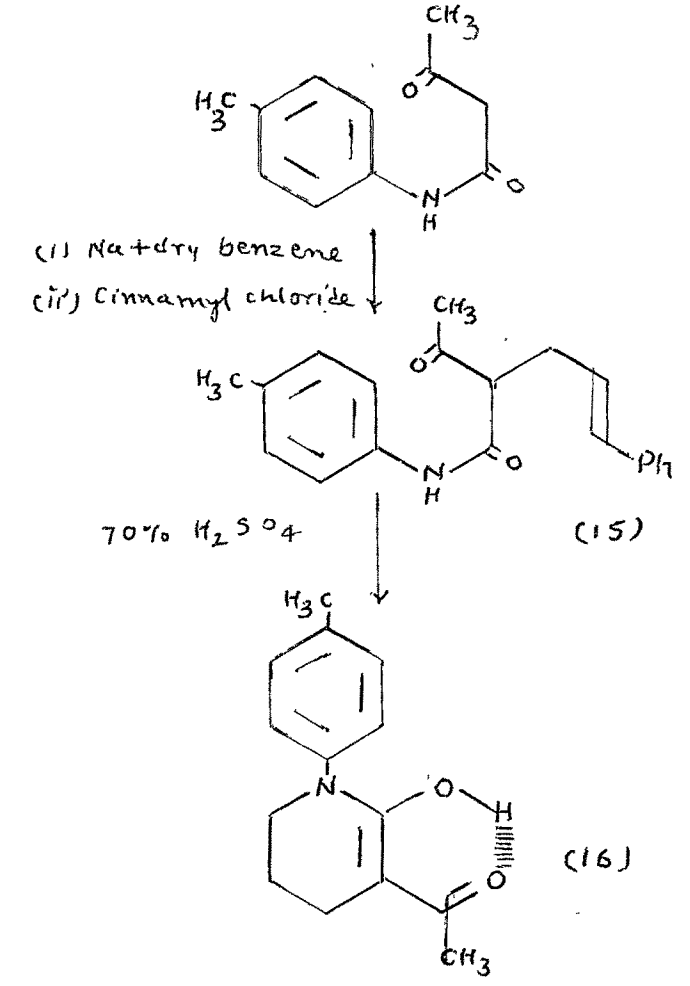
α-sodium salt of acetoacet-p-toluidide was condensed with cinnamyl chloride in dry benzene to give α-cinnamyl acetoacet-p-toludide (15). The structure of (15) was confirmed on the basis of IR and NMR spectra. IR spectram (nujol) showed bands at 3270 cm^{-1} for -NH, at 1725 cm^{-1} for $-CO-CH_3$ and at 1650 cm^{-1} for -CONH group. The NMR ($CDCl_3$) showed signals at δ; 2.3, singlet, 6H, two $-CH_3$ groups, $-COCH_3$ and $-ArCH_3$; 2.85, triplet, J = 8Hz, 2H, $-\underline{CH_2}-CH=CH-Ph$; 3.62, triplet, J = 8Hz, 1H, $-CO-\underset{\underset{CH_2}{|}}{\underline{CH}}-CO-$; 6.2, quartate, J = 8Hz, 1H, $-CH_2-\underline{CH}=CH-Ph$; 6.5, doublet, J = 16Hz, 1H, $=\underline{CH}-Ph$; 7.05 to 7.42, multiplet, 9H, aromatic and 8.2, singlet, 1H, -NH group. The (15) was cyclised as above gave N-(p-methyl phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (16). The structure of (16) was assigned by IR and NMR spectra. The IR spectrum of (16) (nujol) was not showing -NH band at 3270 cm^{-1} which had been shown by (15), also -NH-C=O band was absent at 1650 cm^{-1}, which was shown by (15). The NMR spectrum ($CDCl_3$) of (16) showed signals at δ; 1.95, singlet, 3H, $-CO-CH_3$; 2.02, singlet, 1H, $-CH_2-\underset{\underset{H}{|}}{\underline{CH}}-\underset{|}{\underline{CH}}-Ph$; 2.22, singlet, 3H, $-CH_3$ group on aromatic ring ; 2.3, singlet, broad , 3H, $-\underline{CH_2}-\underset{\underset{H}{|}}{\underline{CH}}-CH-Ph$; 4.92, singlet, 1H, $-\underset{|}{\underline{N}}-\underline{CH}-Ph$ and 7.05 to 7.4, multiplet, 9H, aromatic.


WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
CH3
H3C
O
N
H
O
Ph
(S)
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM-1
WHEN REORDERING SPECIFY CHART NO. 106541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.




WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM
WHEN REORDERING SPECIFY CHART NO. 10554
CH3
Ph
N
O
O
Amino
CH3
(16)

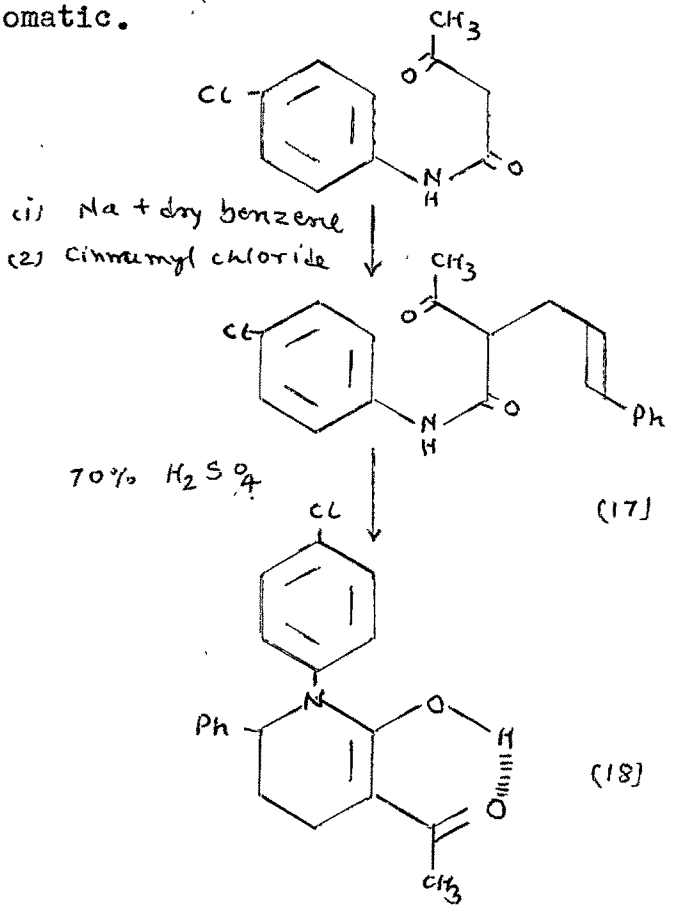


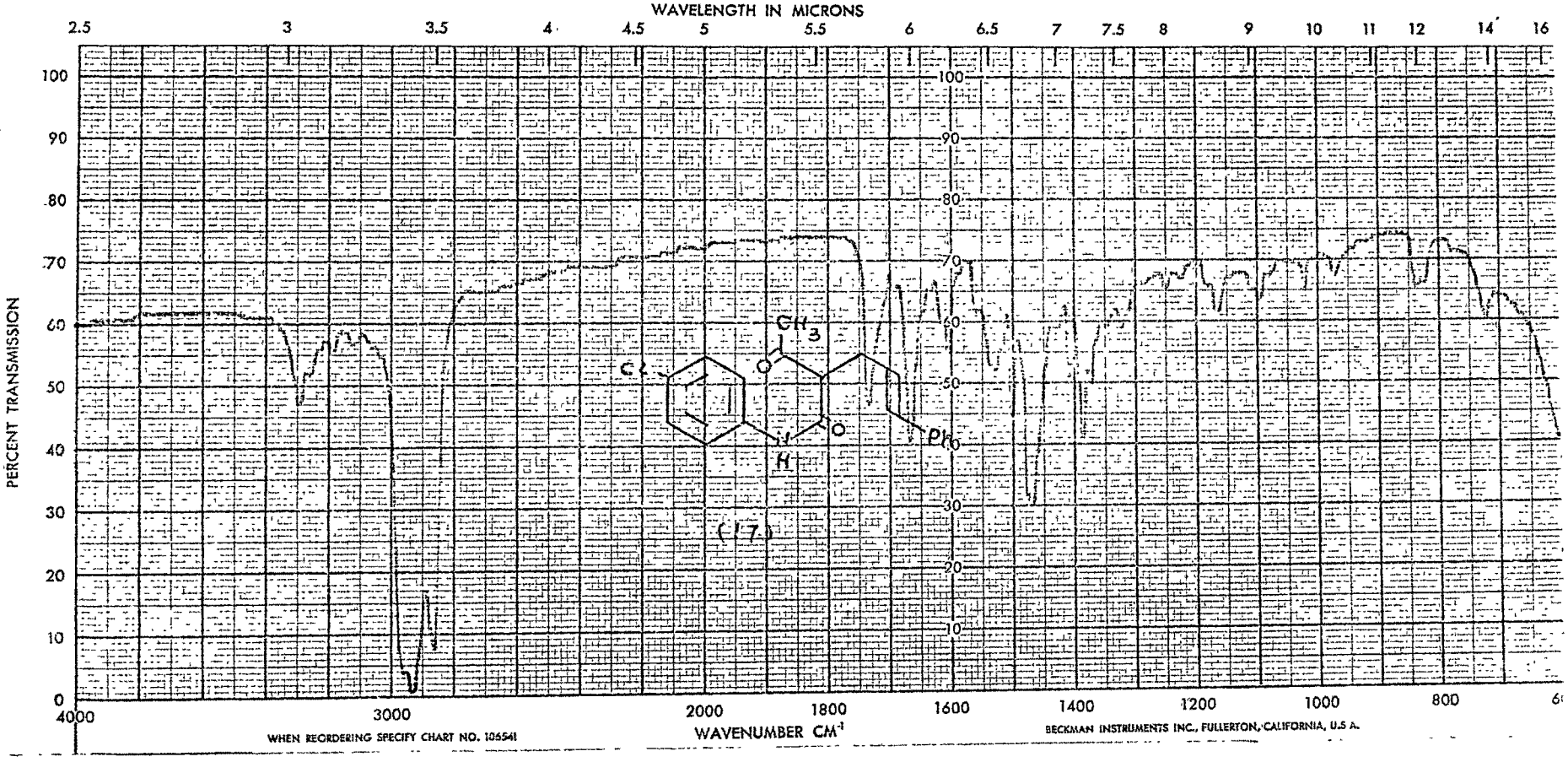


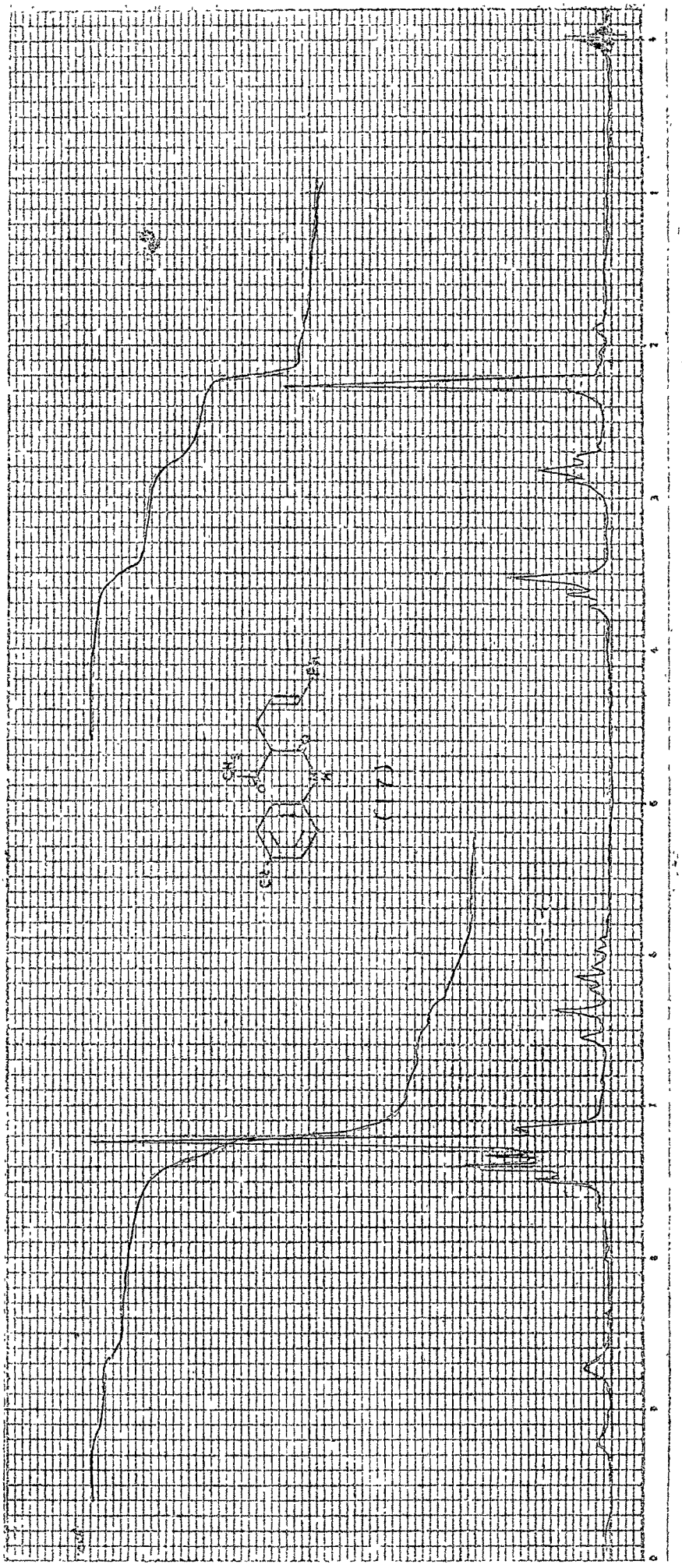
Synthesis of N-(p-chloro phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (18) :

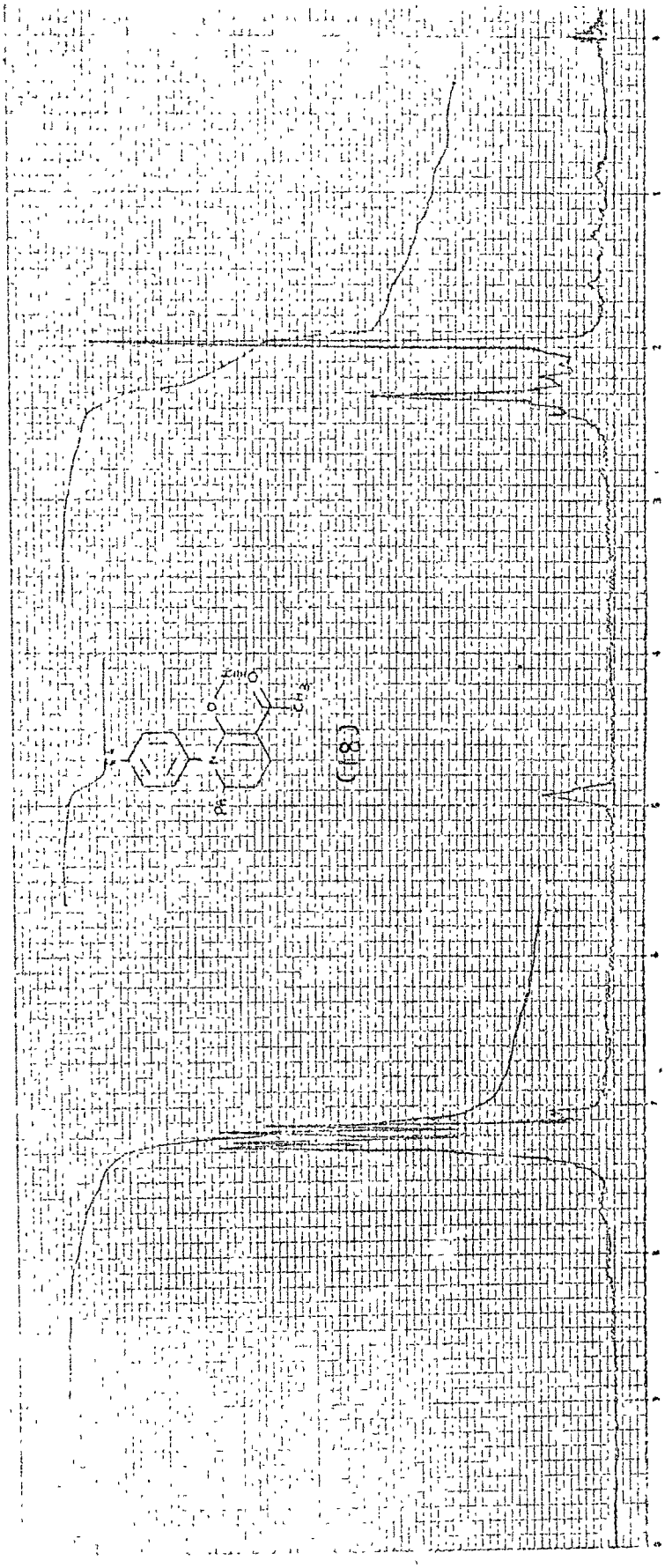
α-sodium salt of acetoacet-p-chloroanilide was condensed with cinnamyl chloride as above to give α-cinnamyl acetoacet-p-chloroanilide (17). The structure of (17) was assigned on the basis of IR and NMR spectra. The IR (nujol) of (17) showed bands at 3330 cm^{-1} for -NH,

1740 cm^{-1} for $-CO-CH_3$ and at 1670 cm^{-1} for -CONH group. The NMR ($CDCl_3$) of (17) showed signals at δ; 2.38, singlet, 3H, $-CO-CH_3$, ; 2.82, triplet, J = 8Hz, 2H, $-\underline{CH_2}-CH=CH-Ph$; 3.62, triplet, J = 8Hz, 1H, $-CO-\underline{CH}(CH_2)-CO$; 6.15, quartate, J = 8Hz, 1H, $CH_2-\underline{CH}=CH-Ph$; 6.45, doublet, J = 16Hz, 1H, $=\underline{CH}-Ph$; 7.15 to 7.5, multiplet, 9H, aromatic and 8.7, singlet, 1H, -NH. The (17) was cyclised as above to give N-(p-chloro phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (18). The NMR ($CDCl_3$) of (18) showed signals at δ, 1.98, singlet, 3H, $-CH_3$ group of $-COCH_3$; 2.1 to 2.4, multiplet, 4H, $-\underline{CH_2}-\underline{CH_2}-\underline{CH}-Ph$; 4.92, singlet (broad), 1H, $-\underline{CH}-Ph$; and 7.05 to 7.35, multiplet, 9H, aromatic.




WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
CH3
O
C2
O
Ph
H
(17)
WHEN REORDERING SPECIFY CHART NO. 105541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.

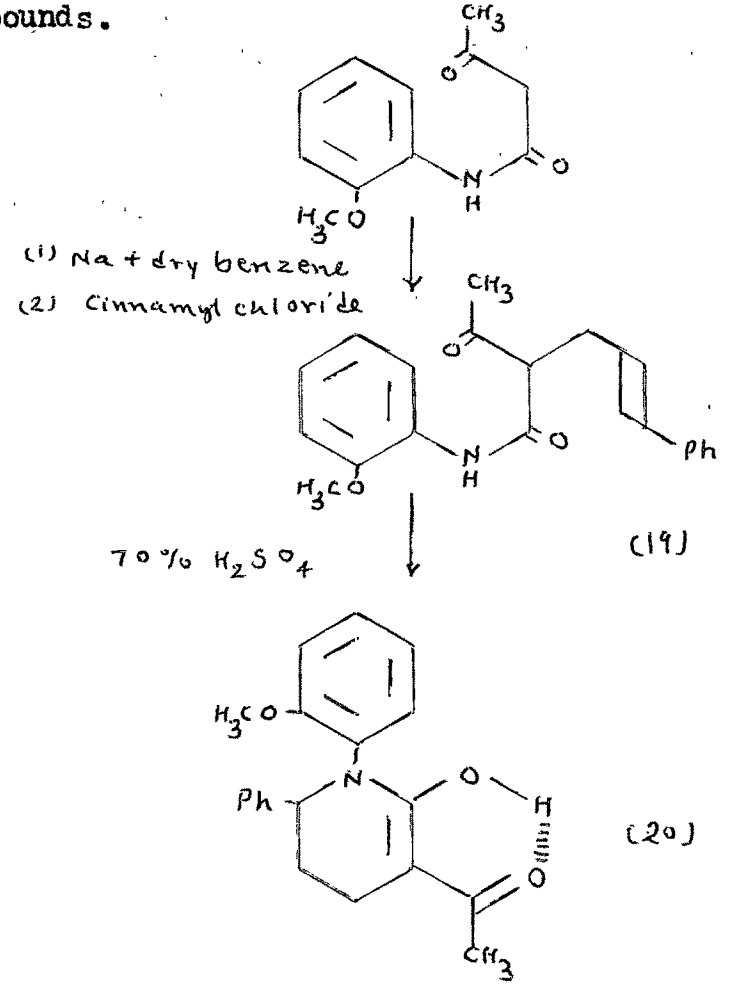

(17)



(18)

Synthesis of N-(o-methoxy phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (20) :

α-sodium salt of acetoacet-o-anisidide was condensed with cinnamyl chloride as above to give α-cinnamyl acetoacet-o-anisidide (19), which was cyclised by 70 % sulphuric acid as above to give N-(o-methoxy phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (20). The structure of (19) and (20) were confirmed on the basis of the analogy with the above compounds.



EXPERIMENTAL

Synthesis of 2,4-dimethyl-3-phenyl-2,3-dihydro furo (3,2-c) quinoline (37) and 3,4-dimethyl-2-phenyl-2,3-dihydro furo (3,2-c) quinoline (39) :

2-Methyl-4-cinnamyloxy quinoline (35) :

2-Methyl-4-hydroxyquinoline (1.6 g) was refluxed with cinnamyl chloride (1.5 g) in the presence of potassium carbonate (5.0 g) was potassium iodide (1.0 g) in ethylmethylketone as solvent, for 20 hr in water bath. The solvent was removed and reaction mixture was poured into water. It was then extracted with ether and organic layer was washed with water. The ether was removed and obtained product was crystallised from benzene-petroleum ether (1:1) mixture, Yield 1.2 gm, m.p. 123°. (Found : C, 83.05, H, 6.60, N, 5.37 ; $C_{19}H_{17}NO$; required, C, 82.90, H, 6.28, N, 5.09 %.)

Claisen rearrangement of 2-methyl-4-cinnamyloxy quinoline :

2-Methyl-4-cinnamyloxy quinoline (1.0 g) was heated without solvent at 200° in an oil-bath for 30 min. After cooling, 50 ml. of benzene was added and again heated on water bath to digest the pyrolysed product. Cooled to room temperature and filter the rearranged product as

benzene insoluble fraction ; washed with benzene, crystallised from ethanol, yield 0.5 gm, m.p. 293° (m.p. is of mixture of both isomers). (Found : C, 83.34, H, 6.53, N, 5.57 ; $C_{19}H_{17}NO$; required : C, 82.90, H, 6.28 N, 5.09 %).

2,4-Dimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (37) and 2-phenyl-3,4-dimethyl-2,3-dihydro furo (3,2-c) quinoline (39) :

The mixture of rearranged products (1.0 g) was dissolved in PPA (10 ml) and was heated at 140° in an oil-bath for 4-5 hrs. The reaction mixture was decomposed by pouring over crushed ice with constant stirring ; neutralised with 10 % Na_2CO_3 solution and was extracted with ether. The solvent was removed and crude product was chromatographed over silica gel using benzene-petroleum ether (1:2) mixture as elutting solvent. The chromatographed product was further separated by preparative thin layer chromatography (silica gel), using benzene-petroleum ether (1:2:3) mixture as eluent. Observing though U.V. lamp the higher Rf-valued fraction was showing very much bright bluish violet fluorescent while the lower Rf-valued fraction was showing dull-greenish yellow fluorescent. On the basis of NMR spectra, the structure of higher Rf value fraction was assigned as 2,4-dimethyl-3-phenyl-2,3-

dihydro furo (3,2-c) quinoline (37) and 2-phenyl-3,4-dimethyl-2,3-dihydro furo (3,2-c) quinoline (39), structure was assigned to lower Rf-valued fraction. The m.p. of (37) was 82° (Found : C, 82.90 H, 5.95 N, 5.35 : $C_{19}H_{17}NO$: required : C, 82.90 H, 6.28 N, 5.09 %). The m.p. of (39) was 150° (Found : C, 83.10 H, 6.55 N, 5.12 : $C_{19}H_{17}NO$: required : C, 82.90, H, 6.28 N, 5.09 %).

Synthesis of 2,4,6-trimethyl-3-phenyl-2,3-dihydro furo (3,2-c) quinoline (45) and 2-phenyl-3,4,6-trimethyl-2,3-dihydro furo (3,2-c) quinoline (46) :

2,8-Dimethyl-4-cinnamyloxy quinoline (42) :

2,8-Dimethyl-4-hydroxyquinoline (2.0 g) was refluxed with cinnamyl chloride (1.5 g) in the present of potassium carbonate (5.0 g) and potassium iodide (1.0 g) in ethyl-methylketone as solvent, for 20 hr. in water bath. The solvent removed and reaction mixture was poured into water. It was extracted with ether and organic layer was washed with water. Then ether was removed and obtained product was crystallised from benzene-petroleum ether (1:1) mixture, Yield 1.0 gm, m.p. 142° (Found C, 82.83 H, 6.80 N, 5.06 ; $C_{20}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %).

Claisen rearrangement of 2,8-dimethyl-4-cinnamyloxy quinoline :

2,8-Dimethyl-4-cinnamyloxy quinoline (1.0 g) was heated without solvent at 200° in an oil-bath for 30 min. After cooling 50 ml. of benzene was added and again heated in water bath to digest the pyrolysed product. Cooled to room temperature and filter the rearranged product as benzene insoluble fraction ; washed with benzene, crystallised from ethanol, yield 0.7 gm, m.p. 273° (m.p. is of mixture of both isomers). (Found ; C, 82.77, H, 6.70 N, 4.94 ; $C_{20}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %).

2,4,6-Trimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (45) and 2-phenyl-3,4,6-trimethyl-2,3-dihydro furo (3,2-c) quinoline (46) :

The mixture of rearranged products (1.0 g) was dissolved in PPA (10 ml) and was heated at 140° in an oil-bath for 5 hrs. It was decomposed over crushed ice with stirring, neutralised with 10 % Na_2CO_3 solution and extracted with ether. The solvent was removed and crude product was chromatographed over silica gel using benzene-petroleum ether (1:2) mixture as elutting solvent. The chromatographed product was further separated by preparative thin layer chromatography (silica gel), using

benzene-petroleum ether (1:2) mixture as eluent. Observing through U.V. lamp, the higher Rf-valued fraction was showing very much bright bluish violet fluorescent while the lower Rf-valued fraction was showing dull-greenish yellow fluorescent. The higher Rf-valued fraction was assigned 2,4,6-trimethyl-3-phenyl-2,3-dihydro-furo (3,2-c)quinoline (45), m.p. 118°. (Found ;, C, 82.83 H, 6.62 N, 5.20 ; $C_{22}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %). and lower Rf-valued fraction was 2-phenyl-3,4,6-trimethyl-2,3-dihydro furo (3,2-c)quinoline (46), m.p. 98° (Found ; C, 83.38 H, 6.74 N, 5.22 ; $C_{20}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %).

2,4,8-Trimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (50) and 2-phenyl-3,4,8-trimethyl-2,3-dihydro furo (3,2-c) quinoline (51) :

2,6-Dimethyl-4-cinnamyloxy quinoline (47) :

2,6-Dimethyl-4-hydroxy quinoline (2.0 g), cinnamyl chloride (1.5 g) were dissolved in ethylmethyl-ketone (400 ml) and potassium carbonate (5.0 g) - potassium iodide (1.0 g) were added and reaction mixture refluxed in water bath for 20 hrs. The solvent was removed and decomposed it into water. It was extracted with ether and organic layer was washed with water. After removal of solvent ether, the product crystallised from benzene-petroleum ether mixture (1:1) yield 1.2 gm, m.p. 147° (Found ; C, 83.50

H, 6.77 N, 4.69 ; $C_{20}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %).

Claisen rearrangement of 2,6-dimethyl-4-cinnamyloxy -quinoline :

2,6-Dimethyl-4-cinnamyloxy quinoline (1.0 g) was heated without solvent at 200° in an oil-bath for 30 min. After cooling 50 ml. of benzene was added and again heated in water bath to digest the pyrolysed product. Cooled to room temperature and filtered the rearranged product as benzene insoluble fraction ; washed with benzene, crystallised from ethanol, yield 0.5 gm, m.p. 336° (Found ; C, 83.20 H, 6.56 N, 5.26 ; $C_{20}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %). M.p. and analytical results are of mixture of both isomers.

2,4,8-Trimethyl-3-phenyl-2,3-dihydro furo (3,2-c) quinoline (50) and 2-phenyl-3,4,8-trimethyl-2,3-dihydro furo (3,2-c) quinoline (51) :

The mixture of rearranged products (1.0 g) was dissolved in PPA (10 ml) and was heated at 140° in an oil-bath for 5 hrs. It was decomposed over crushed ice with stirring, neutralised with 10 % Na_2CO_3 solution and extracted with ether. The solvent was removed and crude product was chromatographed over silica gel using benzene-petroleum ether (1:2) mixture as eluting solvent. The

chromatographed product was further separated by preparative thin layer chromatography (silica gel), using benzene-petroleum ether (1:2) mixture as eluent. Observing through U.V. lamp, the higher Rf-valued fraction was showing very much bright bluish violet fluorescent while lower Rf-valued fraction was showing dull-greenish yellow fluorescent. The higher Rf-valued fraction was 2,4,8-trimethyl-3-phenyl-2,3-dihydro furo (3,2-c)quinoline (50), m.p. 122°. (Found ; C, 83.07 H, 6.73 N, 4.82 ; $C_{20}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %) and lower Rf-valued fraction was 2-phenyl-3,4,8-trimethyl-2,3-dihydro furo (3,2-c)quinoline (51), m.p. 145° (Found ; C, 82.94 H, 6.29 N, 4.75 ; $C_{20}H_{19}NO$; required ; C, 83.04 H, 6.58 N, 4.85 %).

2,4-Dimethyl-3-phenyl-8-chloro-2,3-dihydro furo (3,2-c) quinoline (55) and 2-phenyl-3,4-dimethyl-8-chloro-2,3-dihydro furo (3,2-c)quinoline (56) :

2-Methyl-4-cinnamyloxy-6-chloro quinoline (52) :

2-Methyl-4-hydroxy-6-chloro quinoline (2.2 g), cinnamyl chloride (1.5 g), potassium carbonate (5.0 g) and potassium iodide (1.0 g) were added to ethylmethylketone (500 ml) and reaction mixture was refluxed in waterbath for 20 hrs. The solvent was removed and reaction mixture was decomposed by pouring it into water. It was extracted

with ether and organic layer washed with water. After removal of solvent, it was crystallised from benzene, yield 1.0 gm, m.p. 127° (Found ; C, 73.60 H, 5.53 N, 4.43 Cl, 11.5 ; $C_{19}H_{16}NOCl$; required ; C, 73.67 H, 5.17 N, 4.52 Cl, 11.47 %).

Claisen rearrangement of 2-methyl-4-cinnamyloxy-6-chloro quinoline :

The above product (1.0 g) was heated without solvent at 200° in an oil-bath for 30 min. After cooling 50 ml. of benzene was added and again heated in water bath to digest the pyrolysed product, cooled to room temperature and filtered the rearranged product as benzene insoluble fraction ; washed with benzene, crystallised from ethanol, yield 0.7 gm, m.p. 327°. (Found ; C, 73.86 H, 5.64 N, 4.39 Cl, 11.62 ; $C_{19}H_{16}NOCl$; required ; C, 73.67 H, 5.17 N, 4.52 Cl, 11.47 %).

2,4-Dimethyl-3-phenyl-8-chloro-2,3-dihydro furo (3,2-c) quinoline (55) and 2-phenyl-3,4-dimethyl-8-chloro-2,3-dihydro furo (3,2-c)quinoline (56) :

The mixture of rearranged products (1.0 g) was dissolved in PPA (10 ml) and was heated at 140° in an oil-bath for 5 hrs. It was decomposed over crushed ice with stirring, neutralised with 10 % Na_2CO_3 solution and extracted with ether. The solvent was removed and crude

product was chromatographed over silica gel using benzene-petroleum ether (1:2) mixture as elutting solvent. The chromatographed product was further separated by preparative thin layer chromatography (silica gel), using benzene-petroleum ether (1:2) mixture as eluent. Observing through U.V. lamp, the higher Rf-valued fraction was showing very much bright bluish violet fluorescent while lower Rf-valued fraction was showing dull-greenish yellow fluorescent. The higher Rf-valued fraction was 2,4-dimethyl-3-phenyl-8-chloro-2,3-dihydro-furo (3,2-c)quinoline (55) M.p. 111° (Found ; C, 73.89 H, 5.00 N, 4.59 Cl, 11.40 ; $C_{19}H_{16}NOCl$; required ; C, 73.67 H, 5.17 N, 4.52 Cl, 11.47 %) and lower Rf-valued fraction was 2-phenyl-3,4-dimethyl-8-chloro-2,3-dihydro furo (3,2-c)quinoline (56) M.p. 131°. (Found ; C, 74.04 H, 5.66 N, 4.26 Cl, 11.16 ; $C_{19}H_{16}NOCl$; required ; C, 73.67 H, 5.17 N, 4.52 Cl, 11.47 %).

N-(p-methylphenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (16) :

α-Cinnamyl-acetoacet-p-toludide (15) :

Acetoacet-p-toludide (1.9 g) was refluxed with pulverised sodium (0.23 g) in sodium dried benzene for 6 hrs. in water bath. To this reaction mixture cinnamyl chloride (1.5 g) was added and it was further refluxed for

20 hrs. The reaction mixture was decomposed by pouring into water. The organic layer was separated and washed with water. The solvent benzene was removed and obtained product was crystallised from benzene, yield 1.8 gm, m.p. 128°. (Found ; C, 78.65 H, 7.26 N, 4.50 ; $C_{20}H_{21}NO_2$; required ; C, 78.18 H, 6.84 N,456 %).

N-(p-methyl phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (16) :

α-Cinnamyl-acetoacet-p-toluidide (1.0 g) was dissolved in 70 % sulphuric acid and was heated in water bath for 45 minutes. The reaction mixture was cooled and then decomposed by pouring it in ice-water with stirring. The separated product was filtered, washed with water and obtained crude product was chromatographed over silica gel, using benzene-petroleum ether (1:2) mixture as eluent. It was crystallised from petroleum ether, yield 0.5 gm, m.p. 135°. (Found ; C, 78.07 H, 6.7 N, 5.2 ; $C_{20}H_{21}NO_2$; required ; C, 78.18 H, 6.84 N, 4.56 %).

N-(p-chloro phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (18) :

α-Cinnamyl-acetoacet-p-chloroanilide (17) :

Acetoacet-p-chloroanilide (2.0 g) was refluxed with pulverised sodium (0.23 g) in sodium dried benzene for 6 hrs. in water bath. To this reaction mixture cinnamyl chloride (1.5 g) was added and it was further refluxed for 20 hrs. The reaction mixture was decomposed by pouring into water. The organic layer was separated and washed with water. The solvent benzene was removed and obtained product was crystallised from benzene, yield 0.8 gmm m.p. 128°. (Found ; C, 69.31 H, 5.23 N, 4.50 Cl, 11.01 ; $C_{19}H_{18}NO_2Cl$; C, required ; C, 69.62 H, 5.49 N, 4.27 Cl, 10.84 %).

N-(p-chloro phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (18) :

α-Cinnamyl-acetoacet-p-chloroanilide (1.0 g) was dissolved in 70 % sulphuric acid and was heated in water bath for 45 minutes. The reaction mixture was cooled and then decomposed by pouring it in ice-water with stirring. The separated product was filtered, washed with water and obtained crude product was chromatographed over silica gel, using benzene-petroleum ether (1:2) mixture as eluent. It was crystallised from petroleum ether, yield 0.6 gm, m.p.137°. (Found ; C, 69.48 H, 5.50 N, 4.33 Cl, 10.59 ; $C_{19}H_{18}NO_2Cl$; required ; C, 69.62 H, 5.49 N, 4.27 Cl, 10.84 %).

Synthesis of N-(o-methyl phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (14) :

α-Cinnamyl-acetoacet-o-toluidide (13) :

Acetoacet-o-toluidide (1.0 g) was refluxed with pulverised sodium (0.23 g) in sodium dried benzene for 6 hrs. in water bath. To this reaction mixture cinnamyl chloride (1.5 g) was added and it was further refluxed for 20 hrs. The reaction mixture was decomposed by pouring into water. The organic benzene layer was separated and washed with water. The solvent benzene was removed and obtained product was crystallised from benzene : yield 2.0 gm, m.p. 146°. (Found : C, 78.65 H, 6.96 N, 4.33 : $C_{20}H_{21}NO_2$: required : C, 78.18 H, 6.84 N, 4.56 %).

N-(o-methyl phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (14) :

α-Cinnamyl-acetoacet-o-toluidide (1.0 g) was dissolved in 70 % sulphuric acid and was heated in water bath for 45 min. The reaction mixture was cooled and then decomposed by pouring it in ice-water with stirring. The separated product was filtered, washed with water and obtained crude product was chromatographed over silica gel, using benzene-petroleum ether (1:2) mixture as eluent. It was crystallised from petroleum ether, yield 0.3 gm., m.p., 150° (Found : C, 78.03 H, 6.80 N, 5.15 : $C_{20}H_{21}NO_2$: required : C, 78.18 H, 6.84 N, 5.56 %).

N-(o-methoxy phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (20) :

α-Cinnamyl-acetoacet-o-anisidide (19) :

Acetoacet-o-anisidide (1.8 g), pulverised sodium (0.23 g) were added to sodium dried benzene and refluxed for 7 hrs. in water bath. To the above reaction mixtures cinnamyl chloride (1.5 g) was added and it was further refluxed for more 20 hrs. The reaction mixture decomposed by pouring it into water. The organic layer was separated and washed with water. After removal of solvent the obtained product was crystallised from petroleum ether, yield 1.6 gm, m.p. 41°. (Found ; C, 74.02 H, 6.26 N, 4.76 ; $C_{20}H_{21}NO_3$; required ; C, 74.32 H, 6.50 N, 4.33 %).

N-(o-methoxy phenyl)-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro pyridine (20) :

The above product (1.0g) dissolved in 70 % sulphuric acid (5 ml) and heated in water bath for 1 hr. The reaction mixture was cooled and decomposed over crushed ice. The separated product was filtered, washed with water and dried. It was chromatographed over silica gel, using benzene-petroleum ether (1:1) mixture as eluent. It was crystallised from petroleum ether, yield 0.5 gm, m.p. 124°. (Found ; C, 74.00 H, 6.75 N, 4.50 ; $C_{20}H_{21}NO_3$; required ; C, 74.32 H, 6.50 N, 4.33 %).

N-Phenyl-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro-pyridine (22) :

α-Cinnamyl acetoacetanilide (21) :

Acetoacetanilide (1.0 g), pulverised sodium (0.23 g) and dried benzene (100 ml) was refluxed in water bath for 6 hrs. To the above reaction mixture cinnamyl chloride (1.5 g) was added and it was further refluxed for more 20 hrs. The reaction mixture was decomposed by pouring into water. The organic layer was separated, washed with water and after removal of solvent, the product was crystallised from benzene-petroleum ether mixture (1:1) yield 1.5 gm, m.p. 127°. (Found ; C, 78.24 H, 6.50 N, 4.80 ; $C_{19}H_{19}NO_2$; required ; C, 77.80 H, 6.48 N, 4.78%).

N-Phenyl-2-phenyl-5-acetyl-6-hydroxy-1,2,3,4-tetrahydro-pyridine (22) :

The above product (1.0 g) dissolved in 70 % sulphuric aicid (5 ml) and heated in water bath for 1 hr. The reaction mixture was cooled and decomposed over crushed ice . The separated product was found to be oily. It was chromatographed over silica gel, using petroleum ether as eluent. The obtained product was waxy solid even after crystallisation from petroleum ether, yield 0.7 gm, m.p.

115° and b.p. 280°. (Found ; C, 78.00 H, 6.50 N, 5.00 $C_{19}H_{19}NO_2$; required ; C, 77.80 H, 6.48 N, 4.78 %).

References :

1. Willium N. White and Wilmer K. Fife ; J.Am.Chem.Soc., 83, 3846-53, 1961.

2. A.C.Jain, R.K.Gupta ; Chem.Lett., 11, 1353-6, 1974. C.A., 82, 72819 q, 1975.

3. A.C.Jain, R.K.Gupta ; Tetrahedron, 31(6), 511-16, 1975. C.A., 83, 43140 b, 1975.

4. A.C.Jain, D.K.Tuli and A.Kumar ; Current Sci., 46-(24), 839, 1977. C.A., 88, 169897 a, 1978.

5. A.C.Jain, R.C.Gupta, A.Kumar ; Proc.Indian.Acad.Sci., SectionA, 87-A(6), 189-98, 1978. C.A., 89, 215175 j, 1978.

6. V.K.Ahluwalia, Devendrakumar, Y.K.Gupta ; Indian J.Chem., 16-B, 579-583, 1978.

7. A.C.Jain and A.Kumar ; Current Sci., 47-(16), 581-2, 1978. C.A., 89, 197371 p, 1978.

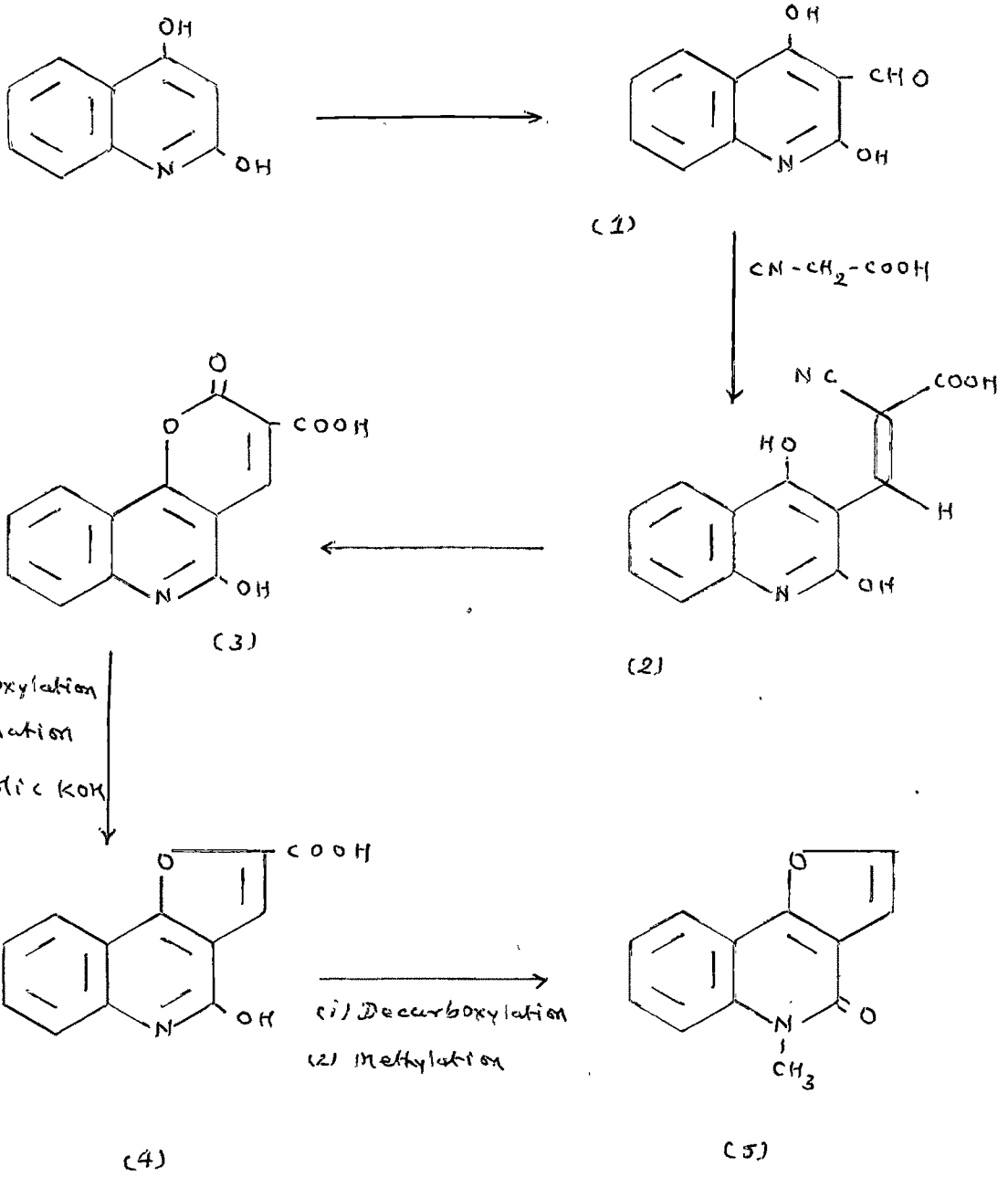
8. A.C.Jain, D.K.Tuli, A.Kumar ; Proc.Indian Acad.Sci., Section A, 87A(10), 389-94, 1978. C.A., 90, 137625 k, 1979.

SECTION-III

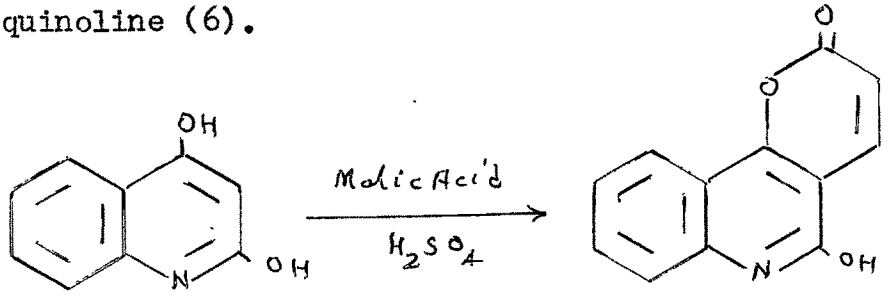
Synthesis of pyrano (3,2-c) quinoline from 2-methyl-3-formyl-4-hydroxyquinoline by Perkin and Knoevenagel' reaction :

The present work was undertaken with a view to synthesise pyranoquinoline derivatives of type 2-oxo-2 H-pyrano (3,2-c) quinoline derivatives as large number of naturally occuring quinoline alkaloids possess the same type of skeleton structure.

In 1932, Asahina and Inubuse[1] attempted to synthesise dictamine but obtained the isomeric pseudo-dictammine. They prepared 2,4-dihydroxy-3-formyl quinoline (1) by Reimer - Tiemann reaction on 2,4-dihydroxy quinoline. The 3-formyl derivative was further treated with cyanoacetic acid in the presence of alkali to give nor-dictammal- cyanoacetic acid (2), which on treatment with conc. sulphuric acid gave 5-hydroxy-2-oxo-2 H-pyrano (3,2-c) quinoline-3-carboxylic acid (3). This carboxylic acid when subjected to decarboxylation, bromination and hydrolysis by alcoholic alkali gave 4-hydroxy furo (3,2-c) quinoline-2-carboxylic acid (4) which on decarboxylation subsequent methylation gave pseudo-dictamine (5).

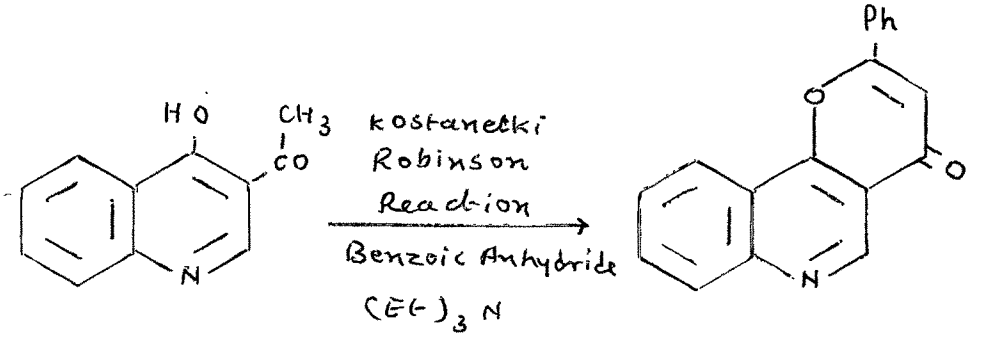

OH
N
OH
OH
CHO
N
OH
(1)
CN-CH2-COOH
NC
COOH
HO
H
N
OH
(2)
O
O
COOH
N
OH
(3)
(i) Decarboxylation
(2) Bromination
(3) Alcoholic KOH
COOH
O
N
OH
(4)
(i) Decarboxylation
(2) Methylation
O
N
O
CH3
(5)

Brown et al[2] carried out the Pechman reaction on 2,4-dihydroxyquinoline with malic acid in the presence of sulphuric acid and obtained 5-hydroxy-2-oxo-2 H-pyrano (3,2-c)quinoline (6).

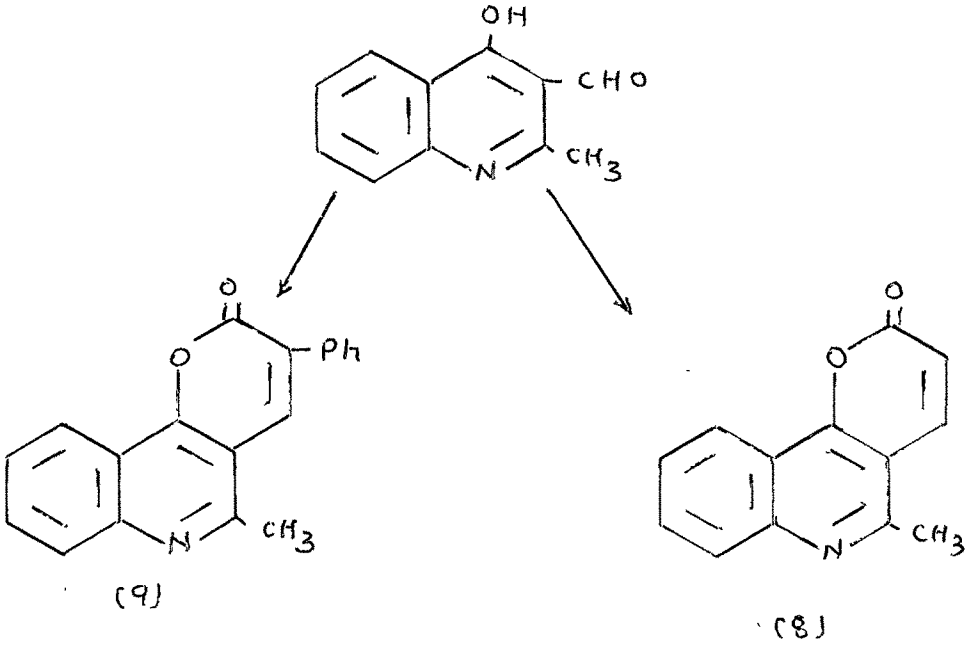


(6)

Elliott and Tittenson[3] synthesised 2-phenyl-4-oxo-4 H-pyrano (3,2-c)quinoline (7) from 3-acetyl-4-hydroxyquinoline by application of Kostanecki-Robinson reaction with benzoic anhydride and triethylamine. Trivedi and Chudgar[4] also synthesised 5-methyl-2-oxo-2 H-pyrano (3,2-c)quinoline (8) and 5-methyl-3-phenyl-2-oxo-2 H-pyrano (3,2-c)quinoline (9) from 2-methyl-3-formyl-4-hydroxyquinoline by Perkin reaction using acetic anhydride and triethylamine and by using phenylacetic acid, acetic anhydride, triethylamine, respectively.



(7)

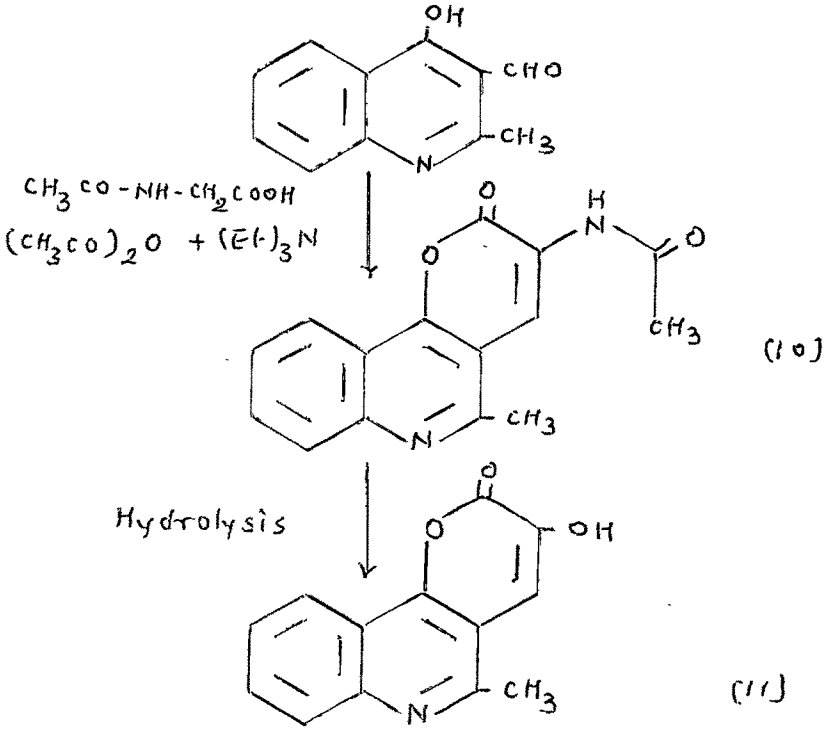


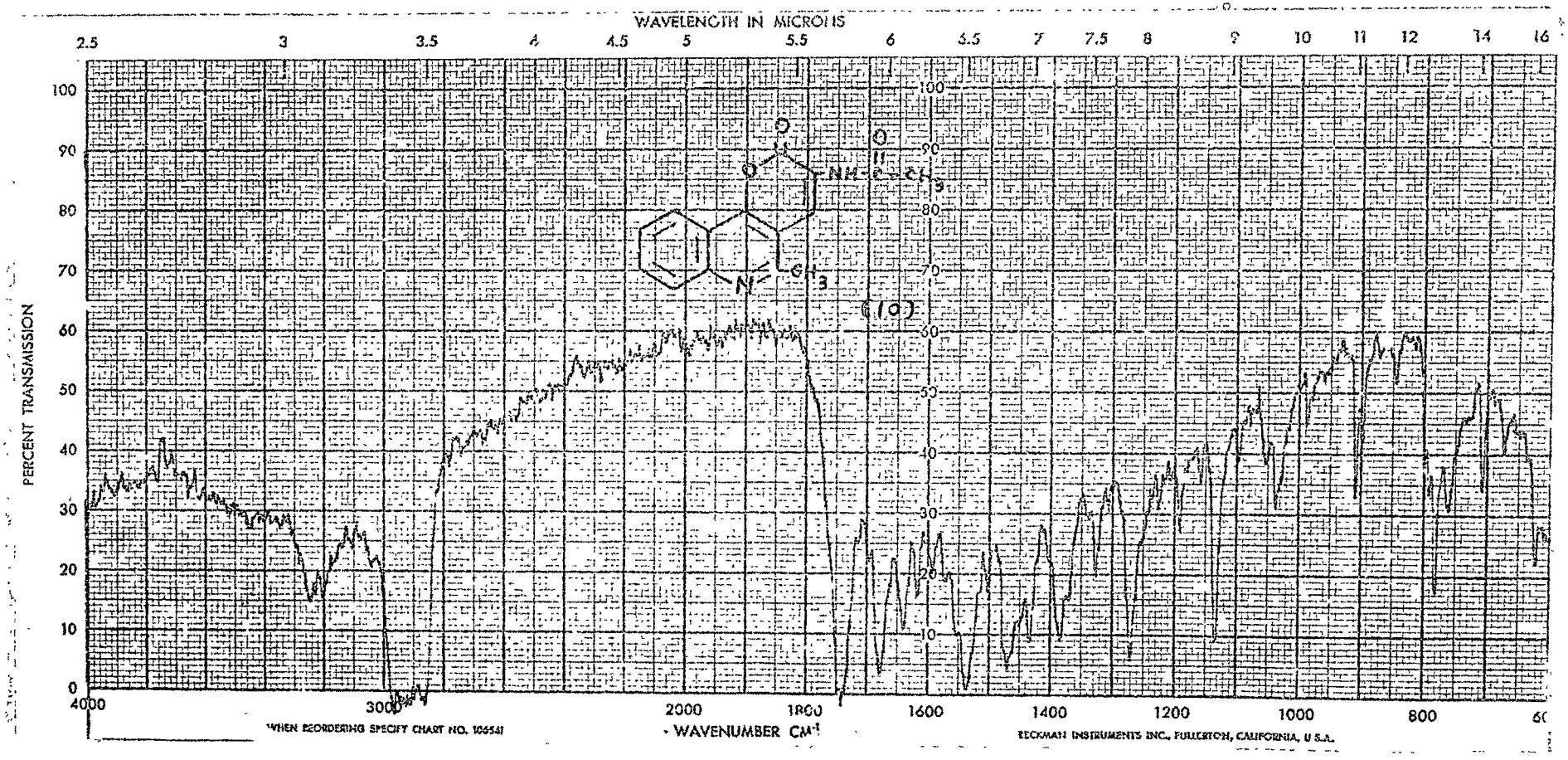
In the present work, the above work has been extended to get 2-oxo-2 H-pyrano (3,2-c)quinoline derivatives by Perkin reaction. 3-Hydroxy-5-methyl-2-oxo-2 H-pyrano (3,2-c)quinoline derivative was synthesised by the condensation of 2-methyl-3-formyl-4-hydroxyquinoline with acetyl glycine, acetic anhydride and triethylamine to give 3-acetylamino-5-methyl-2-oxo-2 H-pyrano (3,2-c) quinoline which on acid hydrolysis with 50% sulphuric acid gave 3-hydroxy derivative. It was observed that for hydrolysis, inert atmosphere of N_2 gas gave good yield of pure product.

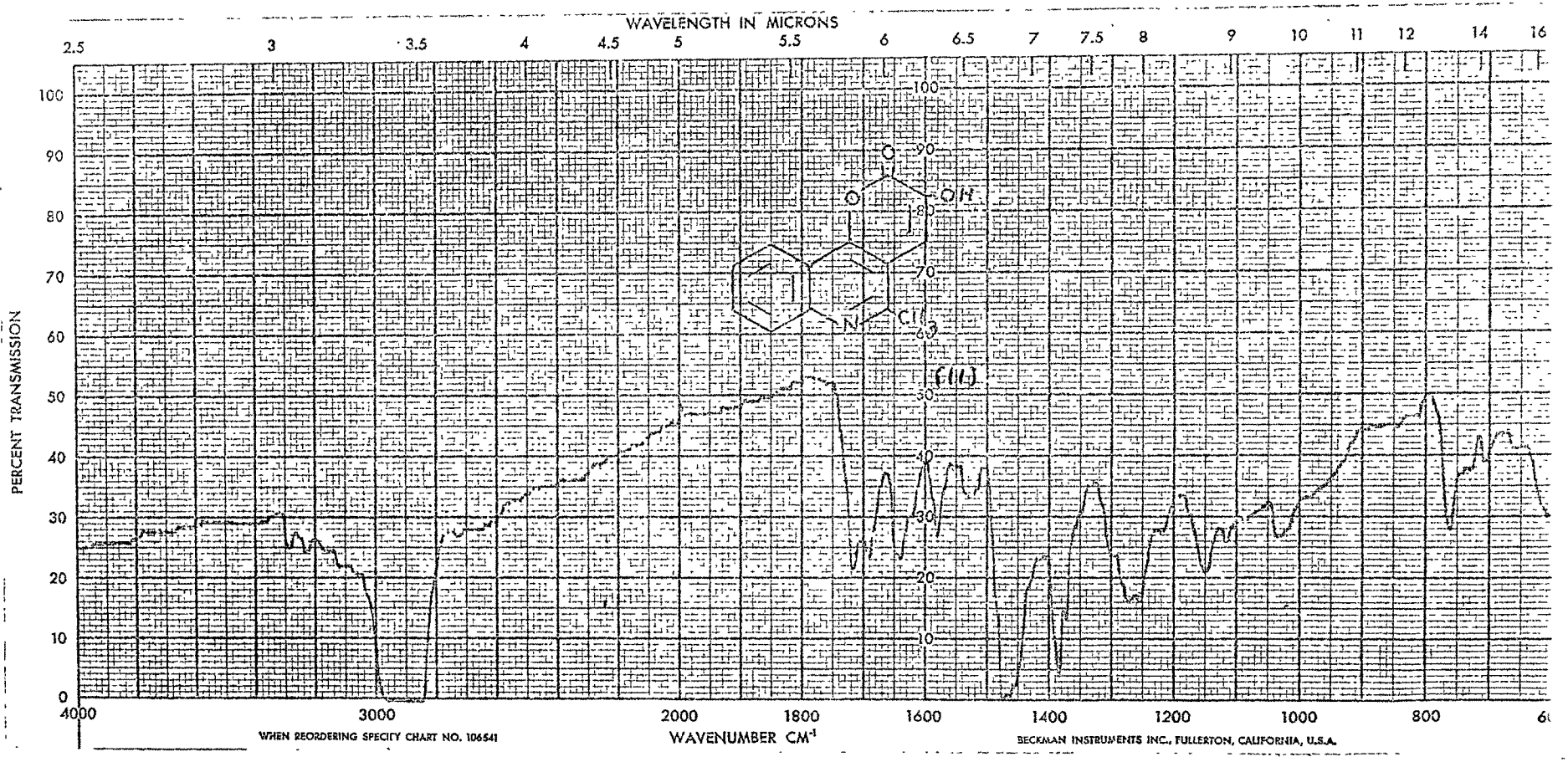
3-Hydroxy-5-methyl-2-oxo-2 H-pyrano(3,2-c)quinoline (11) :

2-Methyl-3-formyl-4-hydroxyquinoline on treatment with acetic anhydride, acetyl glycine and triethylamine

gave 3-acetylamino-5-methyl-2-oxo-2 H-pyrano (3,2-c) quinoline (10). The structure of (10) was assigned on the basis of analytical results and supported by IR spectrum. IR spectrum (nujol) showed a characteristic lactonyl band at 1740 cm^{-1} and amide >C=O band at 1680 cm^{-1}. The (10) on hydrolysis by 50 % sulphuric acid and alcohol (1:1) in nitrogen atmosphere gave 3-hydroxy-5-methyl-2-oxo-2 H-pyrano (3,2-c) quinoline (11). The structure of (11) was assigned on the basis of its IR spectrum. IR spectrum (nujol) showed a characteristic band at 1730 cm^{-1} for >C=O (lactone) and at 3300 cm^{-1} for >-OH. The product developed the characteristic green colour for 3-hydroxycoumarin derivatives with alcoholic ferric chloride solution. The NMR spectrum of above compound was not recorded as it was insoluble in common solvents.



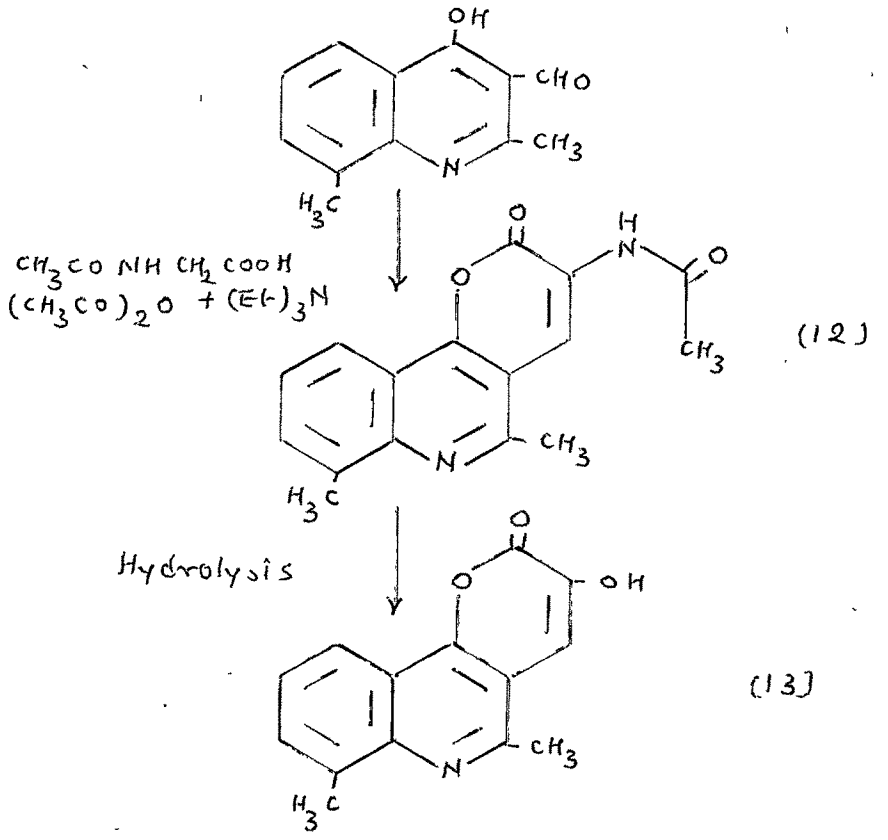

WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
WHEN REORDERING SPECIFY CHART NO. 10654I
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.

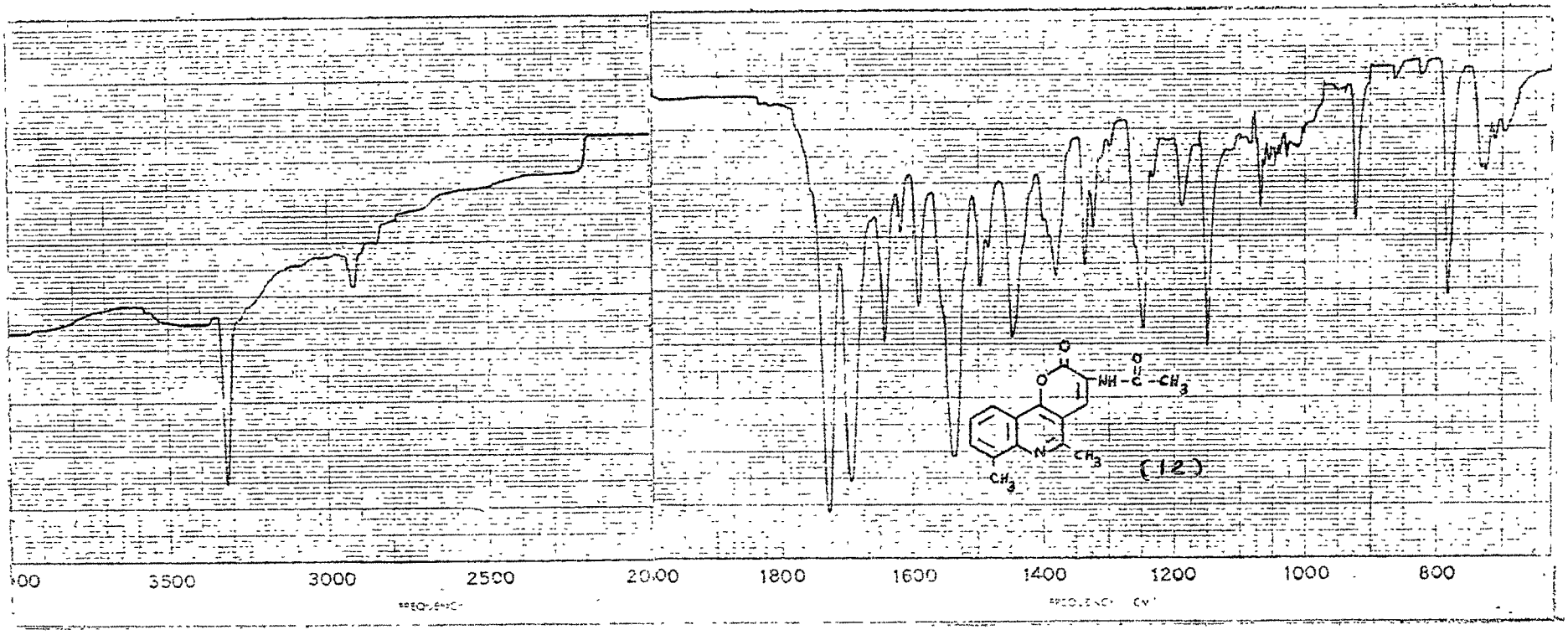

WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
OH
Cl
N
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
WHEN REORDERING SPECIFY CHART NO. 106541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.

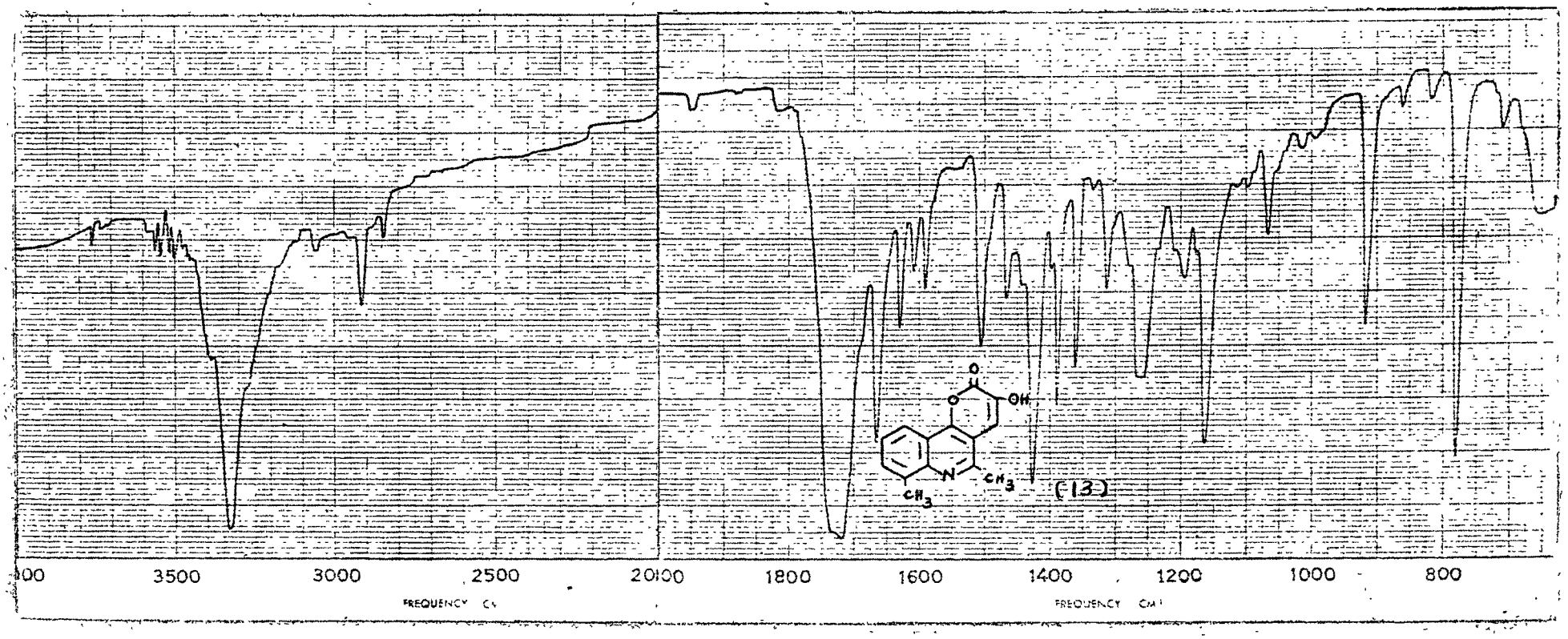
149

3-Hydroxy-5,7-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline(13):

2,8-Dimethyl-3-formyl-4-hydroxyquinoline was condensed with acetic anhydride, acetylglycine and triethylamine to give 3-acetylamino-5,7-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline (12). The IR spectrum (KBr) of (12) showed characteristic lactonyl band at 1725 cm^{-1} and amide >C=O band at 1680 cm^{-1}. (12), on hydrolysis by 50 % sulphuric acid and ethanol (1:1) in the nitrogen atmosphere gave 3-hydroxy-5,7-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline (13). The IR spectrum (KBr) showed a characteristic band at 1730 cm^{-1} for >C=O (lactone) and at 3330 cm^{-1} for -OH group. It showed characteristic green colouration with alcoholic ferric chloride solution.

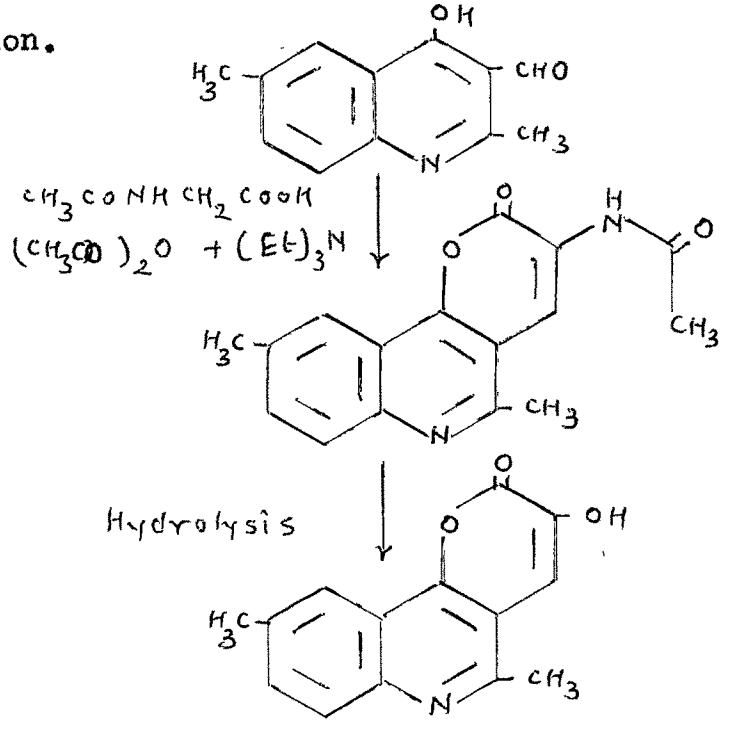



3500
3000
2500
2000
1800
1600
1400
1200
1000
800
NH – C – CH3
CH3
CH3
(12)


3500
3000
2500
1800
1600
1400
1200
1000
800
FREQUENCY
O
O
OH
N
CH3
CH3
(13)

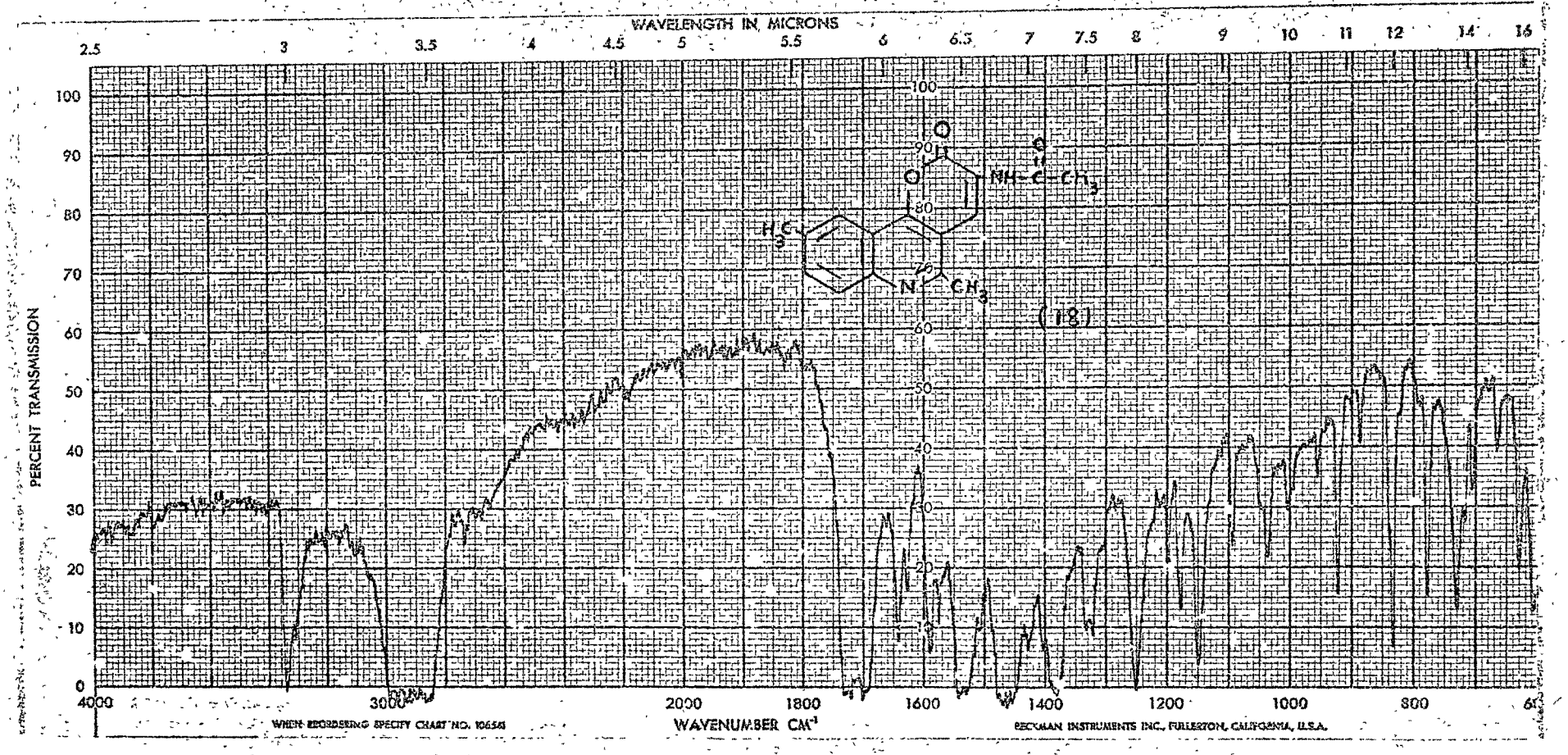
3-Hydroxy-5,9-dimethyl-2-oxo-2 H-pyrano (3,2-c) quinoline (19) :

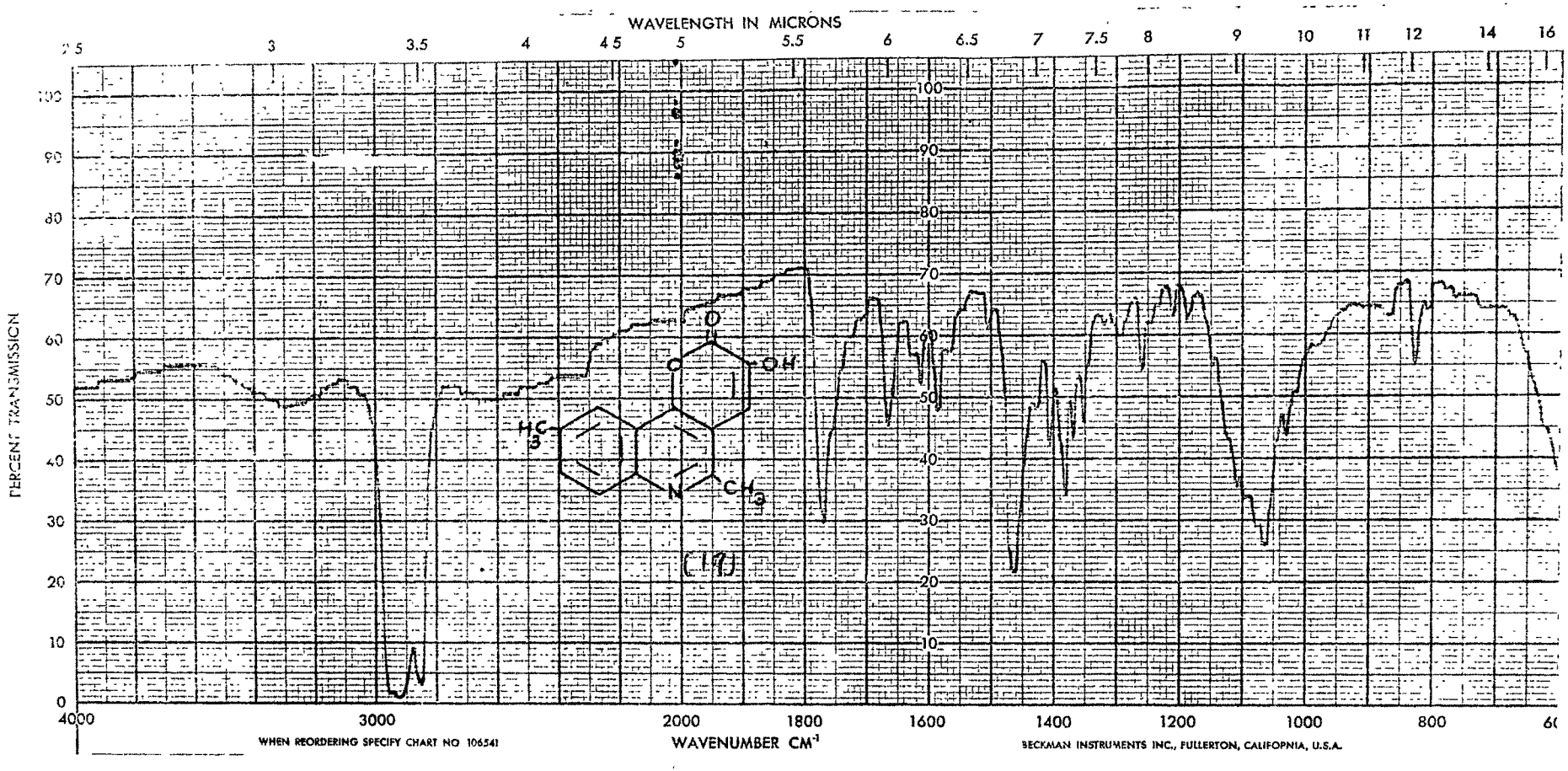
2,6-Dimethyl-3-formyl-4-hydroxyquinoline on similar condensation with acetic anhydride, acetylglycine and triethylamine gave 3-acetylamino-5,9-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline (18). The IR spectrum (KBr) of (18) showed a lactonyl band at 1725 cm^{-1} and amide >C=O band at 1680 cm^{-1}. (18), on hydrolysis by 50 % sulphuric acid and ethanol (1:1) in nitrogen atmosphere gave 3-hydroxy-5,9-dimethyl-2-oxo-2H-pyrano (3,2-c) quinoline (19). The IR spectrum (KBr) showed a characteristic band at 1730 cm^{-1} for >C=O (lactone) and at 3300 cm^{-1} for -OH group. It developed characteristic green colouration with alcoholic ferric chloride solution.



(18)

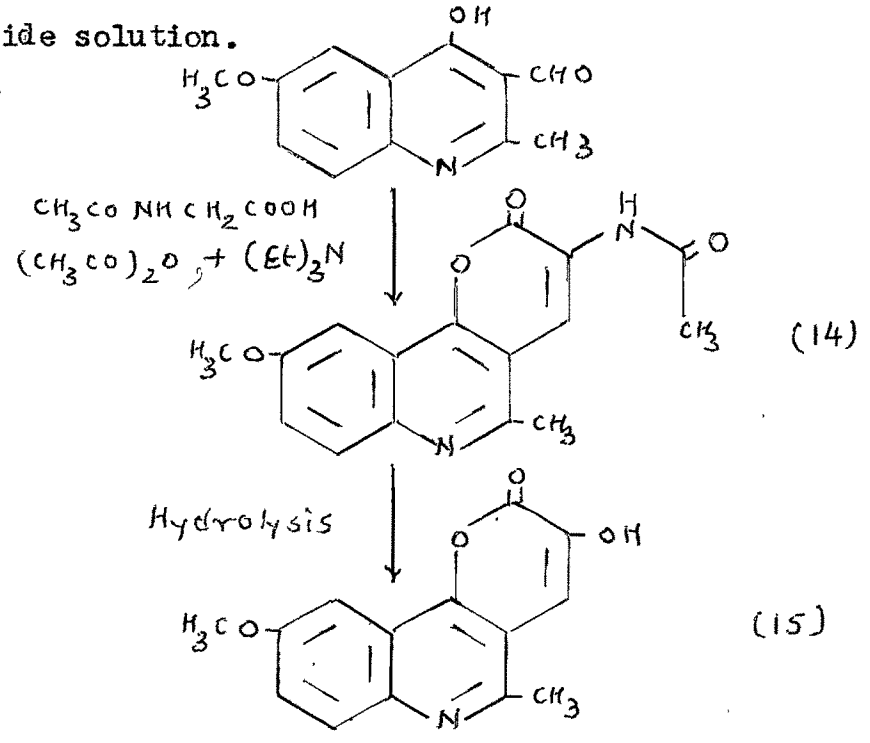
(19)

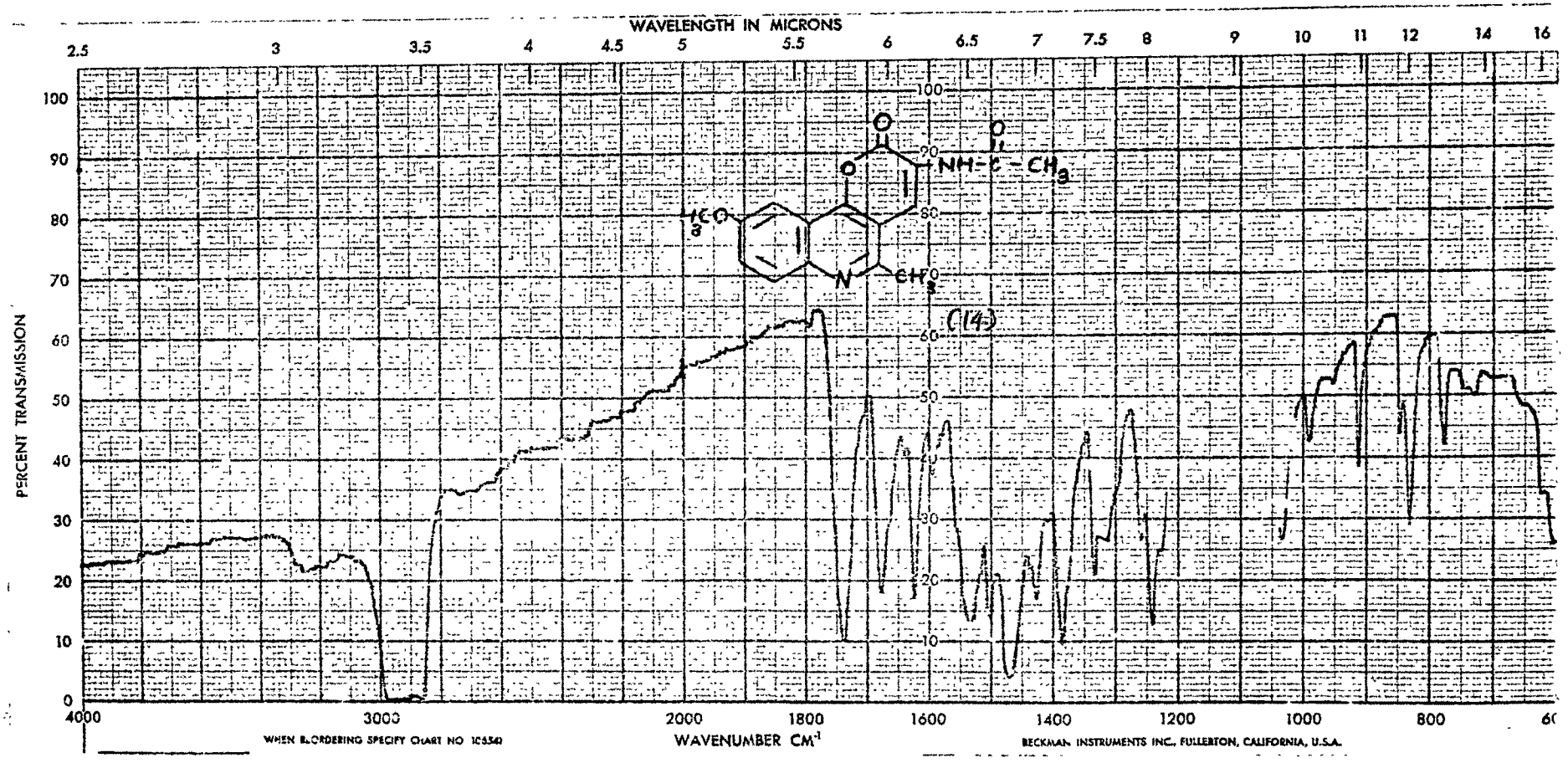

WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER CM⁻¹
WHEN REORDERING SPECIFY CHART NO. 10656
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.
(18)

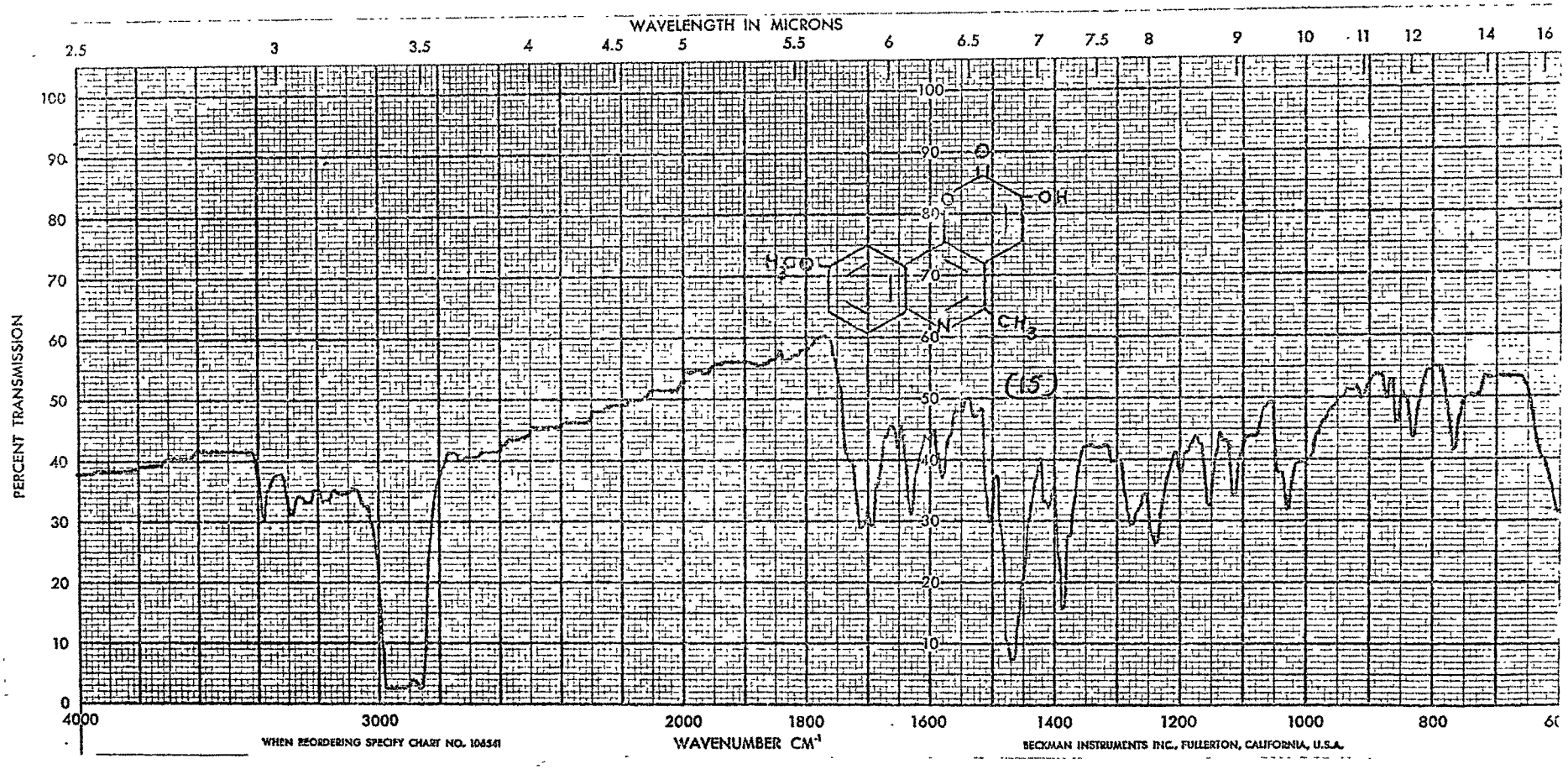

WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
WHEN REORDERING SPECIFY CHART NO 106541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFOPNIA, U.S.A.
O
C
OH
H3C
N
CH3
(19)

3-Hydroxy-5-methyl-9-methoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (15) :

2-Methyl-3-formyl-4-hydroxy-6-methoxyquinoline on condensation with acetic anhydride, acetylglycine and triethylamine gave 3-acetylamino-5-methyl-9-methoxy-2-oxo-2 H-pyrano (3,2-c)quinoline (14). The IR spectrum (nujol) of (14) showed a characteristic lactonyl band at 1740 cm^{-1} and amide >C=O at 1680 cm^{-1}. The (14) on hydrolysis using 50 % sulphuric acid and ethanol (1:1) in the nitrogen atmosphere gave 3-hydroxy-5-methyl-9-methoxy-2-oxo-2 H-pyrano (3,2-c)quinoline (15). The IR spectrum (nujol) showed characteristic lactonyl band at 1720 cm^{-1} and hydroxyl band at 3300 cm^{-1}. It developed characteristic green colouration with alcoholic ferric chloride solution.

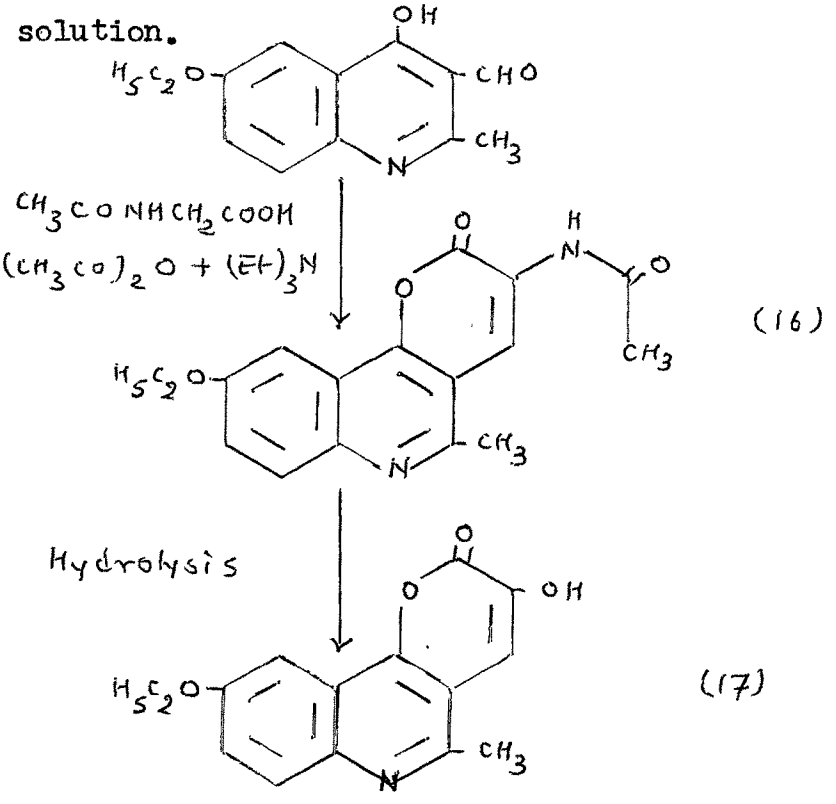


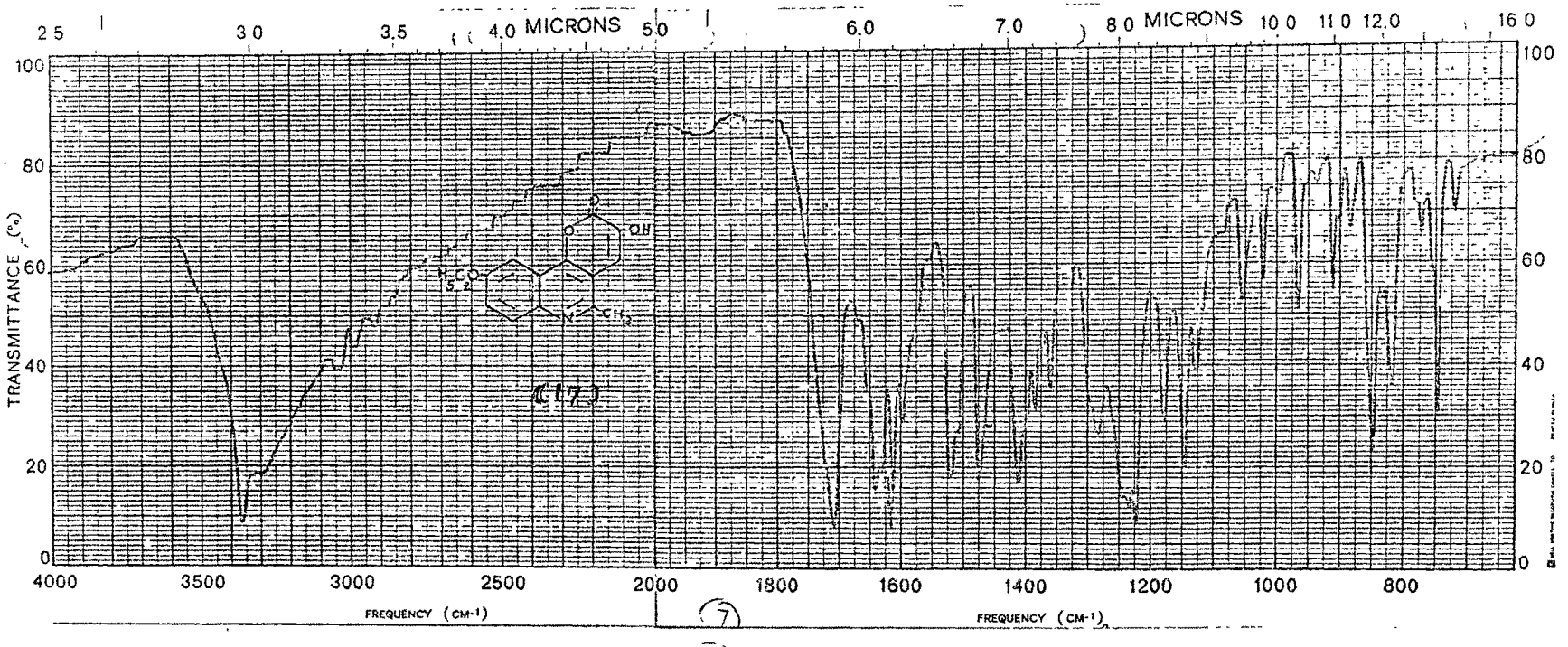

WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM⁻¹
WHEN ORDERING SPECIFY CHART NO 10550
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.
NH-C-CH3
H3CO
N
CH3
C(14)


WAVELENGTH IN MICRONS
2.5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
PERCENT TRANSMISSION
100
90
80
70
60
50
40
30
20
10
0
O
OH
H3CO
N
CH3
(15)
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM-1
WHEN REORDERING SPECIFY CHART NO. 106541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.

3-Hydroxy-5-methyl-9-ethoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (17) :

2-Methyl-3-formyl-4-hydroxy-6-ethoxyquinoline on similar condensation with acetic anhydride, acetylglycine and triethylamine gave 3-acetylamino-5-methyl-9-ethoxy-2-oxo-2 H-pyrano (3,2-c)quinoline (16). The (16) on hydrolysis in similar conditions gave 3-hydroxy-5-methyl-9-ethoxy-2-oxo-2 H-pyrano (3,2-c)quinoline (17). The structures of (16) and (17) were confirmed by IR spectra. IR spectra of (17) (KBr) showed a lactonyl band at 1710 cm^{-1} and hydroxy band at 3350 cm^{-1}. It developed characteristic green colouration with alcoholic ferric chloride solution.




2.5
3.0
3.5
4.0 MICRONS
5.0
6.0
7.0
8.0 MICRONS
10.0
11.0
12.0
16.0
100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
FREQUENCY (CM-1)
OH
H3CO
CH3
N
(17)

Synthesis of 2-oxo-2 H-pyrano (3,2-c)quinoline derivatives by Knoevenagel Reaction :

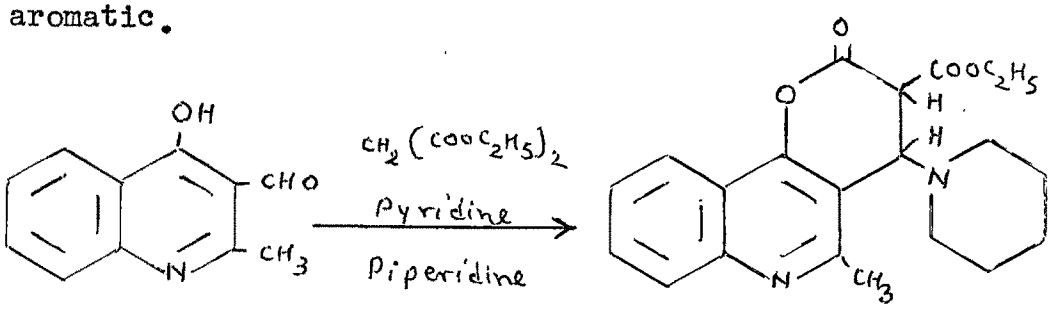
In the present work the synthesise of 2-oxo-2 H-pyrano (3,2-c)quinoline was carried out by Knoevenagel reaction. 2-Methyl-3-formyl-4-hydroxyquinoline was condensed with ethyl acetoacetate or diethylmalonate or ethyl cyanoacetate using piperidine-pyridine as condensing agent. Instead of getting the normal product, 2-oxo-2 H-pyrano (3,2-c)quinoline derivatives, novel products having piperidine nucleus attached with pyran ring at the C_4 position were obtained.

Thus by using different 2-methyl-3-formyl-4-hydroxyquinoline derivatives and condensing them with ethylacetoacetate, diethylmalonate and ethyl cyanoacetate, 3-substituted-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline derivatives were synthesised. The structures of all these products were assigned on the basis of its IR, mass, and NMR spectra and also supported by analytical results.

3-Carbethoxy-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (20) :

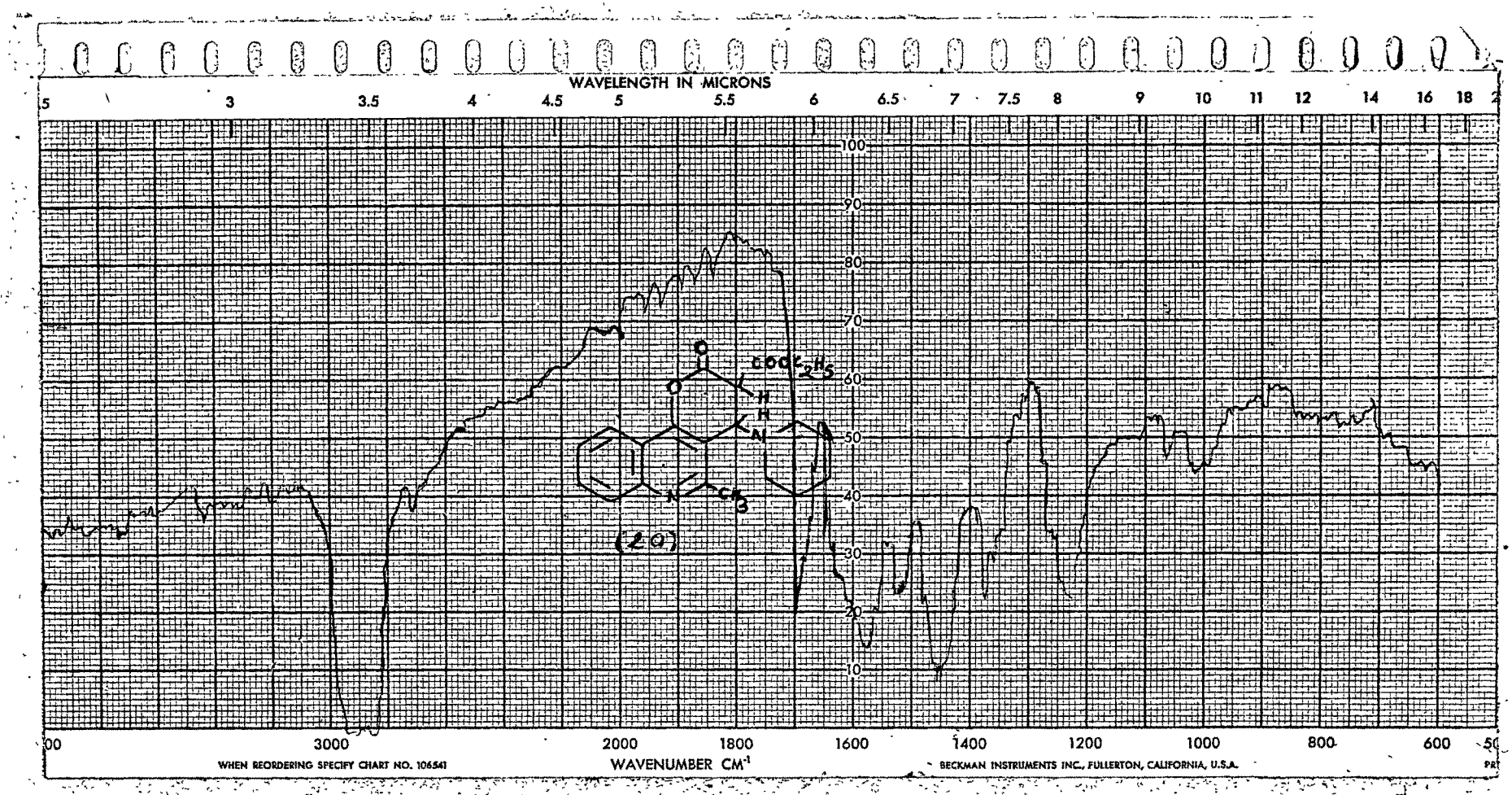
2-Methyl-3-formyl-4-hydroxyquinoline was condensed with diethyl malonate by using pyridine-piperidine as

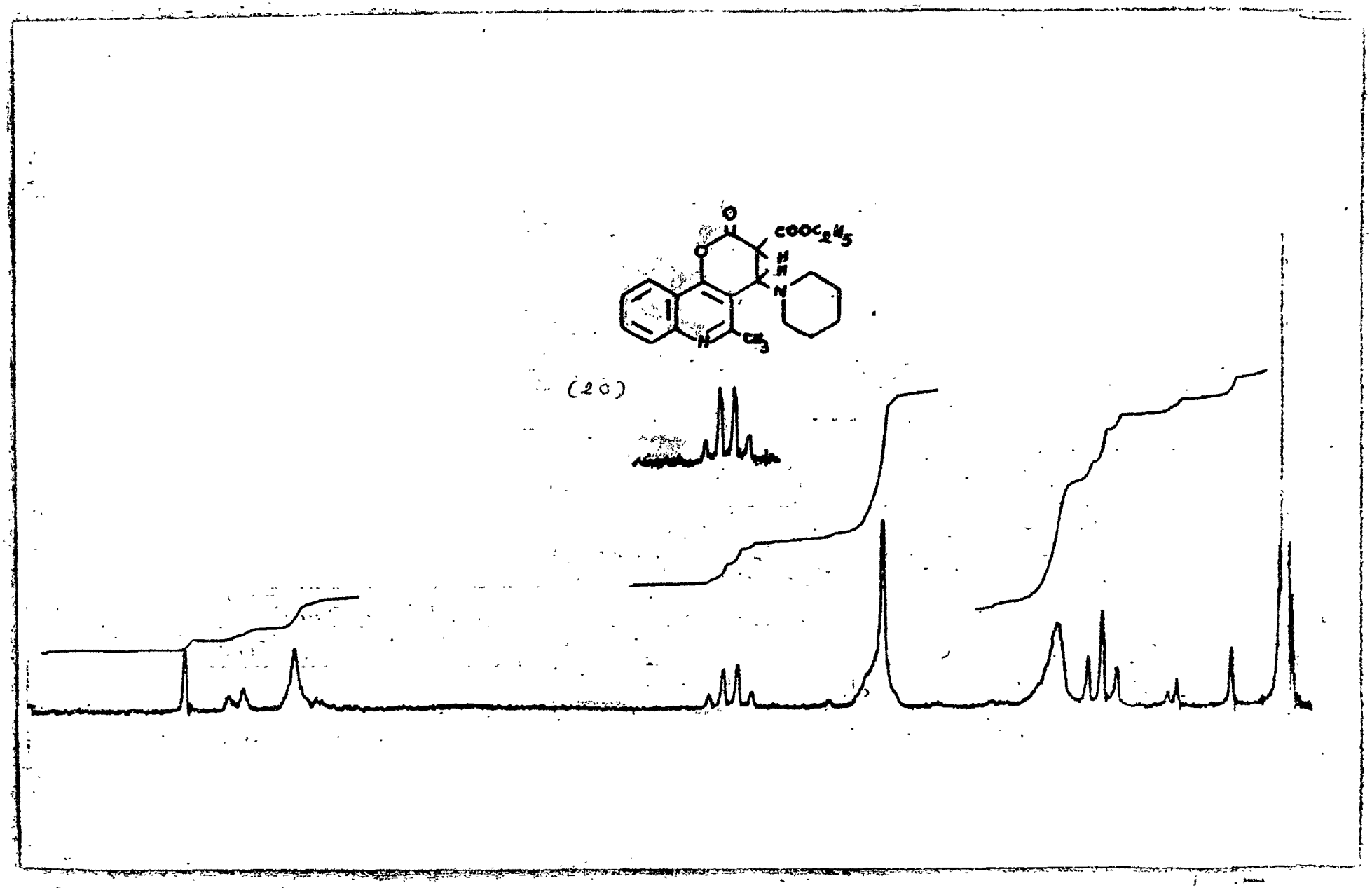
condensing agent. The reaction mixture was left overnight at room temperature and worked out to obtain 3-carbethoxy-4-(N-piperidine)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (20). The structure of (20) was assigned on the basis of its analytical results supported by its IR, NMR spectra. The IR spectrum (nujol) showed band at 1700 cm^{-1} lactonyl >C=O group. NMR spectrum (CF_3COOH) showed resonance signals at δ; 1.55, triplet, J = 8Hz, 3H, $-CH_3$ group of ester ; 1.80, broad singlet, 6H, $-CH_2-$ groups at C_3', C_4', C_5' of piperidine ; 2.25, singlet, 3H, $-CH_3$ group at C_5 ; 3.65, doublet, J = 6Hz, 1H, at C_4 ; 4.00, doublet, J = 6Hz, 1H at C_3 ; 3.35, broad singlet, 4H, $-CH_2-$groups at C_2', C_6' of piperidine ; 4.6, quartate, J = 8Hz, 2H, $-CH_2-$ group of ester and 8.2 - 8.8, multiplet, 4H, aromatic.



(20)

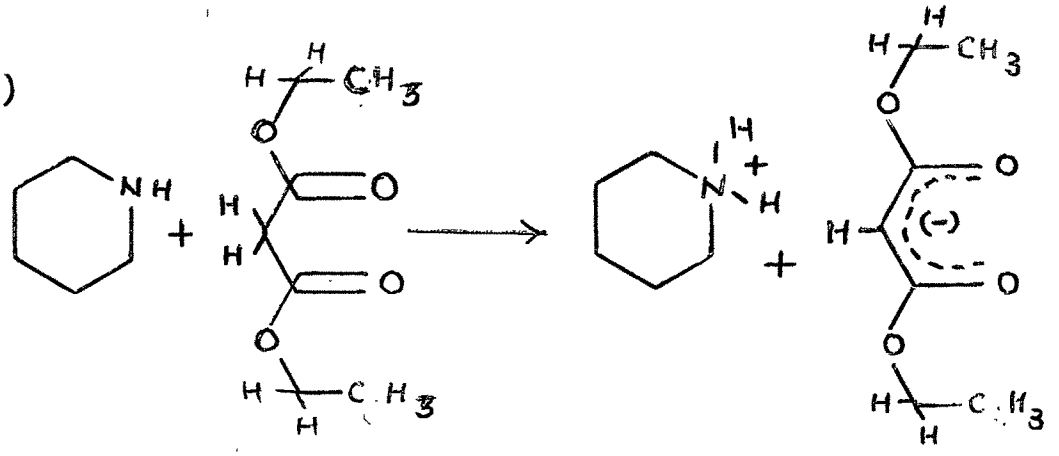
On the basis of reaction mechanism suggested by Knoevenagel[5,6,7,8,9,10,11,12,13,14,15], a series of reaction can be represented to obtain 4-(N-piperidyl) derivative of 3-carbethoxy-5-methyl-2-oxo-2 H-pyrano


WAVELENGTH IN MICRONS
5
3
3.5
4
4.5
5
5.5
6
6.5
7
7.5
8
9
10
11
12
14
16
18
100
90
80
70
60
50
40
30
20
10
3000
2000
1800
1600
1400
1200
1000
800
600
WAVENUMBER CM-1
WHEN REORDERING SPECIFY CHART NO. 106541
BECKMAN INSTRUMENTS INC., FULLERTON, CALIFORNIA, U.S.A.
(20)

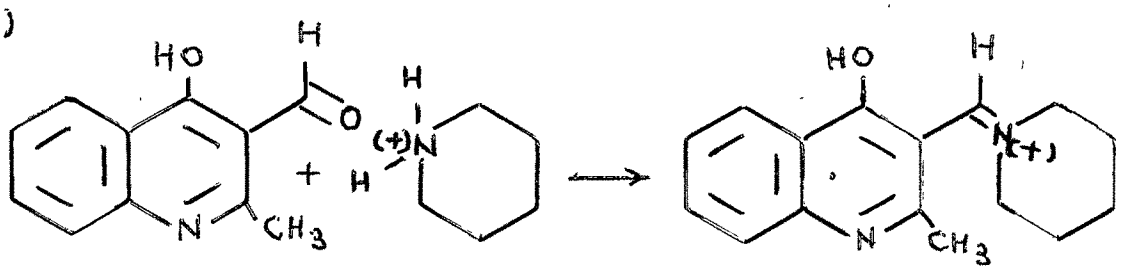

COOC2H5
(20)

(3,2-c)quinoline by condensing 2-methyl-3-formyl-4-hydroxyquinoline with diethylmalonate in the presence of pyridine and piperidine, as follow :-

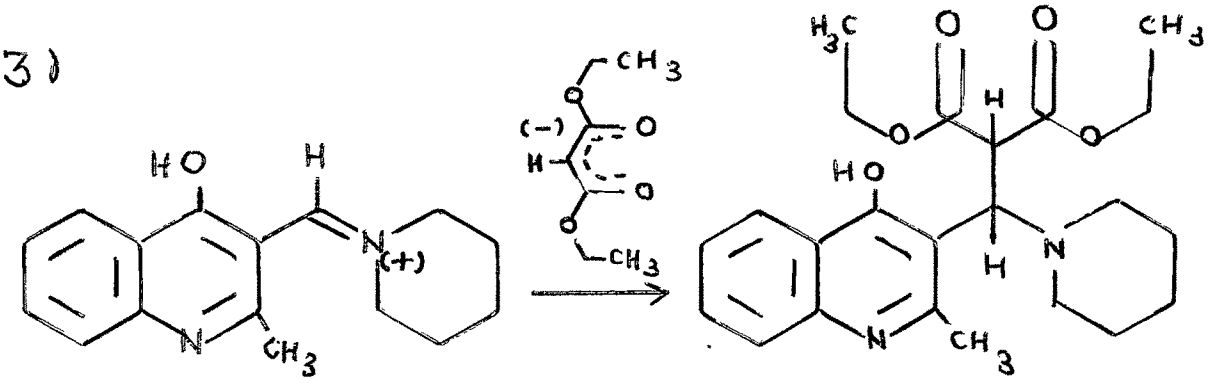
(1)



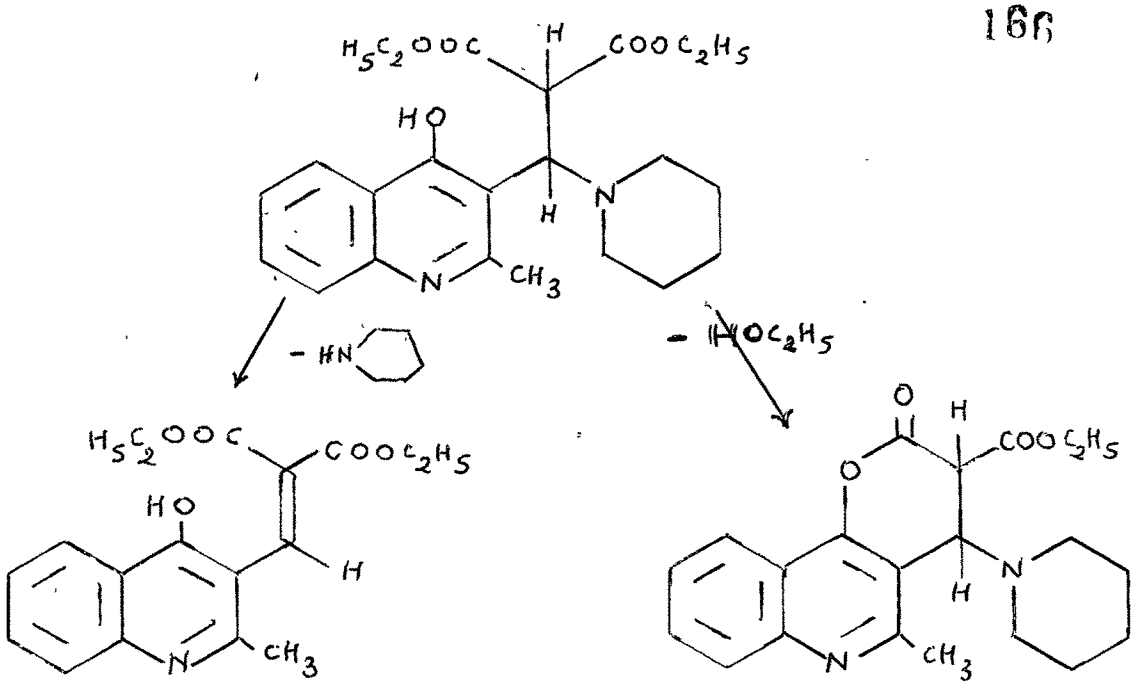
(2)



(3)



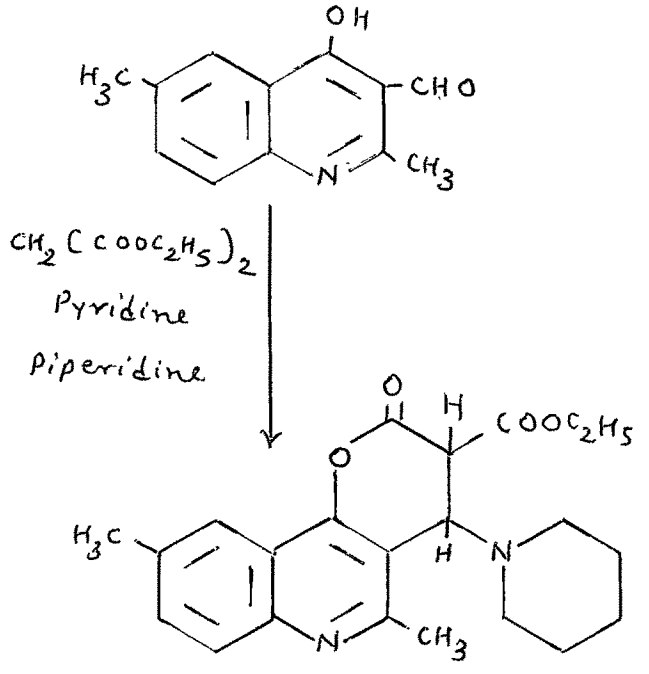
(4)



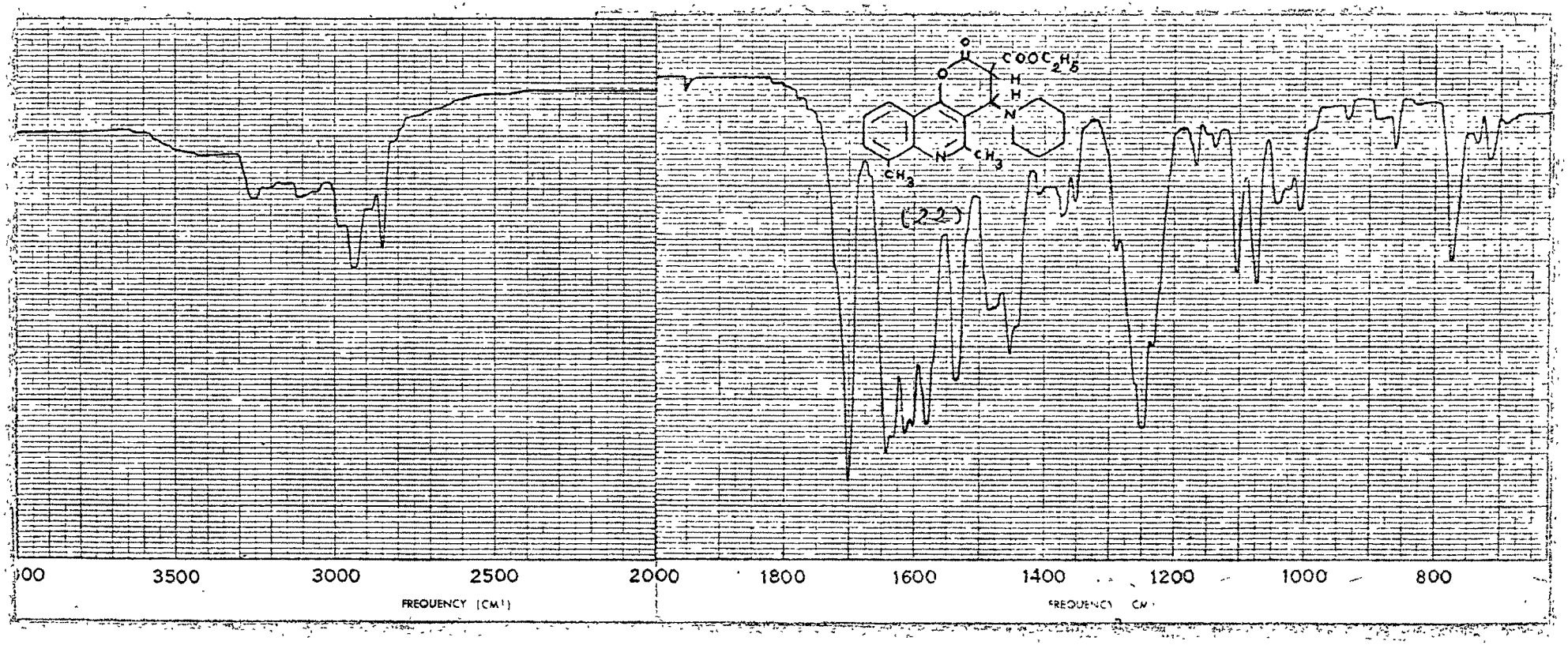
As shown in above series of reactions, step (iii) gives an intermediate (complex) which can directly cyclize to obtain the 3-carbethoxy-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline. Also the same intermediate compound can loose piperidine nucleus to give a cinnamic acid derivative. In the present work no such intermediate complex in which piperidine nucleus linked with β-carbon atome of propionic acid derivative could be isolated. But in the literature many evidences[16,17,18] are reported which showed that such type of intermediate complex could be isolated and converted into corresponding condensed product.

3-Carbethoxy-4-(N-piperidyl)5,9-dimethyl-3,4-dihydro 2-oxo-2 H-pyrano (3,2-c)quinoline (21) :

2,6-Dimethyl-3-formyl-4-hydroxyquinoline was condensed with dimethylmalonate by using pyridine-piperidine as condensing agent and worked up as before to get 3-Carbethoxy-4-(N-piperidyl)5,9-dimethyl-3,4-dihydro -2-oxo-2H-pyrano (3,2-c)quinoline (21). The structure of (21) was confirmed on the basis of the analogy with the above compound.

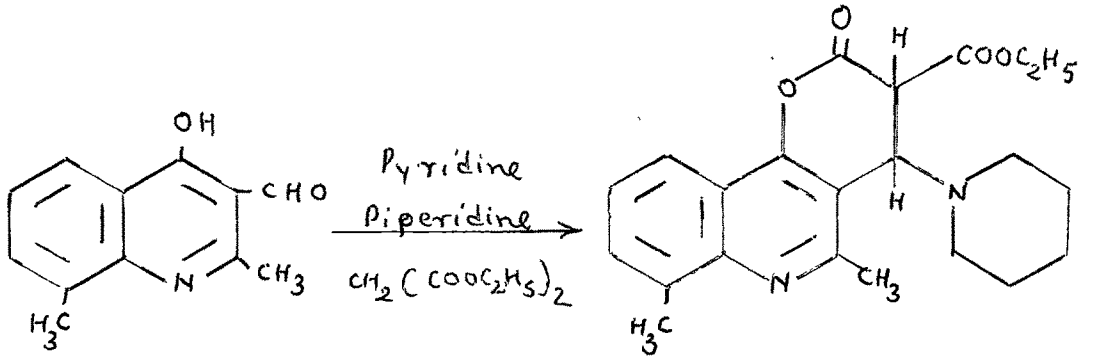


(21)


3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY (CM⁻¹)
COOC2H5
CH3
CH3
(22)

3-Carbethoxy-4-(N-piperidyl)-3,4-dihydro-5,7-dimethyl-2-oxo-2 H-pyrano-(3,2-c)quinoline (22) :

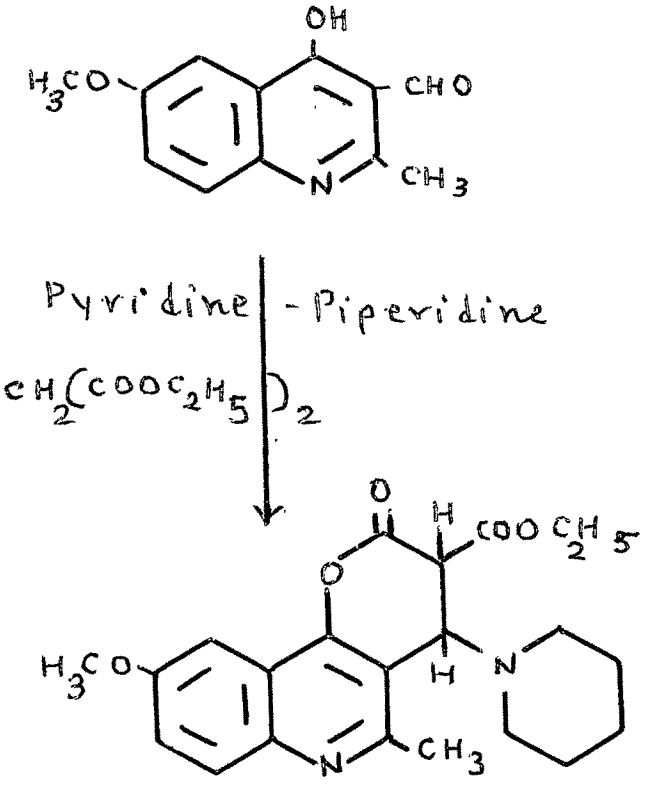
2,8-Dimethyl-3-formyl-4-hydroxyquinoline when condensed with diethylmalonate by using pyridine-piperidine as condensing agent, gave 3-carbethoxy-4-(N-piperidyl)-3,4-dihydro-5,7-dimethyl-2-oxo-2 H-pyrano-(3,2-c)quinoline (22). The structure of (22) confirmed by IR spectra, (nujol) showed characteristic bands at 1700 cm^{-1} for lactonyl >C=O group.



(22)

3-Carbethoxy-4-(N-piperidyl)-5-methyl-9-methoxy-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (23) :

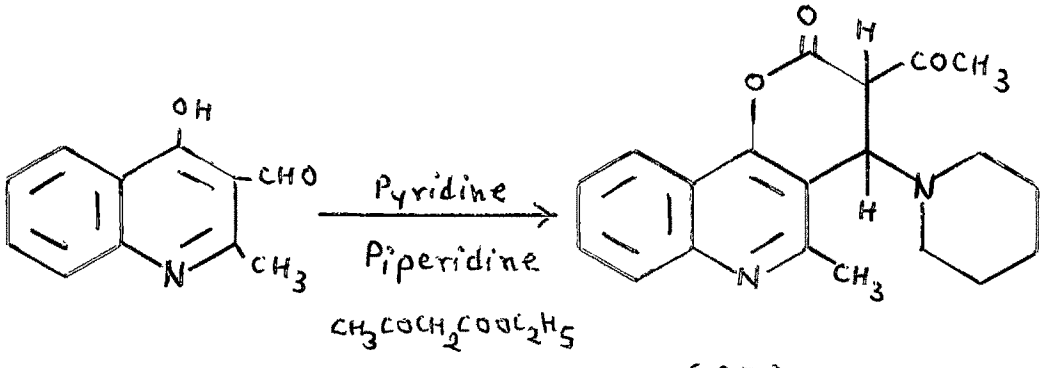
2-Methyl-3-formyl-4-hydroxy-6-methoxyquinoline was condensed with diethylmalonate by using pyridine piperidine as condensing agent gave 3-carbethoxy-4-(N-piperidyl)-5-methyl-9-methoxy-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (23). The structure of (23) was confirmed on the basis of the analogy with the above compound.


OH
H3CO
CHO
N
CH3
Pyridine
- Piperidine
CH2(COOC2H5)2
O
H
COOC2H5
O
H3CO
H
N
N
CH3

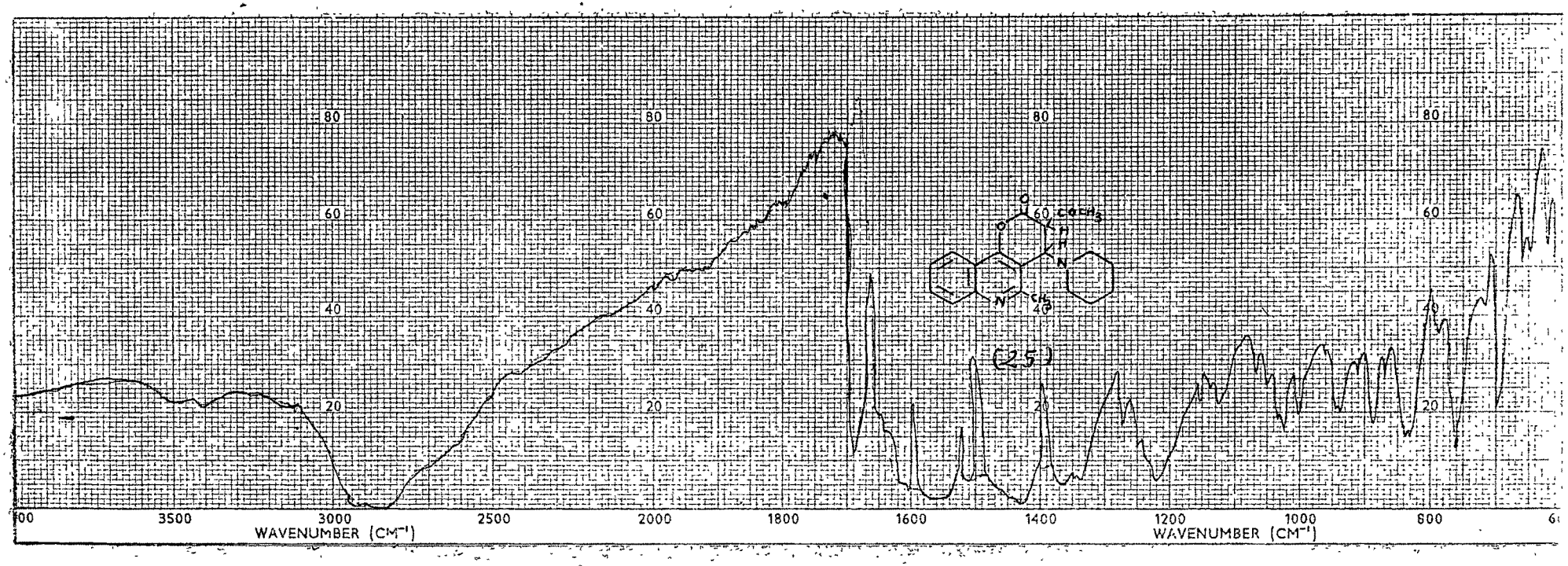
(23)

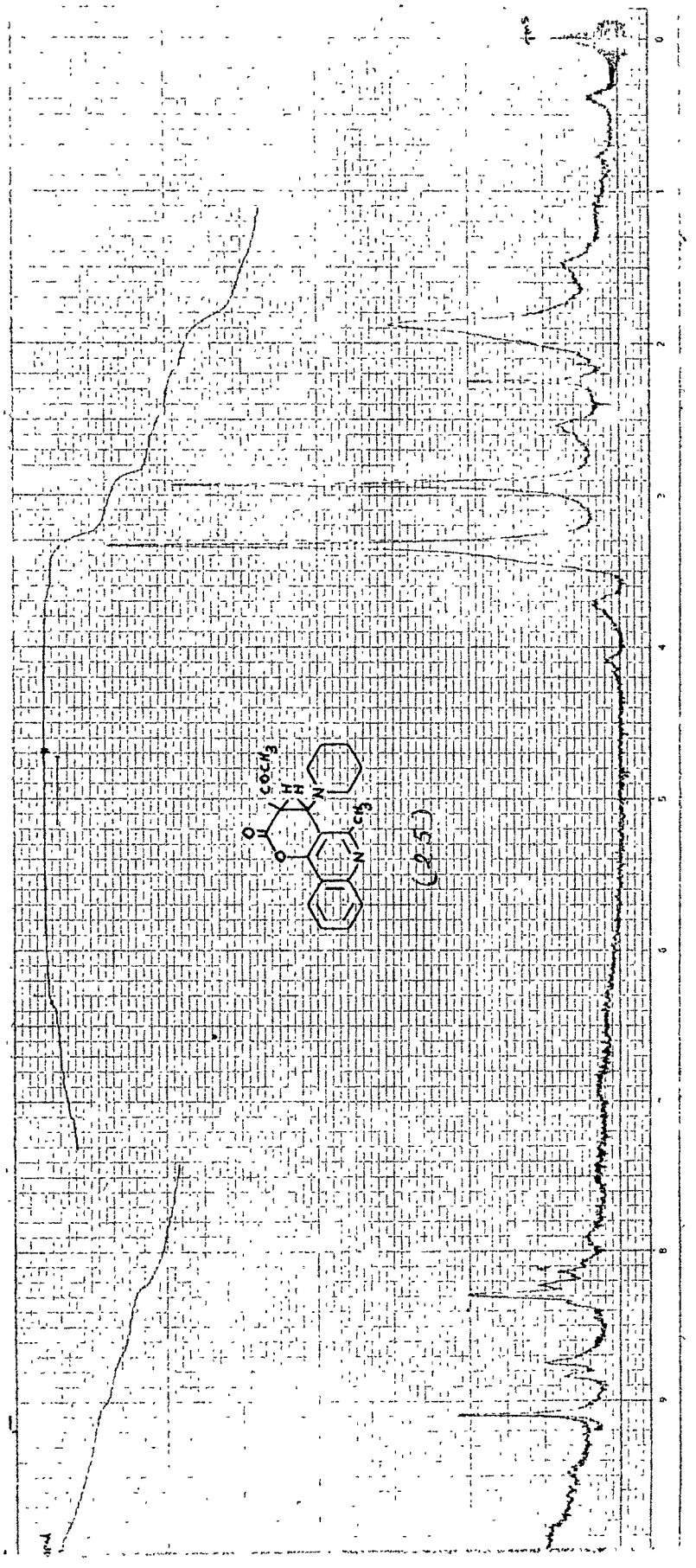
3-Acetyl-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (25) :

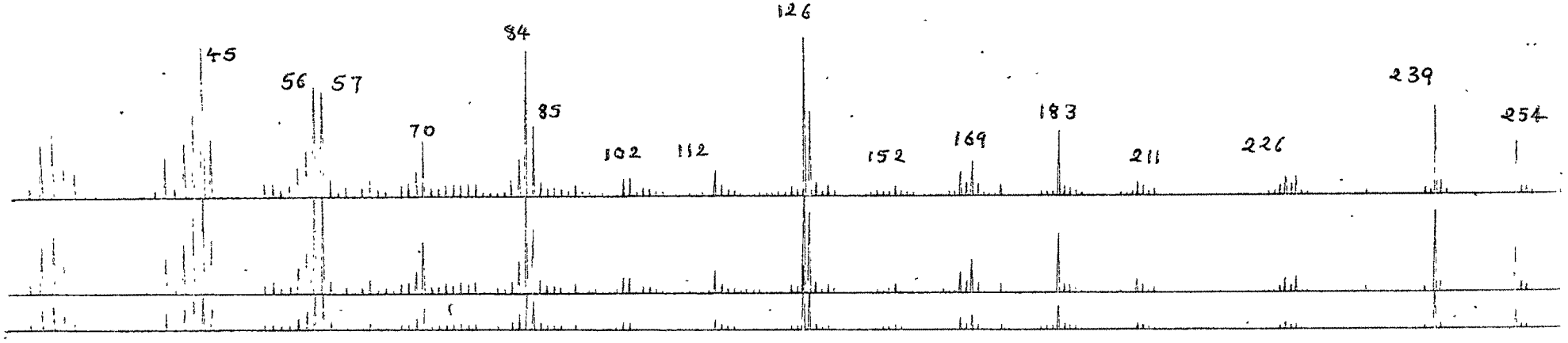
2-Methyl-3-formyl-4-hydroxy quinoline was condensed with ethylacetoacetate using pyridine-piperidine as condensing agent and worked up as before to get 3-acetyl-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (25). The structure of (25) was assigned on the basis of analytical results and confirmed by IR, and NMR spectra. The IR spectra (nujol) of (25) showed characteristic band at 1725 cm^{-1}, lactonyl $>C=O$ group. NMR (CF_3COOH) of (25) showed resonance signals at δ; 1.88, broad singlet, 6H, $-CH_2-$ group at C_3', C_4', C_5' of piperidine ; 2.25, singlet, 3H, $-CH_3$ group at C_5 ; 2.95, singlet, 3H, $-CH_3$ group of acetyl ; 3.3, broad singlet, 4H, $-CH_2-$groups at C_2', C_6' of piperidine and 8.2 - 8.8, multiplet, 4H, aromatic. Mass spectrum of (25) did not show the molecular ion peak, but the following peaks were prominent ; m/e ; 254, M^+-piperidyl group ; 226, M^+-piperidyl-C=O, group ; 84, piperidyl.

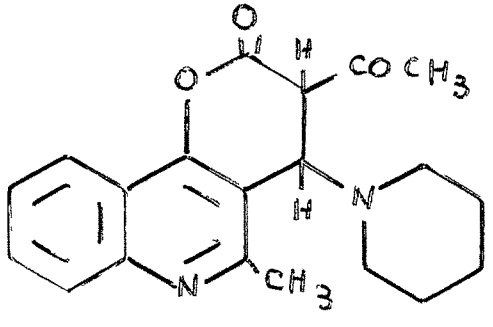


(25)


80
60
40
20
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
O
O
COCH3
H
N
N
CH3
(25)


TMS
0
1
2
3
4
5
6
7
8
9
10
COCH3
NH
N
O
O
CH3
N
(25)

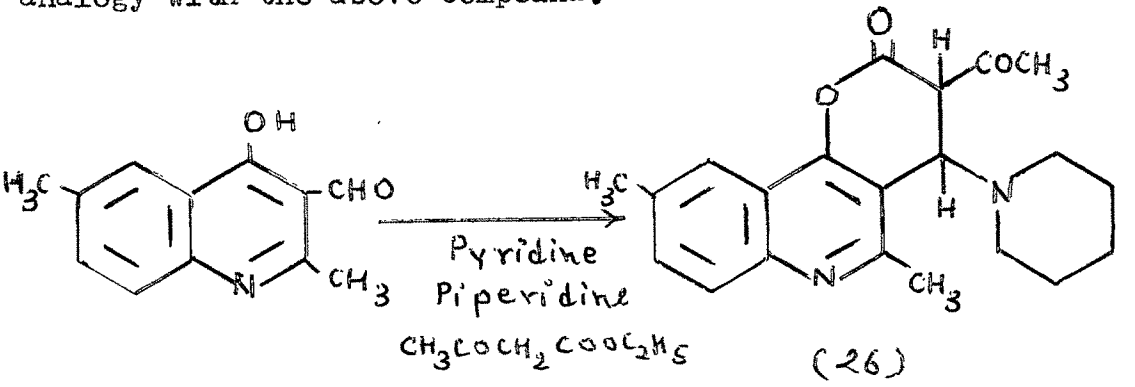

45
56
57
70
84
85
102
112
126
152
169
183
211
226
239
254


O
H
CO CH3
O
H
N
N
CH3

(25)

3-Acetyl-4(N-piperidyl)-5,9-dimethyl-3,4-dihydro-2-oxo 2 H-pyrano (3,2-c)quinoline (26) :

2,6-Dimethyl-3-formyl-4-hydroxyquinoline when condensed with ethylacetoacetate by using pyridine-piperidine as condensing agent gave 3-Acetyl-4-(N-piperidyl) -5,9-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (26) : The structure of (26) was confirmed on the basis of analogy with the above compound.

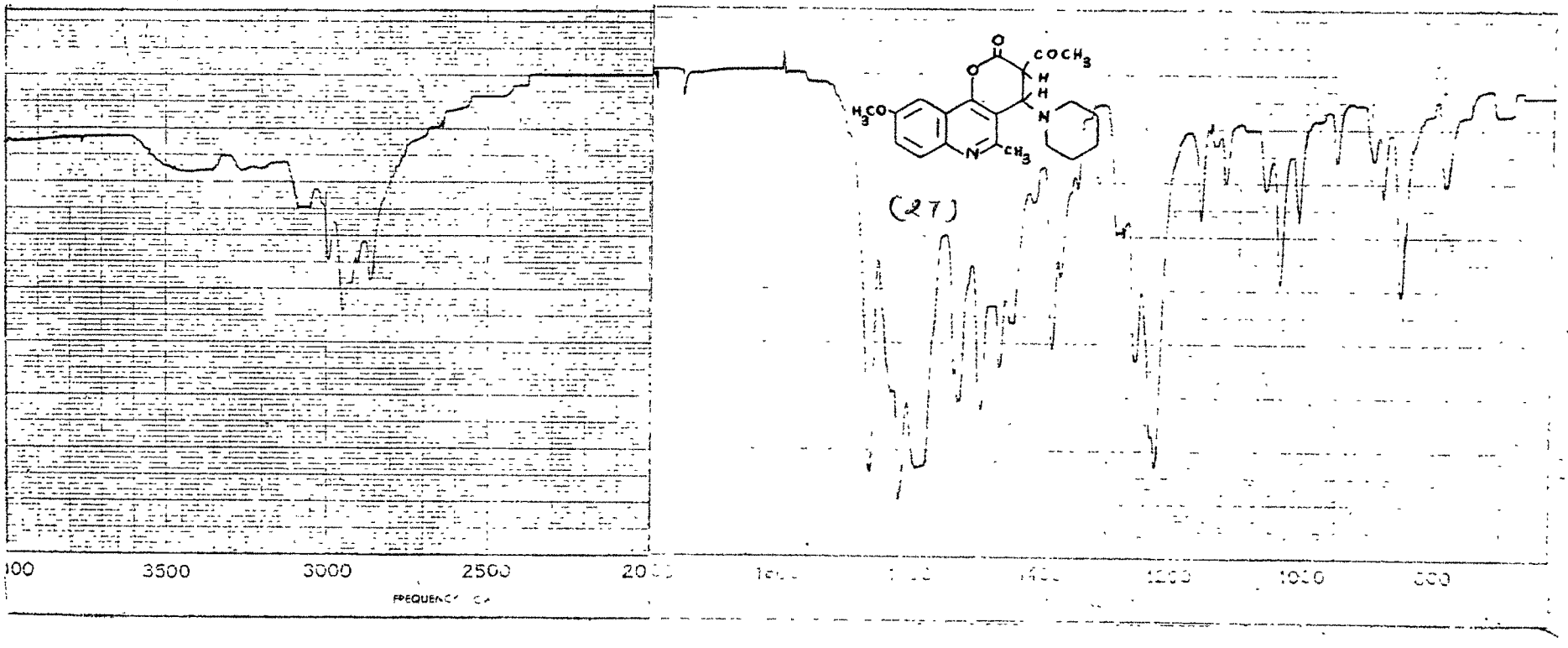


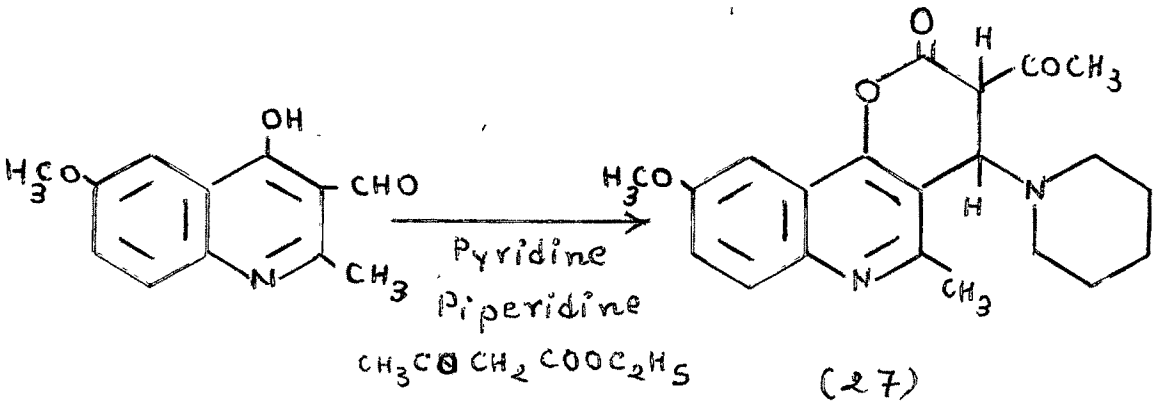
(26)

3-Acetyl-4-(N-piperidyl)-5-methyl-9-methoxy-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (27) :

2-Methyl-3-formyl-4-hydroxy-6-methoxyquinoline when condensed with ethylacetoacetate by using pyridine-piperidine as condensing agent gave 3-Acetyl-4-(N-piperidyl) -5-methyl-9-methoxy-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c) quinoline (27). The structure of (27) was confirmed on the basis of the analogy with the above compound.

(26)
100
3500
3000
2600
2000
1800
1600
1400
1200
1000
800

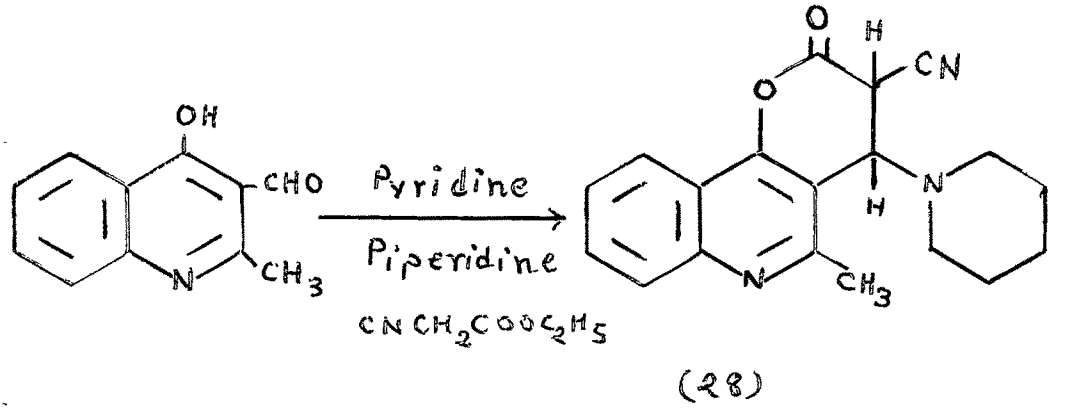

COCH3
H
H
H3CO
N
N
CH3
(27)
3500
3000
2500



(27)

3-Cyano-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (28) :

2-Methyl-3-formyl-4-hydroxyquinoline was condensed with ethylcyanoacetate using pyridine-piperidine as condensing agent and worked up as before to give 3-cyano-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (28). The structure of (28) was confirmed on the basis of analogy with the above compound.

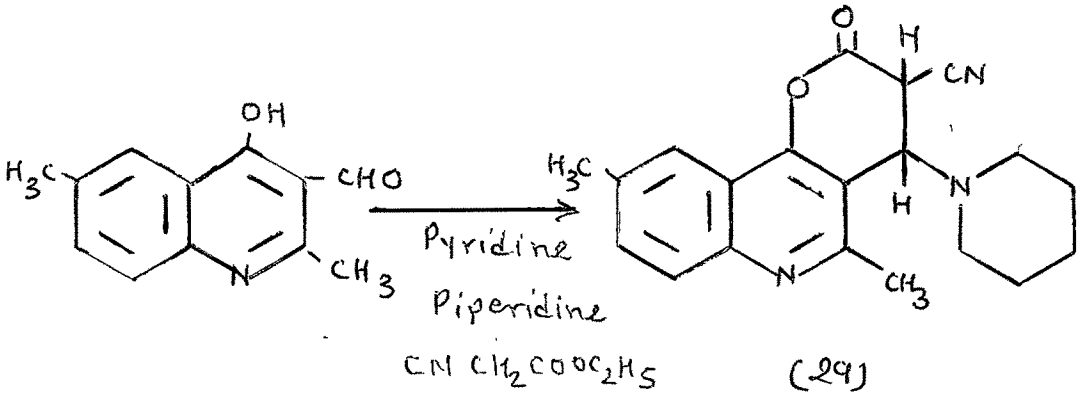


(28)

3-Cyano-4-(N-piperidyl)-5,9-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (29) :

CN
H
N
O
O
N
CH3
(2-S)
800
1000
1200
1400
1600
1800
2000
2500
3000
3500
FREQUENCY (CM-1)

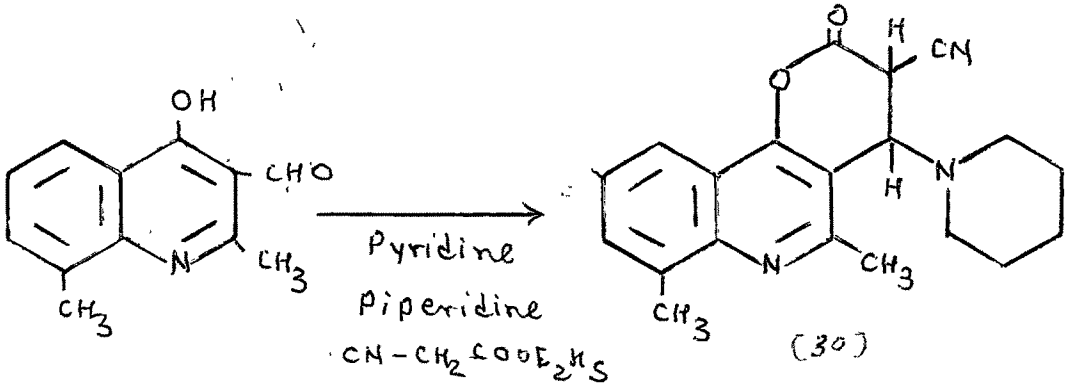
2,6-Dimethyl-3-formyl-4-hydroxyquinoline was condensed with ethylcyanoacetate using pyridine-piperidine as condensing agent and worked up as before to give 3-cyano-4-(N-piperidyl)-5,9-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c) quinoline (29). The structure of (29) was confirmed on the basis of analogy with above compound.



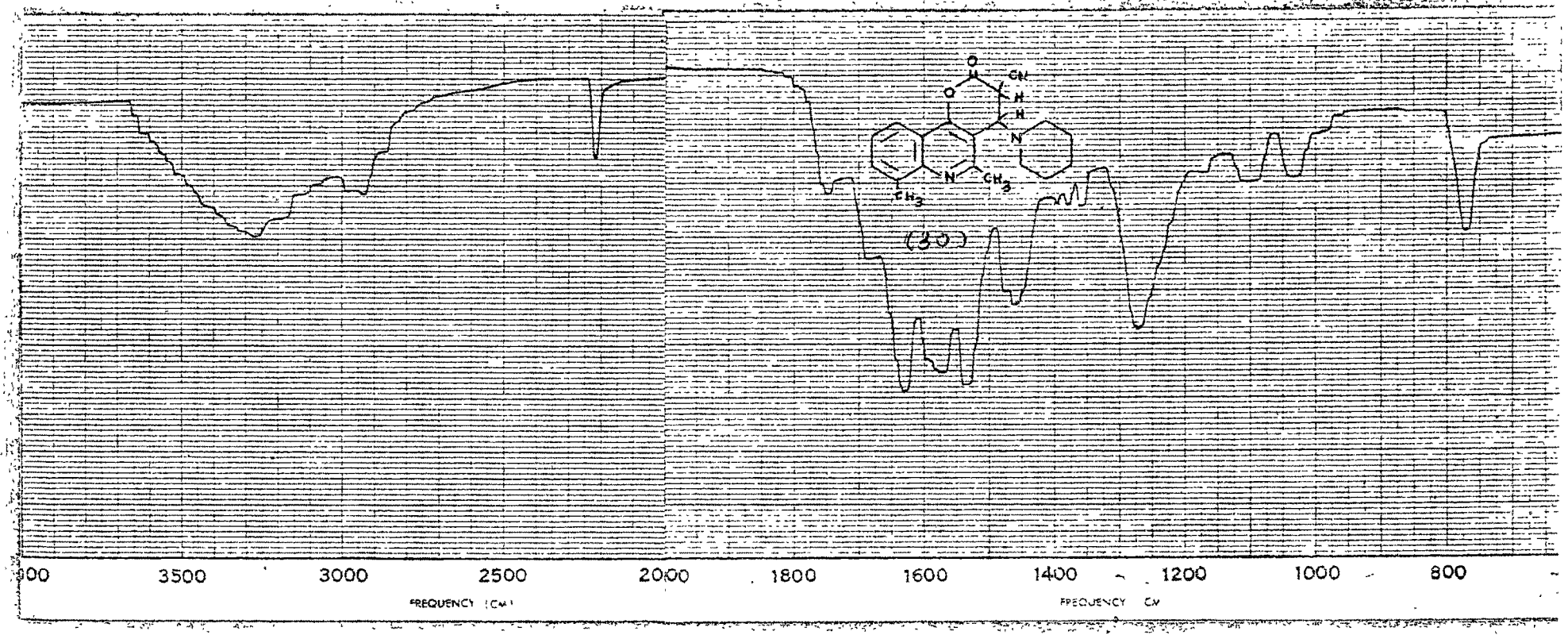
(29)

3-Cyano-4-(N-piperidyl)-5,7-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c) quinoline (30) :

2,8-Dimethyl-3-formyl-4-hydroxyquinoline was condensed with ethylcyanoacetate using pyridine-piperidine as condensing agent and worked out as before to give 3-cyano-4-(N-piperidyl)5,7-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c) quinoline (30). The structure of (30) was confirmed on the basis of analogy with above compound.



(30)


3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM-1)
FREQUENCY CM
(30)

EXPERIMENTAL

3-Hydroxy-5-methyl-2-oxo-2 H-pyrano(3,2-c)quinoline by Perkin reaction on 2-methyl-3-formyl-4-hydroxyquinoline (11) :

3-(N-acetylamino)-5-methyl-2-oxo-2 H-pyrano (3,2-c) quinolines (10) :

A mixture of 2-methyl-3-formyl-4-hydroxyquinoline (1.0 g), acetylglycine (1.17 g) acetic anhydride (10 ml) and triethylamine (4.0 ml) was heated in an oil-bath at 110° for 16 hours. The reaction mixture was poured in ice cold water and the separated product was filtered, washed with water and crystallised from acetic acid ; yield 2.0 gm, m.p. 298° (Found ; C, 67.05, H, 4.54 N, 9.99 ; $C_{15}H_{12}N_2$; required ; C, 67.18 H, 4.48, N, 10.45 %).

3-Hydroxy-5-methyl-2-oxo-2 H-pyrano (3,2-c)quinoline (11):

The above product (1.0 g) was dissolved in 20 ml alcohol and 20 ml 50 % H_2SO_4 and was heated on sand bath in the presence of an innert atmosphere of nitrogen for about 5 hrs. The reaction mixture was poured over ice-water and neutralised by Na_2CO_3 (10 %) solution. The

separated product was filtered, washed with water and crystallised from ethanol ; yield 0.2 gm. m.p., 251°. (Found ; C, 68.56 H, 4.12 N, 6.08 ; $C_{13}H_9NO_3$; required ; C, 68.70 H, 3.96 N, 6.17 %).

3-Hydroxy-5,7-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline (13) :

3-Acetylamino-5-7-dimethyl-2-oxo-2 H-pyrano (3,2-c) quinoline (12) :

A mixture of 2,8-dimethyl-3-formyl-4-hydroxy-quinoline (1.2 g), acetylglycine (1.17 g) acetic anhydride (10 ml) and triethylamine (4.0 ml) was heated in oil-bath at 110° for 16 hours. The reaction mixture was poured in ice cold water and the separated product was filtered, washed with water and crystallised from acetic acid ; yield 1.7 gm, m.p. 307° (Found ; C, 68.36 H, 4.65 N, 9.62 ; $C_{16}H_{14}N_2O_3$; required ; C, 68.10 H, 4.96 N, 9.93 %).

3-Hydroxy-5,7-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline (13):

The above product (1.0 g) was dissolved in 20 ml alcohol and 20 ml 50 % H_2SO_4 and was heated on sand bath in the presence of an innert atmosphere of nitrogen for about 5 hrs. The reaction mixture was poured over ice-water and was neutralised by Na_2CO_3 (10 %) solution. The

separated product was filtered, washed with water and crystallised from ethanol ; yield 0.3 gm, m.p., 274°. (Found ; C, 69.26 H, 4.48 N, 5.48 ; $C_{14}H_{11}NO_3$; required ; C, 69.72 H, 4.56 N, 5.81 %).

3-Hydroxy-5,9-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline (19) :

3-Acetylamino-5,9-dimethyl-2-oxo-2 H-pyrano (3,2-c) quinoline (18) :

A mixture of 2,6-dimethyl-3-formyl-4-hydroxy-quinoline (1.2 g), acetylglycine (1.17 g) acetic anhydride (10 ml) and triethylamine (4.0 ml) was heated in oil-bath at 110° for 16 hrs. The reaction mixture poured in ice cold water and the separated product was filtered, washed with water and crystallised from acetic acid ; yield 1.5 gm, m.p.311°. (Found ; C, 68.00 H, 4.58 N, 9.95 ; $C_{16}H_{14}N_2O_3$; required ; C, 68.10 H, 4.96 N, 9.93 %).

3-Hydroxy-5,9-dimethyl-2-oxo-2 H-pyrano (3,2-c)quinoline (19) :

The above product (1.0 g) was dissolved in 20 ml alcohol and 20 ml 50 % H_2SO_4 and was heated on sand bath in the presence of an innert atmosphere of nitrogen for about 5 hrs. The reaction mixture was poured over ice-

water and was neutralised by Na_2CO_3 (10 %) solution. The separated product was filtered, washed with water and crystallised from ethanol ; yield 0.3 gm, m.p., [redacted] 320° (Found ; C, 69.57 H, 4.80 N, 5.73 ; $C_{14}H_{11}NO_3$; required ; C, 69.72 H, 4.56 N, 5.81 %).

3-Hydroxy-5-methyl-9-methoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (15) :

3-Acetyl amino-5-methyl-9-methoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (14) :

A mixture of 2-methyl-3-formyl-4-hydroxy-6-methoxy-quinoline (1.5 g), acetylglycine (1.17 g) acetic anhydride (10 ml) and triethylamine (4.0 ml) was heated in oil-bath at 110° for 16 hrs. The reaction mixture was poured in ice cold water and the separated product was filtered, washed with water and crystallised from acetic acid ; yield 1.0 gm, m.p. 275°. (Found ; C, 63.98 H, 4.58 N, 8.93 ; $C_{16}H_{14}N_2O_4$; required ; C, 64.43 H, 4.69 N, 9.40%).

3-Hydroxy-5-methyl-9-methoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (15) :

The above product (1.0 g) was dissolved in 20 ml alcohol and 20 ml 50 % H_2SO_4 and was heated on sand bath in the presence of an innert atmosphere of nitrogen for

about 5 hrs. The reaction mixture was poured over ice-water and was neutralised by Na_2CO_3 (10 %) solution. The separated product was filtered, washed with water and crystallised from ethanol ; yield 0.5 gm, m.p. 221°. (Found ; C, 65.67 H, 4.47 N, 5.85 ; $C_{14}H_{11}NO_4$; required ; C, 65.38 H, 4.28 N, 5.44 %).

3-Hydroxy-5-methyl-9-ethoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (17) :

3-Acetylamino-5-methyl-9-ethoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (16) :

A mixture of 2-methyl-3-formyl-4-hydroxy-6-ethoxy-quinoline (1.7 g) acetylglycine (1.17 g) acetic anhydride (10 ml) and triethylamine (4.0 ml) was heated in oil-bath at 110° for 16 hrs. The reaction mixture was poured in ice cold water and the separated product was filtered, washed with water and crystallised from acetic acid ; yield 1.3 gm, m.p. 272°. (Found ; C, 64.97 H, 5.16 N, 8.83 ; $C_{17}H_{16}N_2O_4$; required ; C, 65.38 H, 5.12 N, 8.97 %).

3-Hydroxy-5-methyl-9-ethoxy-2-oxo-2 H-pyrano (3,2-c) quinoline (17) :

The above product (1.0 g) was dissolved in 20 ml alcohol and 20 ml 50 % H_2SO_4 and was heated on sand bath

in the presence of an innert atmosphere of nitrogen for about 5 hrs. The reaction mixture was poured over ice-water and was neutralised by Na_2CO_3 (10 %) solution. The separated product was filtered washed with water and crystallised from ethanol ; yield 0.5 gm, m.p. 242°. (Found ; C, 66.63 H, 4.45 N, 4.85 ; $C_{15}H_{13}NO_4$; required ; C, 66.42 H, 4.79 N, 5.16 %).

3-Carbethoxy-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (20) :

2-Methyl-3-formyl-4-hydroxyquinoline (1.0 g) was dissolved in pyridine (10 ml) and was refluxed with diethylmalonate (1.0 ml) in the presence of few drops of piperidine on steambath for 2 hrs. The reaction mixture was then left overnight at room temperature. The product obtained was filtered and washed with petroleum ether to remove unreacted compounds. The product crystallised from ethanol, yield 1.0 gm, m.p. 220°(d) (Found ; C, 68.68 H, 6.55 N, 7.39 ; $C_{21}H_{24}N_2O_4$; required ; C, 68.50 H, 6.52 N, 7.61 %).

3-Carbethoxy-4-(N-piperidyl)-5,9-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (21) :

2,6-Dimethyl-3-formyl-4-hydroxyquinoline (1.2 g) was dissolved in pyridine (10 ml) and was refluxed with diethylmalonate (1.0 ml) in the presence of few drops of

piperidine on steambath for 2 hrs. The reaction mixture was then left overnight at room temperature. The product obtained was filtered and washed with petroleum ether to remove unreacted compounds. The product crystallised from ethanol, yield 1.2 gm, m.p. 242° . (Found ; C, 69.21 H, 6.62 N, 7.80 ; $C_{22}H_{26}N_2O_4$; required ; C, 69.10 H, 6.80 N, 7.33 %).

3-Carbethoxy-4-(N-piperidyl)-5,7-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (22) :

2,8-Dimethyl-3-formyl-4-hydroxyquinoline (1.2 g) was dissolved in pyridine (10 ml) and was refluxed with diethylmalonate (1.0 ml) in the presence of few drops of piperidine on steambath for 2 hrs. The reaction mixture was then left overnight at room temperature. The product obtained was filtered and washed with petroleum ether to remove unreacted compounds. The product crystallised from ethanol, yield 1.0 gm, m.p. 213°. (Found ; C, 68.96 H, 6.75 N, 7.45 ; $C_{20}H_{26}N_2O_4$; required C, 69.10 H, 6.80 N, 7.33 %).

3-Carbethoxy-4-(N-piperidyl)-5-methyl-9-methoxy-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (23) :

2-Methyl-3-formyl-4-hydroxy-6-methoxyquinoline was (1.5 g) was dissolved in pyridine (10 ml) and was refluxed with diethylmalonate (1.0 ml) in the presence of few drops of piperidine on steambath for 2 hrs. The reaction mixture

was then left overnight at room temperature. The product obtained was filtered and washed with petroleum ether to remove unreacted compounds. The product crystallised from ethanol, yield 0.8 gm, m.p. 231°(d). (Found ; C, 66.87 H, 6.32 N, 7.19 ; $C_{22}H_{26}N_2O_5$; required ; C, 66.33 H, 6.53 N, 7.03 %).

3-Carbethoxy-4-(N-piperidyl)-5-methyl-9-ethoxy-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (24) :

2-Methyl-3-formyl-4-hydroxy-6-ethoxy quinoline (1.7 g) was dissolved in pyridine (10 ml) and was refluxed diethylmalonate (1.0 ml) in the presence of few drops of piperidine on steambath for 2 hrs. The reaction mixture was then left overnight at room temperature. The product obtained was filtered and washed with petroleum ether to remove unreacted compounds. The product crystallised from ethanol, yield 1.2 gm, m.p. 188°(d). (Found ; C, 67.19 H, 6.46 N, 7.54 ; $C_{23}H_{28}N_2O_5$; required ; C, 67.00 H, 6.80 N, 6.80 %).

3-Acetyl-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (25) :

2-Methyl-3-formyl-4-hydroxy-quinoline (1.0 g), pyridine (10 ml), ethylacetoacetate (1.0 ml) and few drops of piperidine were mixed and refluxed on steambath for 3 hrs. The reaction mixture was left overnight at room temperature

and product obtained was filtered and washed with petroleum ether to remove unreacted compounds. It was crystallised from ethanol, yield 1.0 gm, m.p. 192°(d). (Found ;, C, 71.37 H, 6.27 N, 8.21 ; $C_{20}H_{22}N_2O_3$; required ; C, 71.00 H, 6.51 N, 8.28 %).

3-Acetyl-4-(N-piperidyl)-5,9-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (26) :

2,6-Dimethyl-3-formyl-4-hydroxyquinoline (1.2 g), pyridine (10 ml) ethylacetoacetate (1.0 ml) and few drops of piperidine were mixed and refluxed on steambath for 3 hrs. The reaction mixture kept overnight at room temperature and obtained product was filtered, washed with petroleum ether to remove unreacted compounds. It was crystallised from ethanol, yield 0.85 gm, m.p. 220°(d). (Found ; C, 72.08 H, 6.43 N, 8.00 ; $C_{21}H_{24}N_2O_3$; required ; C, 71.60 H, 6.82 N, 8.07 %).

3-Acetyl-4-(N-piperidyl)-5-methyl-9-methoxy-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (27) :

A mixture of 2-methyl-3-formyl-4-hydroxy-6-methoxy-quinoline, (1.7 gm) ethylacetoacetate (1.0 ml), few drops of piperidine and pyridine (10 ml) was refluxed on steambath for 3 hrs. The reaction mixture was left overnight at room temperature and obtained product was filtered, washed with petroleum ether to remove unchanged compounds. It was crystallised from ethanol, yield 1.0 gm, m.p. 216°(d). (Found ; C, 68.28

H, 6.20 N, 7.50 ; $C_{21}H_{24}N_2O_4$; required ; C, 68.50 H, 6.52 N, 7.61 %).

3-Cyano-4-(N-piperidyl)-5-methyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (27) :

A mixture of 2-methyl-3-formyl-4-hydroxyquinoline (1.0 g), ethylcynoacetate (1.0 ml), few drops of piperidine and pyridine (10 ml) was refluxed on steambath for 2 hrs. It was then kept overnight at room temperature. Obtained product was filtered and washed with petroleum ether to remove unreacted compounds. It was crystallised from acetone-petroleum ether (1:2) mixture, yield 0.3 gm, m.p. 156°(d). (Found ; C, 70.52 H, 6.01 N, 12.58 ; $C_{19}H_{19}N_3O_2$; required ; C, 71.02 H, 5.92 N, 13.08 %).

3-Cyano-4-(N-piperidyl)-5,9-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (28) :

2,6-Dimethyl-3-formyl-4-hydroxyquinoline (1.2 g) was dissolved in pyridine (10 ml) and ethylcyanoacetate (1.0 ml) and few drops of piperidine were added and was refluxed on steambath for 2 hrs. It was left overnight at room temperature. The obtained product was filtered and washed with petroleum ether to remove unreacted compounds. It was crystallised from ethanol, yield 0.5 gm, m.p. 278°(d). (Found ; C, 71.99 H, 6.69 N, 12.05 ; $C_{20}H_{21}N_3O_2$; required ; C, 71.65 H, 6.27 N, 12.54 %).

3-Cyano-4-(N-piperidyl)-5,7-dimethyl-3,4-dihydro-2-oxo-2 H-pyrano (3,2-c)quinoline (29) :

A mixture of 2,8-dimethyl-3-formyl-4-hydroxyquinoline (1.2 g), ethylcyanoacetate (1.0 ml) and few drops of piperidine - pyridine (10 ml) was refluxed on steambath for 2 hrs. The reaction mixture was left overnight at room temperature. The obtained product was filtered and washed with petroleum ether to remove unreacted compounds. It was crystallised from ethanol, yield 0.75 gm, m.p. 178°(d). (Found ; C, 71.77 H, 6.50 N, 12.22 ; $C_{20}H_{21}N_3O_2$; required ; C, 71.65 H, 6.27 N, 12.54 %).

References :

1. Yasuiko Asahina and Mototaro Inubuse; Ber., 65 B, 61-3, 1932. C.A. 26, 2196, 1932.
2. B. Bobranski and L.Kochanska ; Roczniki Chem., 17, 30, 1937. C.A., 31, 3048, 1937.
3. H.Fielder, Arch.Pharm. 297(2), 108, 1964. C.A., 60, 10645, 1964.
4. K.Elliott and E.Tittensor ; J.Chem.Soc., 484, 1950, ibid, 2796, 1961.
5. Rodionor and Collaboraters, Ber, 59, 2952, 1926.
6. Verley ; Bull.Soc.Chim.France (3), 21, 414, 1899.
7. Doebner ; Ber., 33, 2141, 1900
8. Doebner ; Ber., 34, 54, 1901.
9. Doebner ; Ber., 35, 1137, 1902.
10. Doebner ; Ber., 35, 1147, 1902.
11. Doebner ; Ber., 35, 2137, 1902.
12. Hann and Lapworth ; J.Chem.Soc., 85, 46, 1904.
13. Hope and Robinson ; J.Chem.Soc., 99, 2117, 1911.
14. G.Charles ; Bull.Soc.Chem., France, 8-9, 1559, 1963.

CHAPTER - II

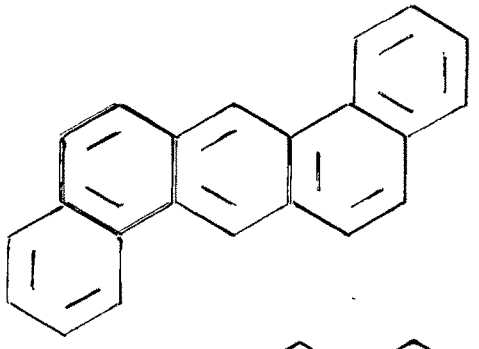
Synthesis of Nitrogen Mustards from Quinoline derivatives

CHAPTER - II

Synthesis of Nitrogen Mustards from Quinoline derivatives :

Since the great plagues of the middle Ages, no disease has spread so much alarm and terroras has "Cancer" in our own time. The very name "Cancer" - "Canker" from the latin for "Crab" - sounds sinister and forbidding in most languages. It is not clear, why Hippocrates gave it that name of adopted the term from popular speech. Was it because of the appearance of many breast cancers which send claws into the surrounding tissues like a Crab ? The nature of disease, of course, is such as to rouse fear and anxiety to the common people and also it is widespread belief that the disease, cancer, is heriditary. It is also observed that cancer is moving remorselessly into second place in the list of fatal diseases and in civilised countries is barely exceeded by Cardiovascular diseases. Of every hundred persons now living, at least twenty must count on dying of cancer, and among those over forty five the figure is one in three. It will be more interesting to note biological nature of the cancercell. It is learnt that the cancercell has a number of properties which are biologically different from most cells of the host. The most unusual property of all, materials, is the escape of cancer cells from the original locus of the tumor

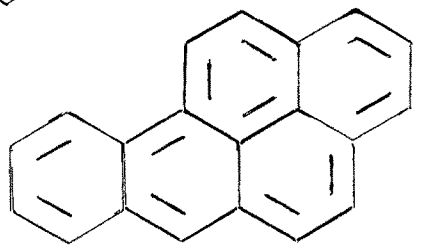
and passage via the blood or lymphatic tissues to another tissue or organ where the lesion lodges and grows into a secondary tumor mass. Another characteristic of tumor cell is resistance to conditions which would produce serious damage to other cells. For example, cells of the brain or heart die within minutes when exposed to an environment lacking in Oxygen or containing Cyanide. On other hand, the tumor cells have remained viable as long as three days in an environment containing cyanide and totally lacking in Oxygen[1]. One of the most important characteristic properties of tumor cells is their rapid growth, it is very much rapid with compare to that of other ordinary cells. It will be also interesting to know the cause of cancer. In 1915, Yamagiwa and Ichikava[2] in Japan, reported the successful production of epitheliomas in rabbits and other laboratory animals by repeated paintings with coal-tar. The successful production of neoplasms in laboratory animals spurred chemical studies on the nature of the carcinogens in coal-tar with the hope that a single agent might be found. Intensive efforts by a group of chemists resulted in the isolation of a group of carcinogens which are classified as "Polycyclic Hydrocarbons". These substances were obtained from coal-tar as well as by direct chemical synthesis. With the finding that the whole families of polycyclic hydrocarbons could produce neoplastic transformations[3,4,5,6,7,8,9,10].



(1)

1, 2, 5, 6- Dibenzo anthracene

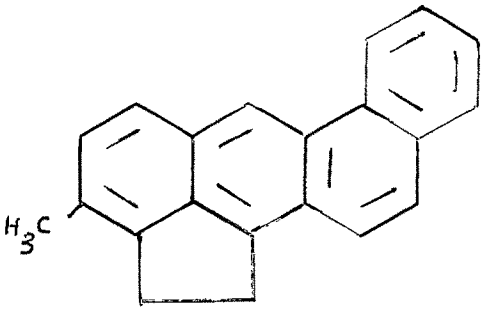
[First- Carcinogenic Hydrocarbon Synthesised.]



(2)

3, 4 - benzpyrene

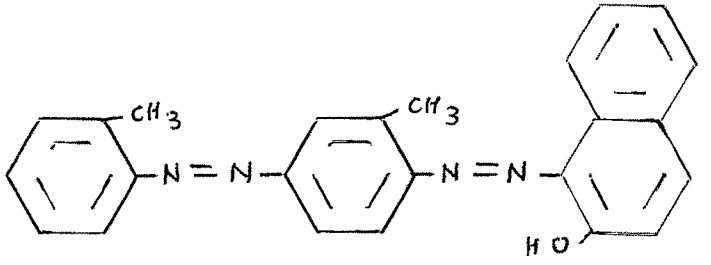
[Carcinogenic Hydrocarbon isolated from Coal - tar]



(3)

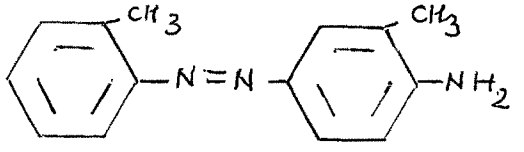
20 - methyl cholenthrene

[Most- powerful Carcinogen Synthesised]



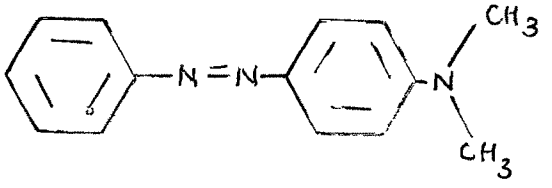
(4)

Scarlet- Red



(5)

Mouse Carcinogen



(6)

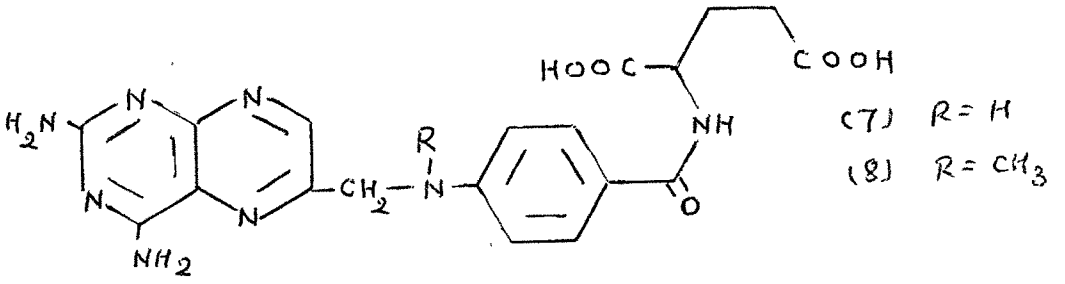
Butter yellow

Further evidence for this conclusion emerged from studies which showed that a variety of chemical compounds different in structure from the polycyclic hydrocarbons also, could produce neoplasia. Such compounds included the azodyes, organic amines and variety of other compounds including steroids, hormones, etc.[3,7,10,11,12,14,15,16,17,18,19,20].

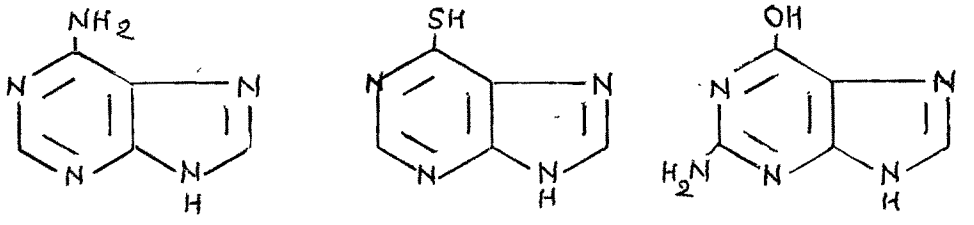
Interest in Hydrocarbon-carcinogenesis has been reawakened and stimulated in recent year by finding of carcinogens in "Cigarette-Smoke"[21,22,23]. The possible relations of inhalation of these substances to the development of Lung cancer has been extensively reviewed and it is not yet cleared whether cigarette-smoke is functioning as a primary carcinogen or as an irritant and promoting agent[24]. Along with these chemical carcinogens, there are some more factors causing the tumor growth, for example viruses. Viruses are closely connected with the cancer problem, but that is something with which we cannot deal until we know a little more about them.

The first successful attempt at cancer-chemotherapy is usually considered to be the introduction of Fowler's solution, potassium arsenite by Lissaur at the suggestion of Rosenerantz in 1865 for the treatment of Leukemia. Despite the annual synthesis of thousand of new compounds,

it is clear that at present time, curative chemotherapy for advanced cases of cancer does not exist. Some of the antitumour agents are known but they are temporarily effective rather than curative. None of the antitumour agents is totally selective against neoplastic cells. The biosynthesis of nucleic acids is a very rapid process in such tissues as the bone marrow, the skin, the mucosal linings of the various body cavities, the lymphoid tissues and the gastrointestinal tract. Agents producing inhibition of "growth" of course, produce inhibition of the growth of these tissues or at least inhibition of new cells production for replacement of superficial cells which are lost. The present antitumour agents are almost equally efficient in preventing new cell formation in non-tumour tissues as in preventing new cell formation in neoplastic tissues. Aminopterin (7) and methotrexate (8) have greatest usefullness in the treatment of Leukemia and also been utilized in therapy of Lymphosarcoma, reticulum cell sarcoma, malignant melanoma and sympathicoblastoma. 6-mercaptopurine (9) is a useful agent in the treatment of the lymphomas. The structure of this compound is very much identical with these of "adenine" and "guanine", the purine bases of DNA. Since these two compounds are essential to the structure of nucleic acids, it is logical that inhibition of their incorporation into nucleic acids might prevent further synthesis of the macromolecules and



(7) R = H
(8) R = CH_3



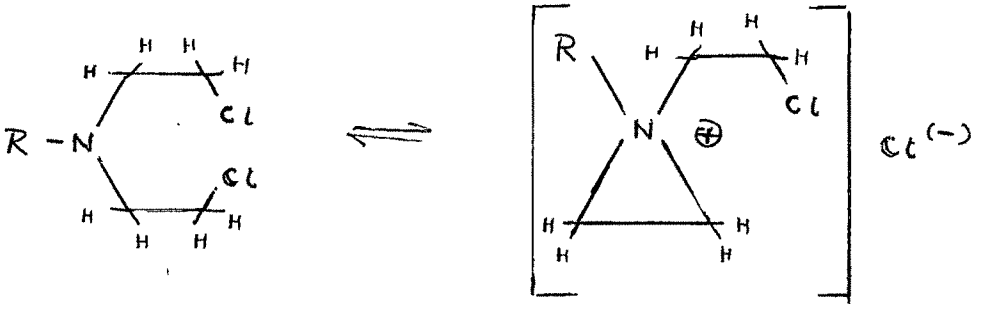
(10) Adenine

(9) 6-Mercapto purine

(11) Guanine

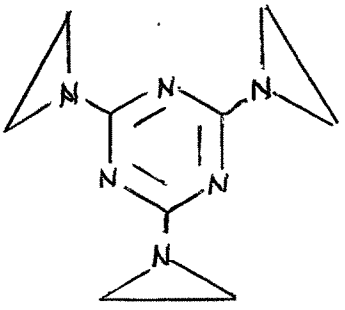
thereby interfere with further growth in rapidly growing tissues. But one drawback is there in adminstration of this 6-mercaptopurine (9) and that is its large toxicity. It is now possible, after long studies and observations, to synthesise new compounds which can directly effects on the function of nucleic acid of cancer cell. It has been learned that the effects of alkylating agents such as nitrogen mustards are much broader in cells than the effects of the other agents discussed. The use of the nitrogen mustards in cancer chemotherapy was not predicated on "rational" approaches to chemotherapy, but rather on the important pharmacological observation that mustards caused a lymphocytopenia and a concomitant diminution in the size of the lymph nodes[25,26]. The therapeutic effects of the mustards in clinical practice are limited to lymphomus

and a number of special neoplasms, such as bronchogenic carcinoma. It is observed that the systemic effect is selective destruction of activity proliferating cells, and this results in its usefulness in treating certain neoplastic diseases. It is said to give a response similar to that of x-ray, therefore, alkylating agent are known as "Radiomimetic" alkylating agents. The activity of β-chloroethylamines is thought to depend upon intramolecular rearrangement to form immonium ions. This takes place readily in alkaline medium. The immonium ion is very reactive[27].

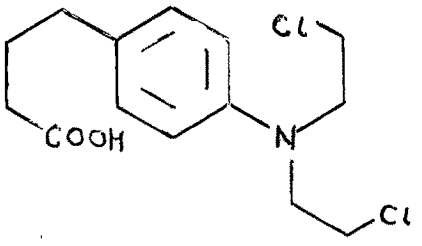


Due to very much similarity in chemical configuration to the active immonium ions, triethylene melamine (TEM) (13) has been studied considerably in the treatment of cancerous condition of the blood and the lymphatic system. It is one of the compounds used for nitrogen mustards therapy and it is employed for treating chronic lymphatic leukemia, Hodgkin's disease, lymphomus and bronchogenic carcinoma. TEM has the advantage over

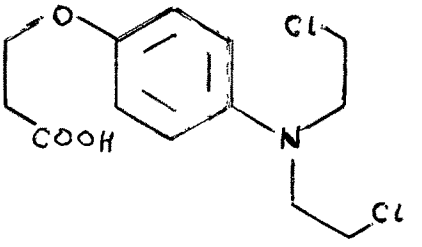
some other treatment in that it can be given by mouth and has few side effects. The maximal activities against Walker carcino-sarcoma 256 exhibited by Chlorambucil (14) and the isosteric phenoxypropionic acid analog (15) among a number of related compounds.



(13)



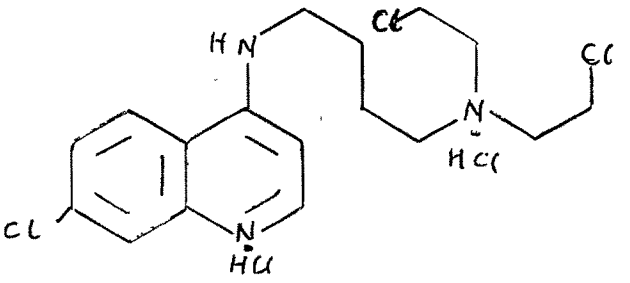
(14)



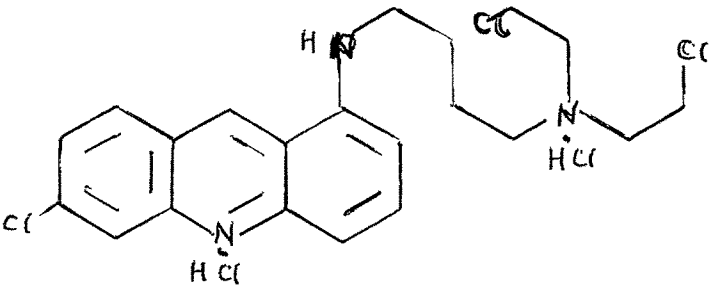
(15)

Interest in nitrogen mustards analogs of the heterocyclic antimalarial drugs stemed from the knowledge that chloroquine and quinacrine localize in cell nuclei. Terminal attachment of the mustard function to the side chain of the typical antimalarial drugs resulted, for example, in chloroquine (16) and quinacrine (17) nitrogen mustards which inhibited the growth of some animal tumors and leukemias and showed some evidence of clinical activity[28,29]. It is also observed that direct attachment of the mustards function to the quinoline ring, as in 7-chloro-4-bis-(2-chloroethyl)amino quinoline hydrochloride

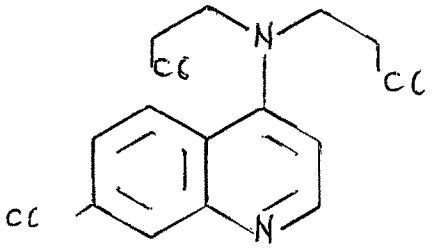
(16)



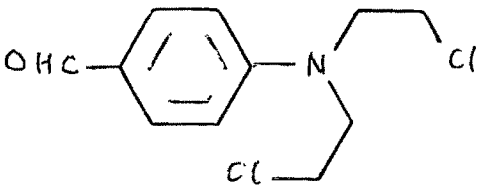
(17)



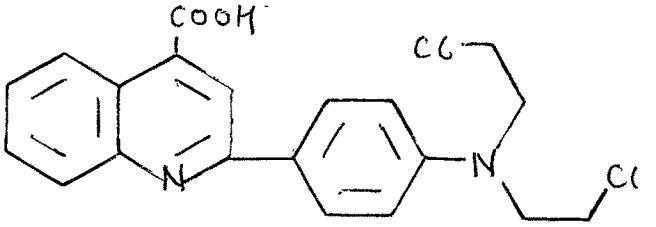
(18)



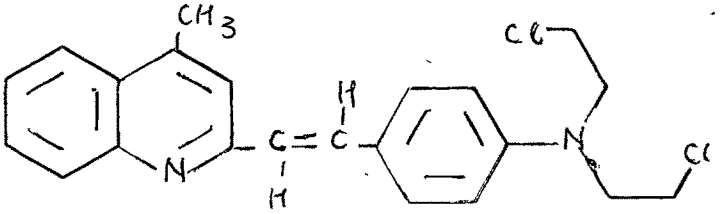
(19)



(20)

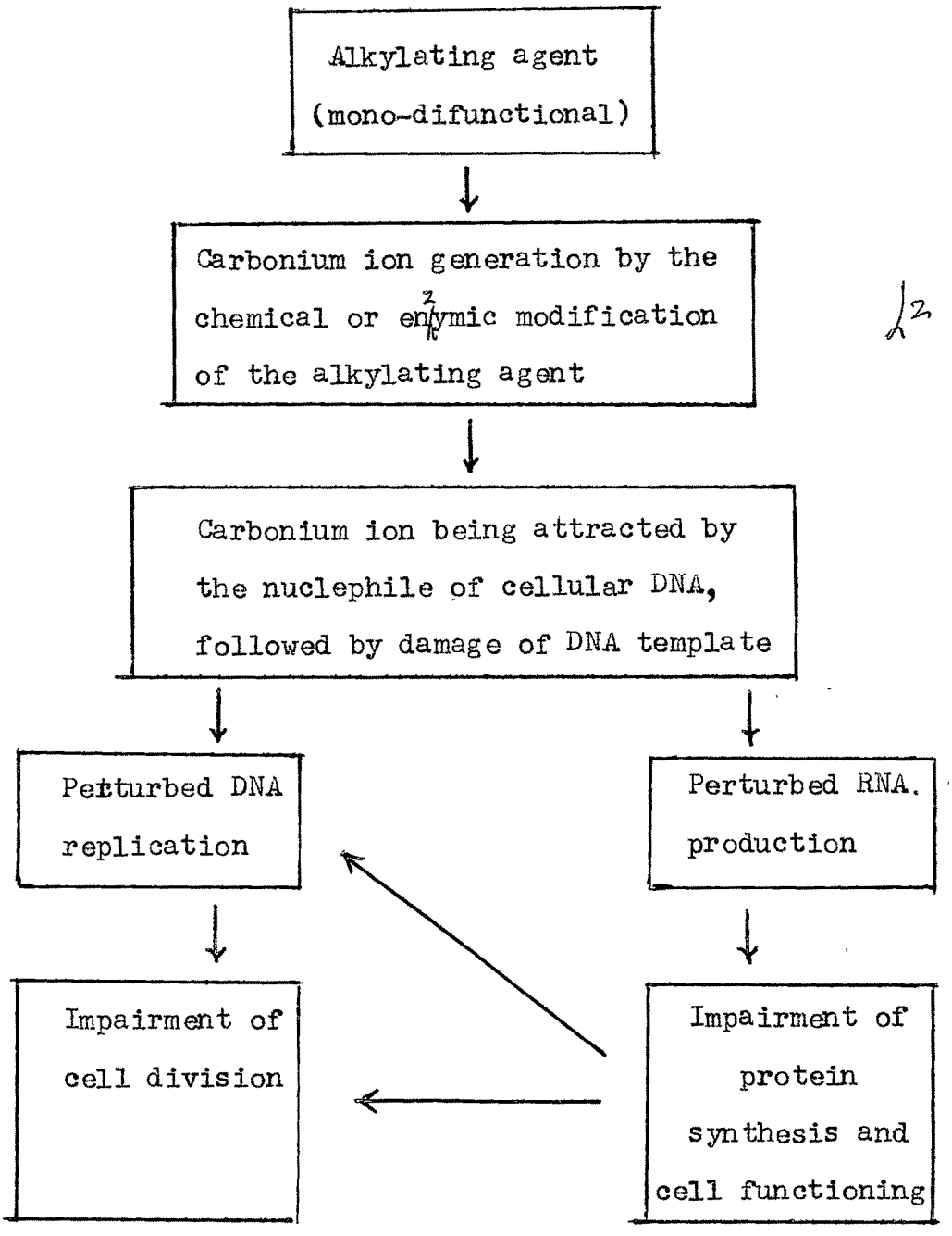


(21)

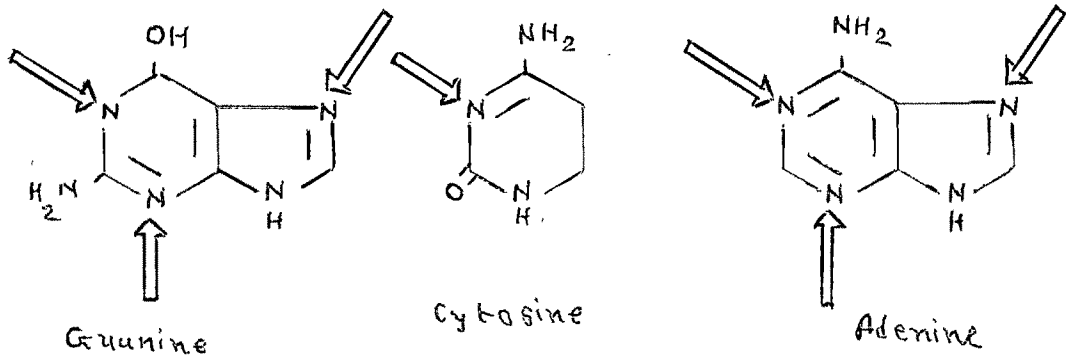


(18) led to inactivity. Nitrogen mustards derived from p-(N,N-Bis(2-chloroethyl)amino)benzaldehyde (19) as a synthetic potential anticancer agents have been described by Elderfield et al[30]. Considerable information were at hand for cinochophen (20), Elderfield thought that the cinchophen might act as a carried molecule to direct a mustards grouping to some effective locus of action. It was well known that, 2-p-(dimethylamino)styryl quinoline (21) is a good tumor growth inhibitor, and 4-p-(dimethylamino) styrylquinoline as good drug, Elderfield et al, synthesised new compound (21) by condensation of (19) with 2,4-dimethyl quinoline in the presence of catalyst such as acetic anhydride, zinc chloride and hydrochloric acid. Cinchophen hydrazide condensed with (19) in the refluxing ethanol gave p-(N,N-bis(2-chloroethyl)amino)benzylidene-cinchophen--hydrazide[31]. Preliminary reports of the p-(N,N-bis(2-chloroethyl)amino)-benzylidene hydrazide of p-aminobenzoic acid[32] have shown activity against the Dunning rate leukemia[33].

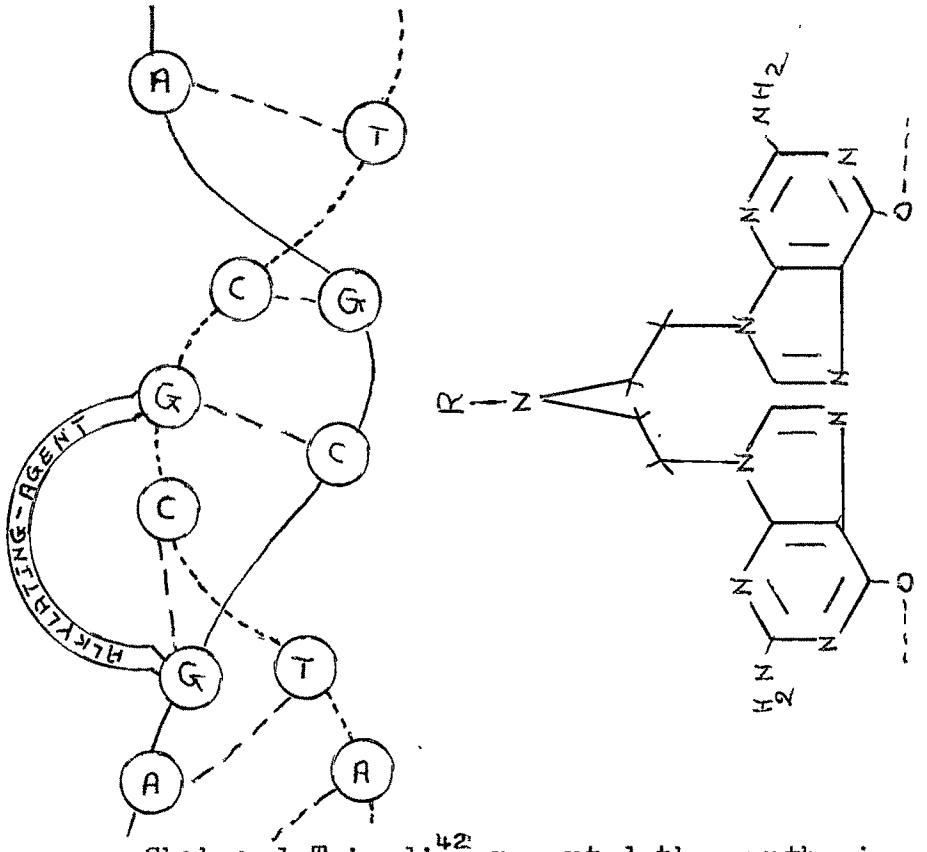
On reviewing literature it was found that biological alkylating agents have probably been more throughly studied than any other class of antitumour agents. Alkylating agents are directly interfering in the DNA system, either by a single substitution reaction on the base or on the phosphate residue or by difunctional substitution reaction to cause inter[34,35,36] or intra strand cross linkage ; as shown in schematic representation as follow :


Alkylating agent
(mono-difunctional)
Carbonium ion generation by the chemical or enzymic modification of the alkylating agent
Carbonium ion being attracted by the nuclephile of cellular DNA, followed by damage of DNA template
Perturbed DNA replication
Perturbed RNA. production
Impairment of cell division
Impairment of protein synthesis and cell functioning

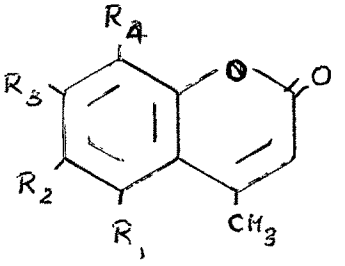
It is observed by various groups of workers that alkylation of purine, pyrimidine, guanine, adenine and cystosine moieties in DNA[37,38] on the reactive positions as shown in figure. The phosphate groups and several portion of the nucleotide bases can be alkylated[39,40].



The alkyl substitution lead to mispairing of the substituted base ((G=G) instead of (G=C)) in nucleic acid. Along with these some times the purine ring opens or the guanine residue excised (depurination) or such other results into a serious damage to the DNA molecules, including chain rupture. Polyfunctional alkylating agent[41] containing two or more than two alkylating groups are much more effective than monofunctional one. When such alkylating agent form a bridge linkage within a molecule is known as 'intrastrand' and bridge linkage between two molecules is known as 'interstrand', as shown in the following figure alkylating agents mispairing basic group in DNA molecule.



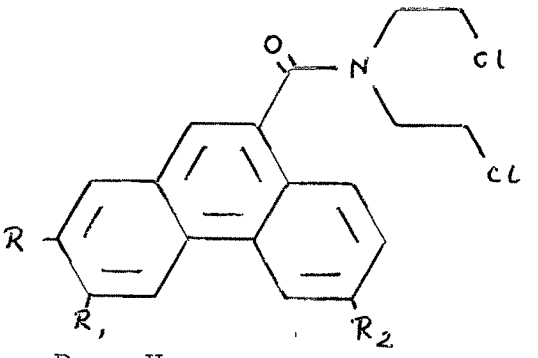
Shah and Trivedi[42] reported the synthesis of nitrogen mustards from coumarin derivatives ; by the condensation of 7-hydroxy-5-methyl coumarin with diethanolamine and para formaldehyde, followed by $SOCl_2$ treatment. On screen test against Rat Walker 256 Carcinosarcoma and P-388 tumour system, most of the nitrogen mustards showed activity. (22), (23) and (24) were active against P 388 tumour system but inactive against L-1210 tumour system. Also they[43] reported the synthesis of nitrogen mustards from 9-phenanthroyl chloride and 2,3,6-trimethoxy-9-phenanthroyl chloride by the condensation with N,N-bis (2-chloroethyl)amine. (25) and (26) were active against Rat Walker 256 carcinosarcoma.



(22) $R_1 = R_2 = R_4 = H$, $R_3 = -CH_2-N-(-CH_2-CH_2-Cl)_2$

(23) $R_1 = -O-CH_3$, $R_2 = R_4 = H$, $R_3 = -CH_2-N-(-CH_2-CH_2-Cl)_2$

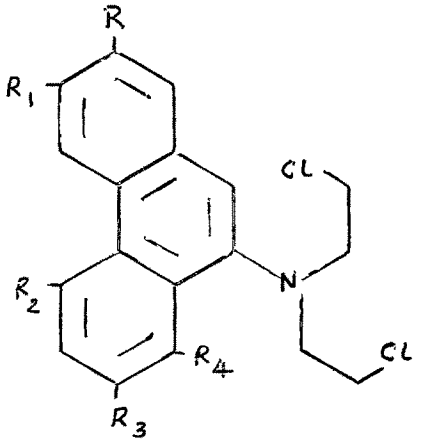
(24) $R_1 = R_2 = H$, $R_3 = -O-CH_3$, $R_4 = -CH_2-N-(-CH_2-CH_2-Cl)_2$



(25) $R = R_1 = R_2 = H$

(26) $R = R_1 = R_2 = -O-CH_3$

By condensing 9-chloromethyl phenanthrene derivative with diethanolamine, followed by $SOCl_2$ treatment, Shah and Trivedi[44] prepared nitrogen mustards. (27) and (28) were active against Rat Walker 256 carcinosarcoma, however, (29) found to toxic. Similarly they[45] synthesised nitrogen mustards from 4-bromo methyl-2-hydroxyquinoline derivatives. In continuation of our work, in the preparation of nitrogen mustards we report here the synthesis of some more nitrogen mustards from quinoline derivatives.

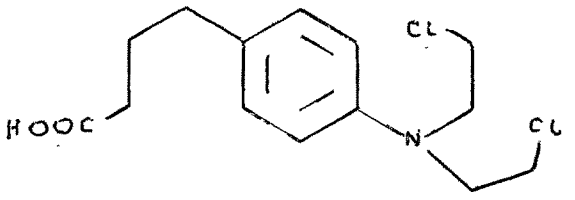


(27) $R = R_1 = R_2 = R_3 = R_4 = H$

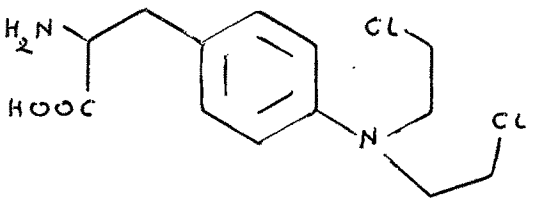
(28) $R = R_1 = R_3 = R_4 = H$, $R_2 = -O-CH_3$

(29) $R = R_1 = R_4 = H$, $R_2 = R_3 = -O-CH_3$

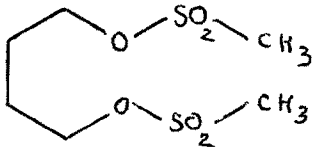
Following alkylating agents are used as antitumor agents.



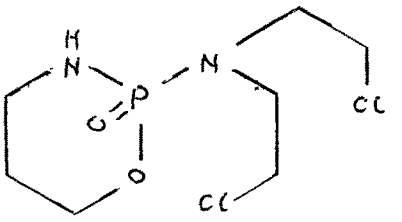
(30) Chlorambucil



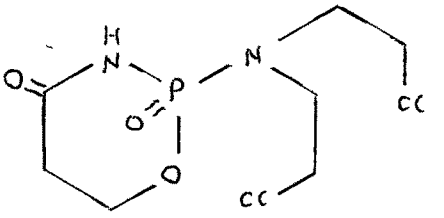
(31) Melphalan



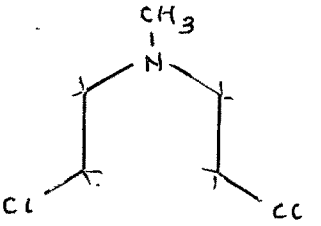
(32) Busulphan



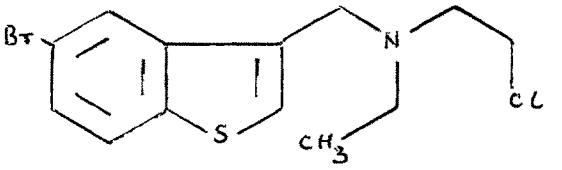
(33) Cyclophosphamide



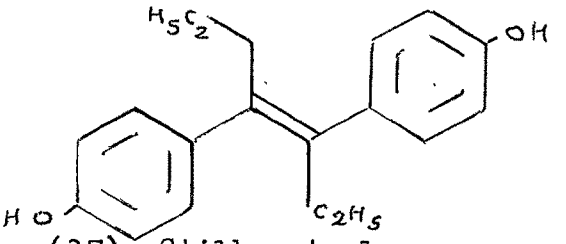
(34) 4-Ketocyclophosphamide



(35) Nitrogen mustards



(36) β-Benzo thiophene Hydrochloride



(37) Stilboestrol

References :-

1. O.Warburg ; Berlin, Springer, 1926.

2. K. Yamagiwa and K. Ichikawa ; J.Cancer Research, 3, 1-29, (1918).

3. G.M. Badger and L.E. Lewis ; Brit.J.Cancer 6, 270-292 1952.

4. N.P. Buu Hoi and P. Jacquingnon ; J.Chem.Soc., 513-515, 1954.

5. N.P. Buu-Hoi, R. Royer, M.Hubert-Habart and P.Mobille ; J.Chem.Soc., 3584-3587, 1953.

6. K.H. Harper ; Brit.J.Cancer 13, 732-745, 1959.

7. W.C. Huper ; Spring field, Illinols, Charles C. Thomas, 1942.

8. A. Lacassagne, N.P. Buu-Hoi, R. Daudel and F. Zajdela ; Advances in Cancer Research, 4, 315-369, 1956.

9. A. Pullman and B. Pullman ; Advances in Cancer Research 3, 117-170, 1955.

10. G. Wolf ; Cambridge, Massachusetts, Harvard Univ. Press, 1952.

11. M.K. Barrett ; J.Chronic Deseases, 8, 136-157, 1958.

12. J.W. Beard ; Physiol. Revs ; 28, 349-367, 1948.

13. B. Fischer ; Munch.med Woschscher, 53, 2041, 1906.

14. W.U. Gardner ; Can.Cancer Conf.2, 207-241, 1956.

15. A. Haddow ; Ann.Rev.Med., 6, 153-186, 1955.

16. I. Hieger ; London and New York, Academic Press, 1961.

17. J.A. Miller and E.C. Miller ; Advances in Cancer Research 1, 339-396, 1953.

18. M. Pages-Flon, N.P. Buu-Hoi and R. Daudel ; Compt. rend.acad.Sci., 236, 2182-2184, 1953.

19. G. Pincus and E.P. Vollmer ; New York, Academic Press ; 1960.

20. G. Rudali, N.P. Buu-Hoi and A. Lacassagne ; Compt. rend.acad.Sci., 236, 2020-2023, 1953.

21. G.R. Clemo and E.W. Miller ; Brit.J.Cancer., 14, 651-656, 1960.

22. A.I. Kosak ; Trans. N.Y. Acad.Sci.,18, 585-591, 1956.

23. E.L. Wynder ; Cancer Research, 21, 858-861, 1961.

24. P. Kotin and H.L. Falk ; Cancer., 13, 250-262, 1960.

25. A. Gilmon and F.S. Philips ; Science, 103, 409-415, 1949.

26. F.S. Philips ; Pharmacol.Revs. 2, 281-323, 1950.

27. J.F. Kerwin, et.al ; Science, 113, 315, 1951.

28. R. Jones Jr., U. Jonsson, M. Browning, H. Lessner, C.C. Rrice and A.K. Sen ; Ann.N.Y. Acad.Sci., 68, 1133, 1958.

29. H.J. Creech ; Ann.N.Y.Acad.Sci., 68, 868, 1958.

30. R.C. Elderfield, Irene S. Covery, Joyce B. Geiduschek, Walker L. Meyer, Alberta B. Ross and Joseph H. Ross ; J.Org.Chem., 23, 1749, 1958.

31. R.C. Elderfield et al ; J.Org.Chem., 23, 1749, 1958.

32. C.T. Bahner and R. Neely ; J.Org.Chem.,22, 1109, 1957.

33. M. Neeman ; J.Chem.Soc., 2525, 1955.

34. A. Loveless ; Nature 223, 206-207, 1969.

35. P.D. Lawley, D.J. Orr and S.A. Shah ; Chem.biol, Interact 4, 431-343, 1972.

36. R.C. Wilhelm and D.B. Ludlum ; Science, 153, 1403-1405, 1966.

37. D.B. Laudlum ; Biochim.biphys.Acta., 142, 282-284, 1967.

38. H.J. Rhase and E. Freese ; Biochim.biphys.Acta., 190, 418-433, 1969.

39. P.Geiduschek, Proc.nat.Acad.Sci., 47, 955, 1961.

40. K.W. Kohn, C.C. Spears and P. Boty ; J.Molec. Biol., 19, 266-288, 1966.

41. P. Hanawalt and R. Haynes ; Biochim.biophys. Commun., 19, 462-467, 1965.

42. D.O. Shah and K.N. Trivedi ; Indian J.Chem., 13(10), 1103-1105, 1975.

43. D.O. Shah and K.N. Trivedi ; Indian J.Chem.Soc., 55, 1079-1081, 1978.

44. D.O. Shah and K.N.Trivedi ; Indian J.Chem., 13, 1272-1274, 1975.

45. D.O.Shah and K.N. Trivedi ; Indian J.Chem., 15B, 286-287, 1977.