CHAPTER-III

Synthesis of 4,3'-methylene bis-(2,2'-dichloro-4'-methyl-quinoline) derivatives :

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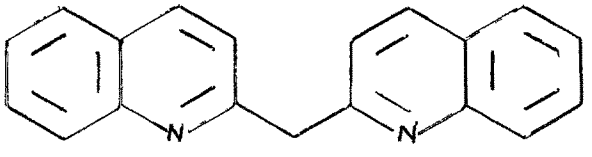
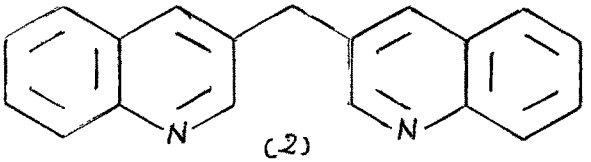
On reviewing the literature it was found that different methylene bis quinoline derivatives are having the point of attachments of quinoline nuclei either from the pyridine ring of the quinoline nucleus or from the benzene ring of the quinoline nucleus to the carbon atom of methane. 2,2'-methylene bis quinolines (1), 3,3'-methylene bis quinolines(2), 4,4'-methylene bis quinolines (3) and 2,4'-methylene bis quinolines (4) are reported in the literature, in which pyridine rings of quinoline nuclei linked through methylene bridge. Similarly, 5,5'-methylene bis quinolines(5), 6,6'-methylene bis quinolines (6), 7,7'-methylene bis quinolines(7) and 8,8'-methylene bis quinolines(8) are also known in the literature.



(I)



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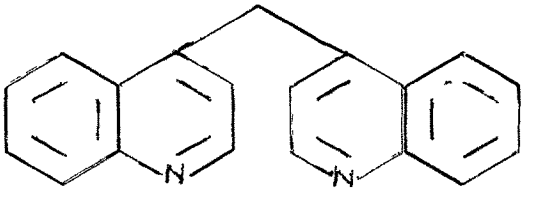

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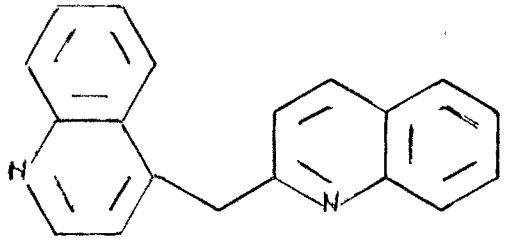

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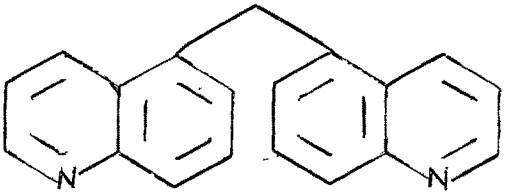

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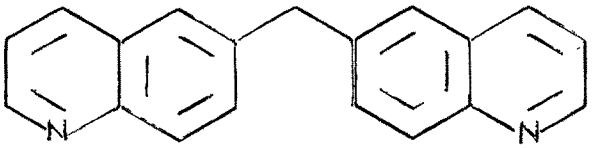

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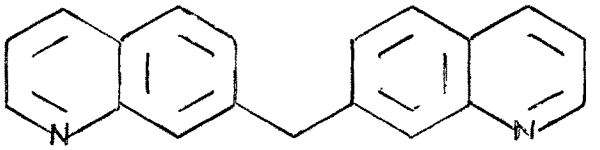

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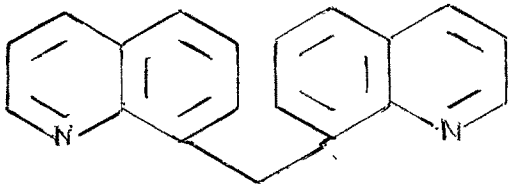
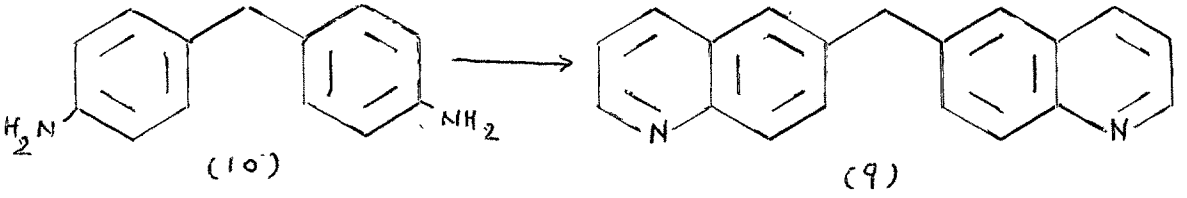


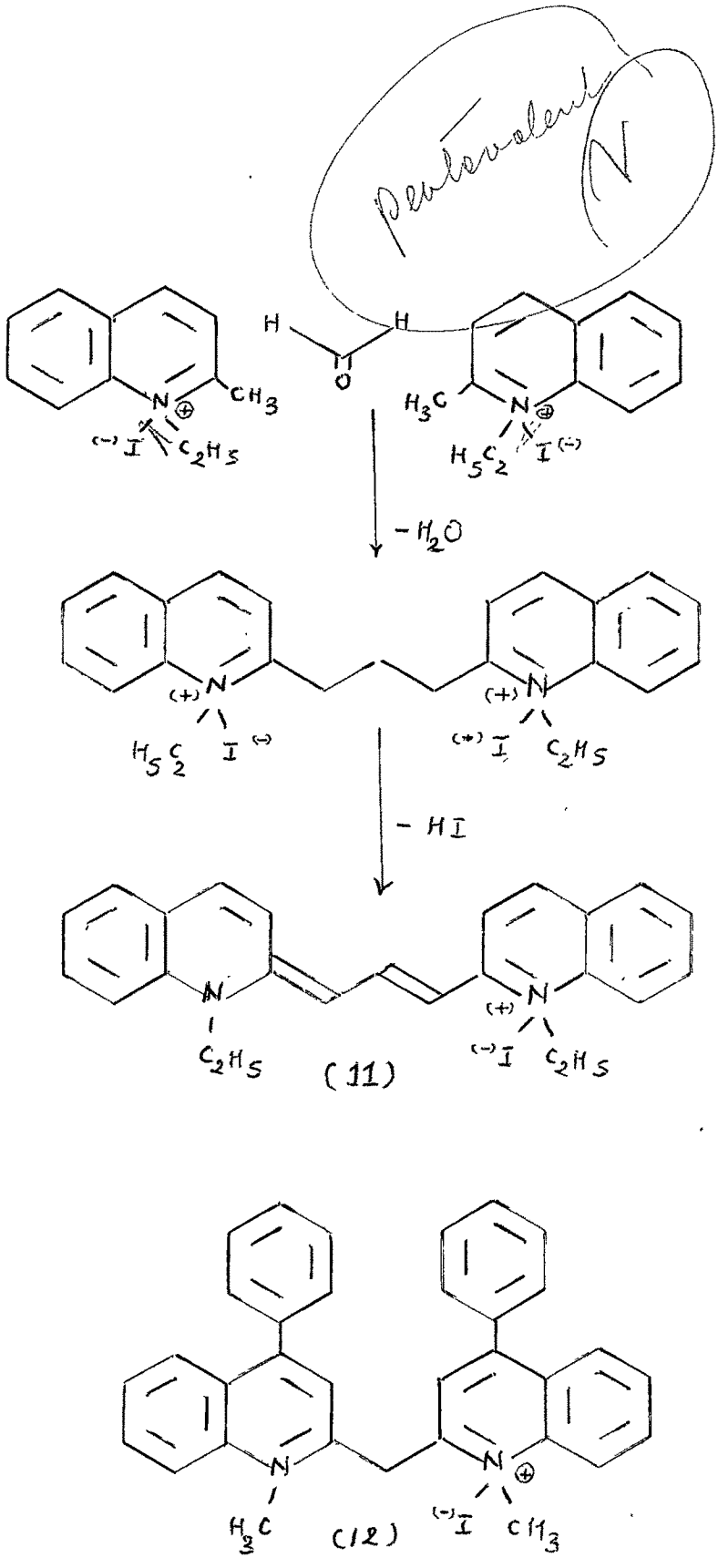
(8)

6,6'-Methylene bis quinoline (9) was synthesised by Borsche and Kienitz[1], by the Skraup synthesis on 4,4'-diamino-diphenyl methane (10).

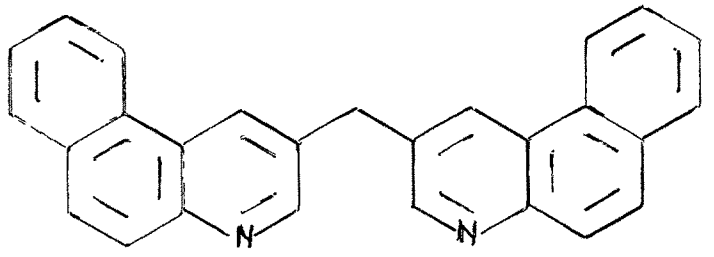


(10) (9)

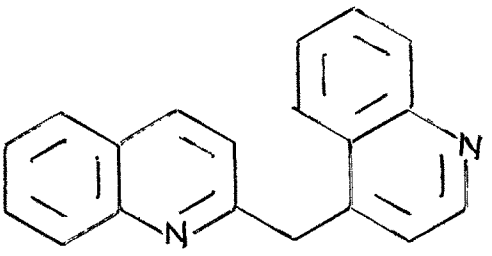
In course of the synthesis of photographic sensisters, Mills and Hammer[2] synthesised 2,2'-methylene bis (1-ethyl-quinaldine) type of compounds (11) by the action of formaldehyde and alkali on a hot alcoholic solution of quinoline ethiodic and quinaldine ethiodide. Fischer and Scheibe[3] prepared red coloured dye, 2,2'-methylene bis (4,4'-diphenyl quinoline) (12) by the action of air and CO_2 on 2-methyl-4-phenyl quinoline methiodide solution in alcohol. They proved that during the reaction one methyl group was eleminated and union of two nuclei took place through the remaining methylene group. 2,2'-methylene bis quinolines[4] were prepared by heating 2-chloro quinolines with 2-methyl quinolinesin a sealed tube at 200°. By heating 3-chloro-benzo(f)quinoline with 3-methyl-benzo(f) quinoline, Scheibe[5] obtained 3,3'-methylene bis benzo(f) quinoline (13) along with little tris quinoline methane (14).


Pentavalent N
H
H
O
CH3
N
(-) I
C2H5
H3C
N
H5C2
I (-)
- H2O
(+) N
H5C2
I (-)
(+) N
(+) I
C2H5
- HI
N
C2H5
(11)
(+) N
(-) I
C2H5
N
H3C
(12)
N
(-) I
CH3

2,4'-methylene bis(quinoline) (15) was prepared by heating 4-chloro quinoline with quinaldine at 300°. Schuller[6] prepared 5,5'-methylene bis (8-hydroxyquinoline) (16) by the treatment of 8-hydroxyquinoline with formaldehyde in concentrated sulphuric acid. Mehta and Patel[7] synthesised 3,3'-methylene bis (2-hydroxy-4-methyl quinoline) (17) by first condensing acetoacetanilide with sodium formaldehyde sulphoxylate followed by cyclisation using acetic anhydride and conc. sulphuric acid.



(13)



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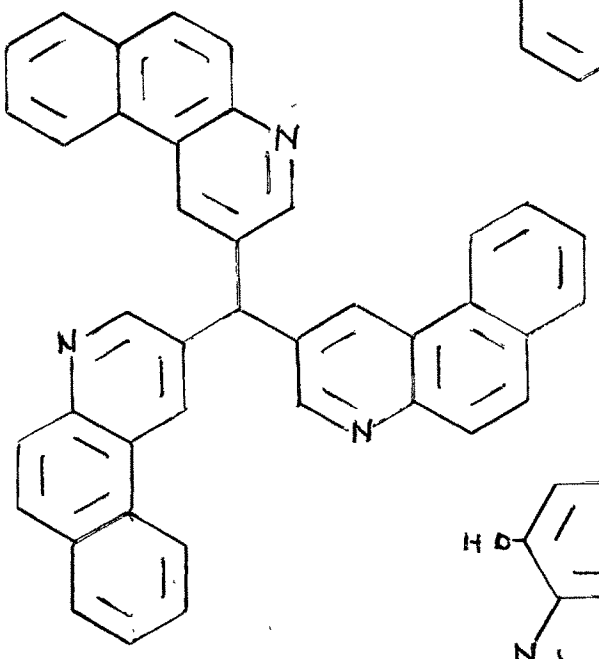
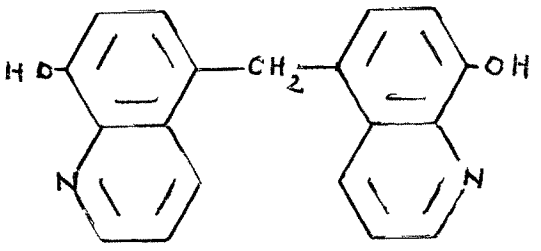
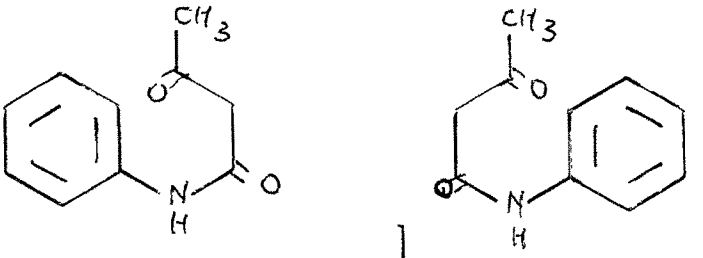


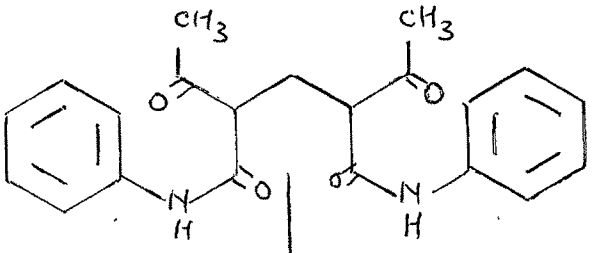
(14)

(16)



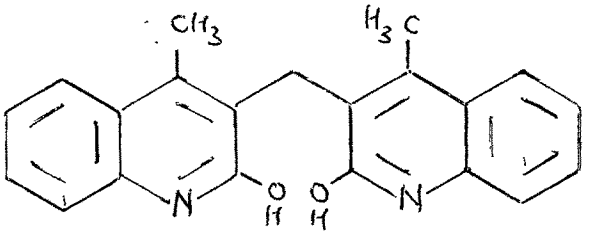


Sodium formaldehyde Sulphoxylate



(18)

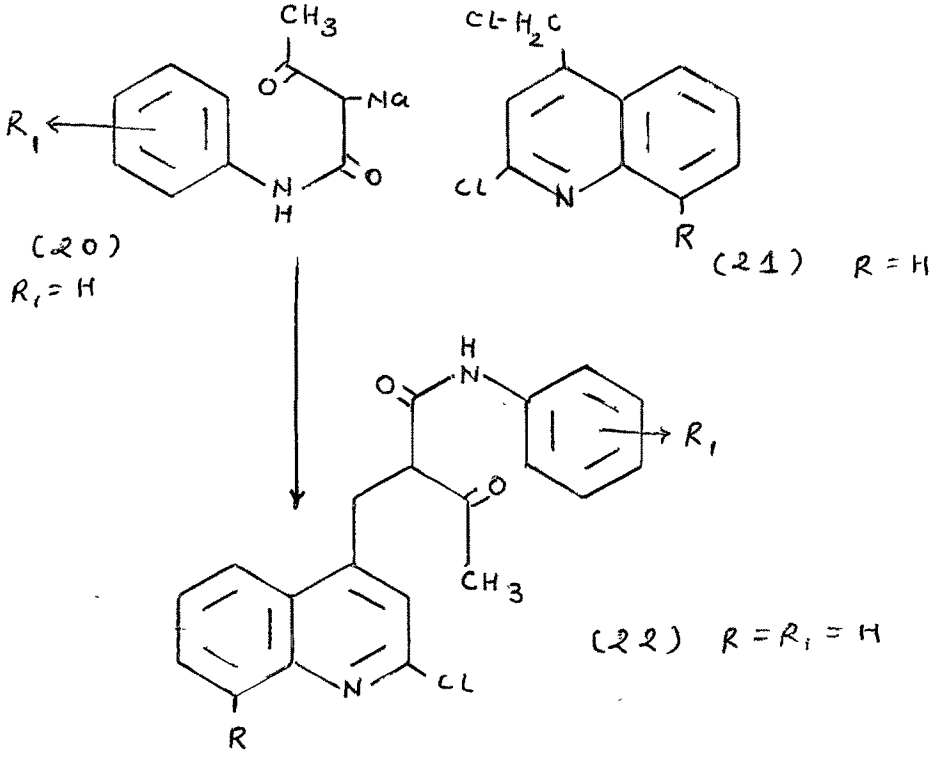
cyclization.

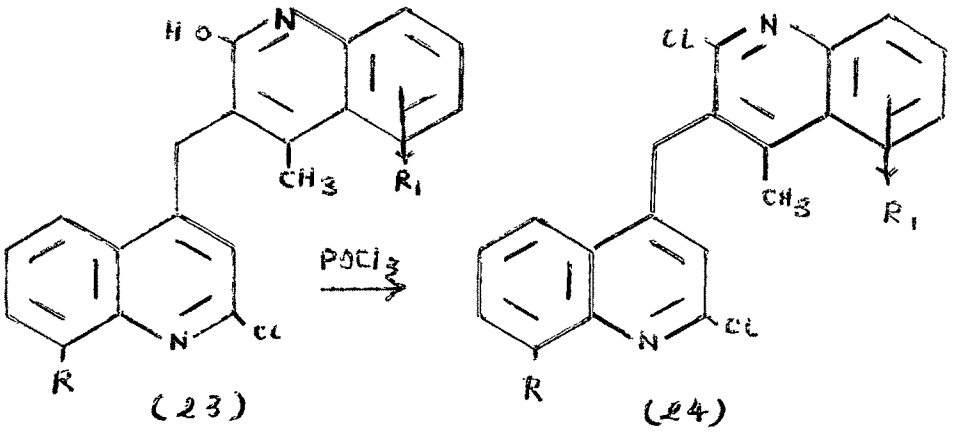


(17)

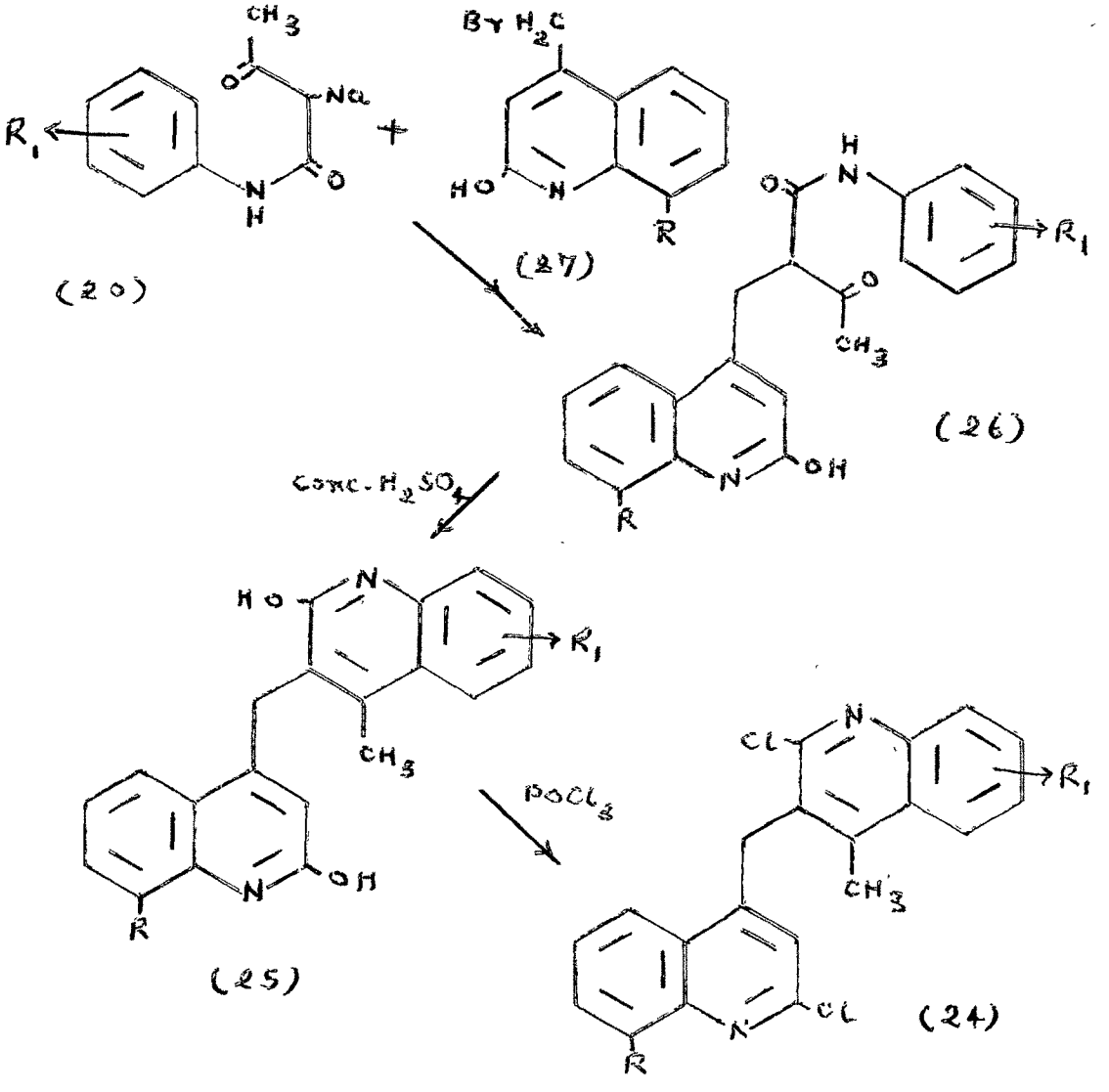
Thus, it was found, on reviewing the literature that the synthesis of 4,3'-methylene bis quinoline derivatives are not reported. In view of the antimalarial activity of the quinoline derivatives, it was thought of interest to synthesise substituted 4,3'-methylene bis quinoline derivatives having substitutents such as bromo, chloro, methoxy and ethoxy and methyl groups in the benzonoid part of quinoline ring system. Chudgar and Trivedi[8] reported that the bromination of acetoacetanilides gave the w-bromo derivatives which on cyclisation gave 4-bromomethyl carbostyril derivatives. These bromomethyl derivatives are used as starting material for the synthesis of different substituted 4,3'-methylene bis quinoline derivatives. 4-Bromomethyl carbostyril derivatives are condensed with substituted α-sodio acetoacetanilide derivatives in the presence of dimethyl sulphoxide to obtain the corresponding α-(2-hydroxy-4-quinonyl methyl) acetoacetanilide derivatives, (26). It has been observed that the condensation of 4-bromomethyl carbostyril and α-sodio acetoacetanilide did not occur in the absence of dimethyl sulphoxide. The α-(2-hydroxy-4-quinolylmethyl) acetoacetanilide derivatives, on cyclisation with conc. sulphuric acid gave 4,3'-methylene bis (2,2'-dihydroxy-4'-methyl quinoline)derivatives (25). The (25) when reacted with phosphorusoxychloride, gave 4,3'-methylene bis (2,2'-dichloro-4'-methyl quinoline) derivatives (24). The same

methylene bis quinoline derivatives were prepared by using 2-chloro-4-chloromethyl quinoline derivatives as starting materials. 4-Bromomethyl carbostyril derivatives were treated with phosphorusoxychloride, to obtain 2-chloro-4-chloromethyl quinoline derivatives, which when condensed with α-sodio acetoacetanilide derivatives in the presence of DMSO, gave α-(2-chloro-4-quinolyl methyl) acetoacetanilide derivatives (22), which were cyclised with conc. sulphuric acid to give 4,3'-methylene bis (2-chloro-2'-hydroxy-4'-methyl quinoline) derivatives, (23). On further treatment with phosphorusoxychloride, (23) gave 4,3'-methylene bis (2,2'-dichloro-4'-methyl quinoline) derivatives (24). The m.ps. and mixed m.ps. with the compounds described above were not depressed.



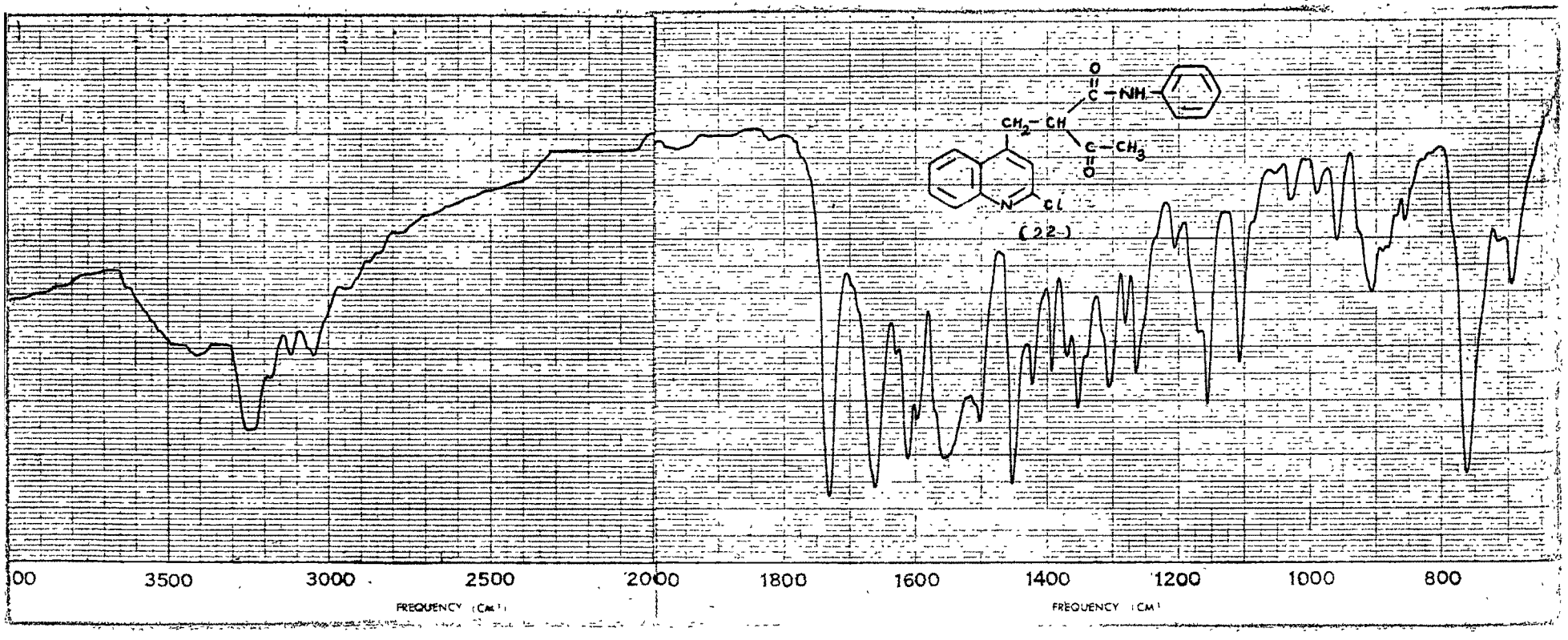

HO
N
CH3
R1
POCl3
Cl
N
CH3
R1
N
Cl
R
N
Cl
R

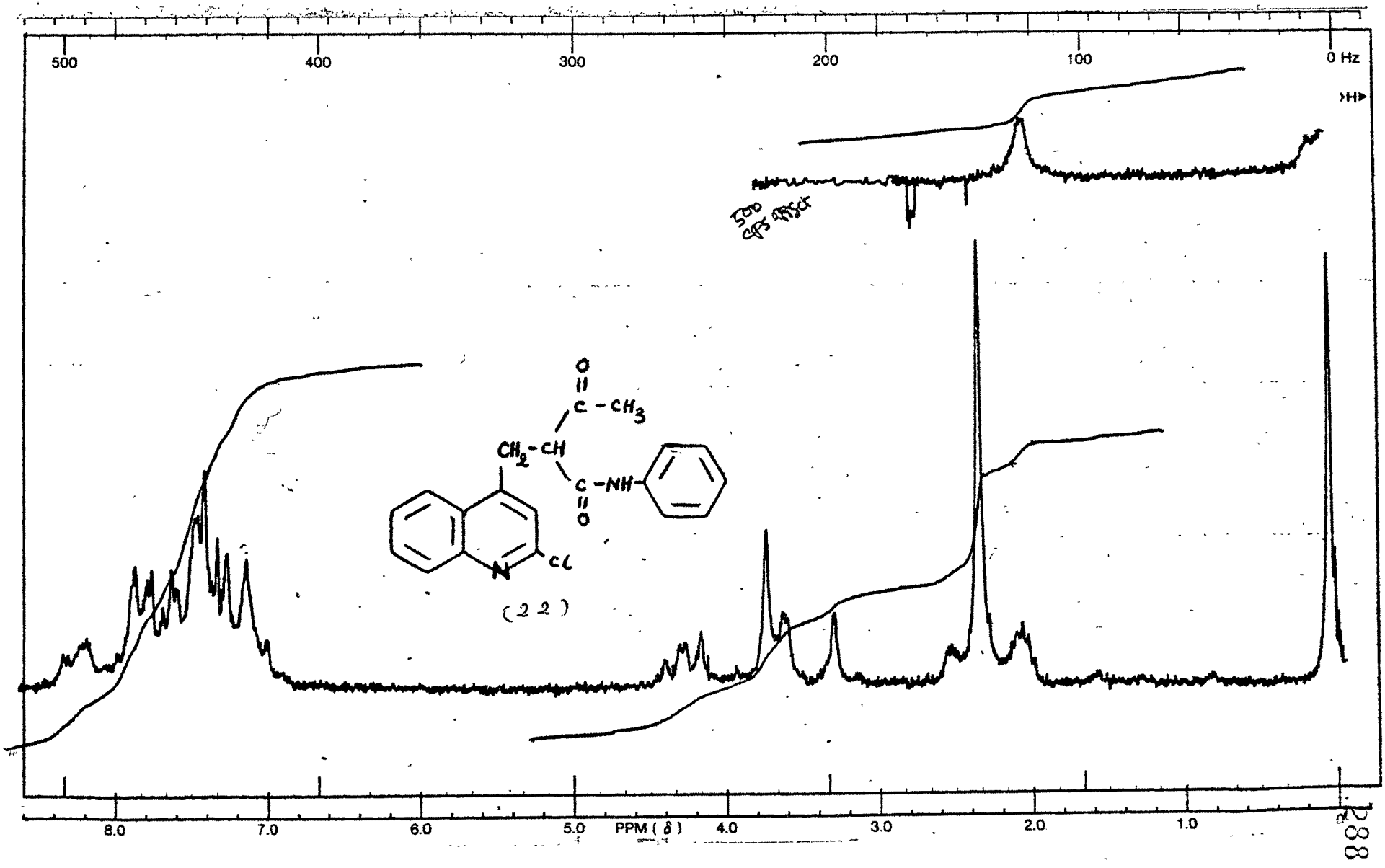
(23) (24)


CH3
O
NO
R1
N
H
O
BrH2C
HO
N
R
(27)
H
N
O
R1
O
CH3
OH
N
R
(26)
Conc. H2SO4
HO
N
R1
CH3
OH
N
R
POCl3
Cl
N
R1
CH3
Cl
N
R

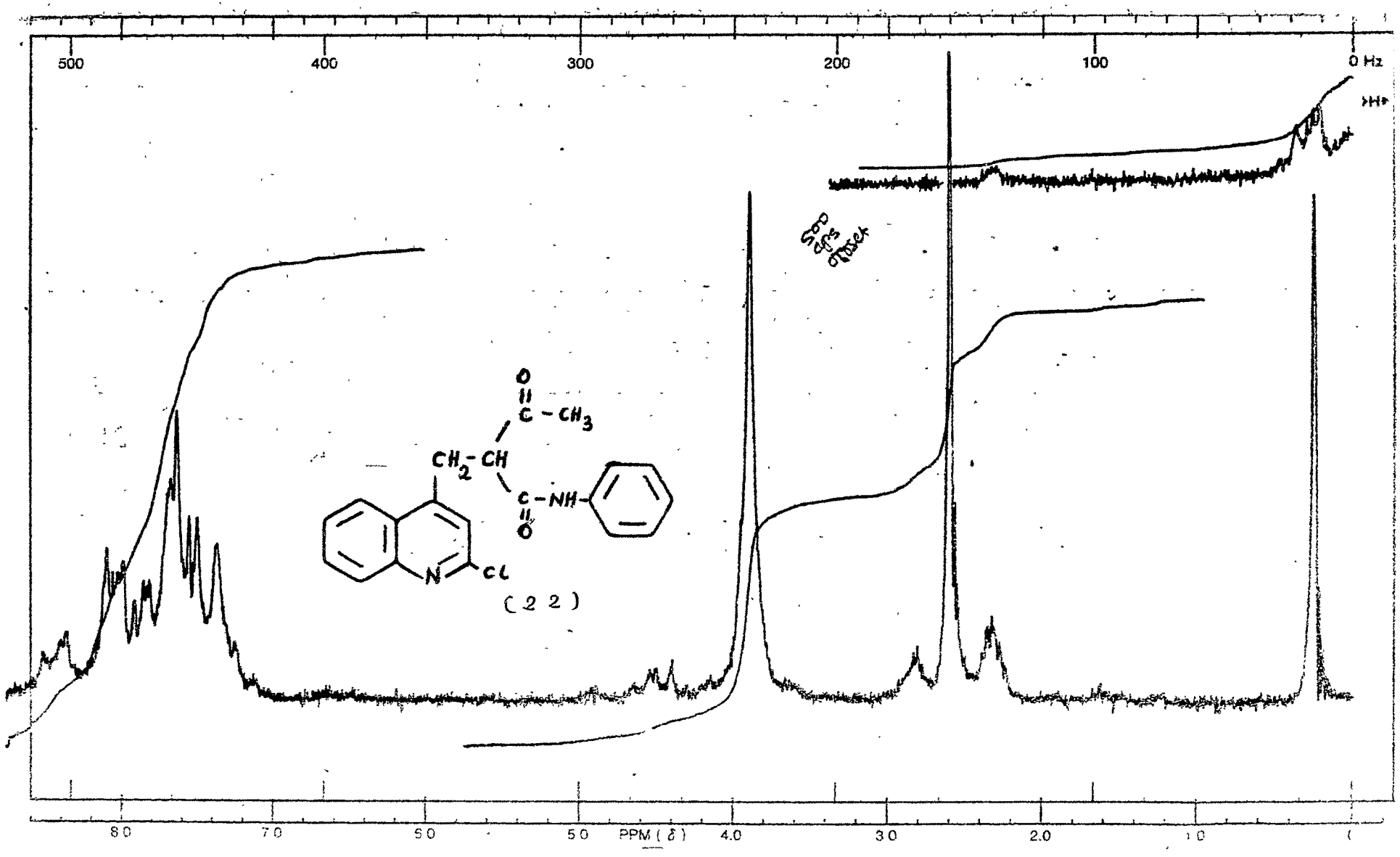
(20) (25) (24)

Thus α-sodium salt of acetoacetanilide(20) condensed with 4-chloromethyl-2-chloroquinoline (21) in dry benzene, in the presence of dimethyl sulphoxide gave α-(2-chloro-4-quinolylmethyl) acetoacetanilide (22). The structure of (22) was confirmed on the basis of IR and NMR spectra. IR (KBr) of (22) showed band at 3250 cm^{-1} for hydroxy group and at 1570 cm^{-1} for >C=O of enol, which suggested that the (22) exists in two forms, ketonic (27-A) and enolic (28) as tautomers. NMR (DMSO-acetone d_6) spectrum of (22) showed the signals at δ; 2.3, singlet, 3H, $-CH_3$ group $-CO-CH_3$; 3.25, singlet, 1H, -NH- group ; 3.65, doublet, J = 8Hz, 2H, $-CH-\underline{CH_2}-$ group ; 4.25, triplet, J = 8Hz, 1H, $-\underline{CH}-CH_2-$; 7.1 - 8.0, multiplet, 9H, aromatic and at 10.6, singlet, 1H, -OH of enolic form ; which slowly disappeared on D_2O exchange. The signal at δ; 3.25 also disappeared on D_2O exchange indication for -NH group. This confirmed that the mixture of Keto and enol forms are obtained during reaction. The lower value obtained for the methylene proton at δ; 3.65 is due to the additional deshielding effect of the carbonyl group as shown in figure (27-B). Also on the basis of integrated values of methyl, methylene and enolic protons, 20 % of enolic form (28) was found to be present. (22) was cyclised with conc. sulphuric acid to give 4,3'-methylene bis (2-chloro-2'-hydroxy-4'-methylequinoline) (23). The structure of (23) was confirmed on the basis of its analytical results and supported by its IR spectrum (KBr) which showed broad band


00
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY (CM⁻¹)
(22)

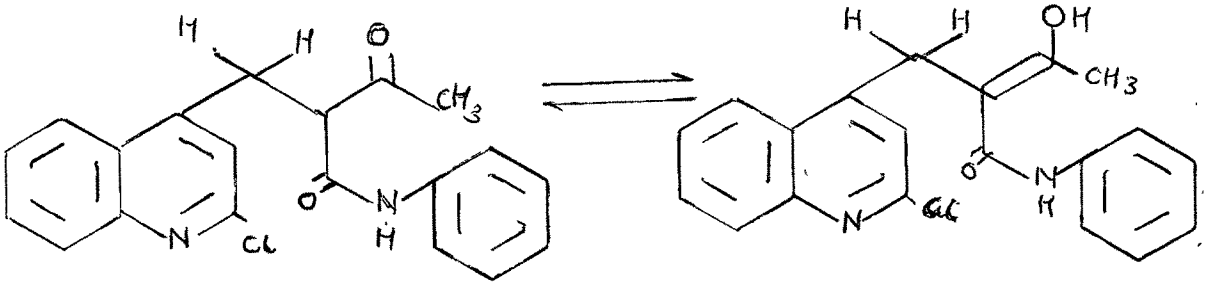


(22)


500
400
300
200
100
0 Hz
8.0
7.0
6.0
5.0
PPM (δ)
4.0
3.0
2.0
1.0
O
C - CH3
CH2 - CH
C - NH
O
N
Cl

(22)

D_2O - shake

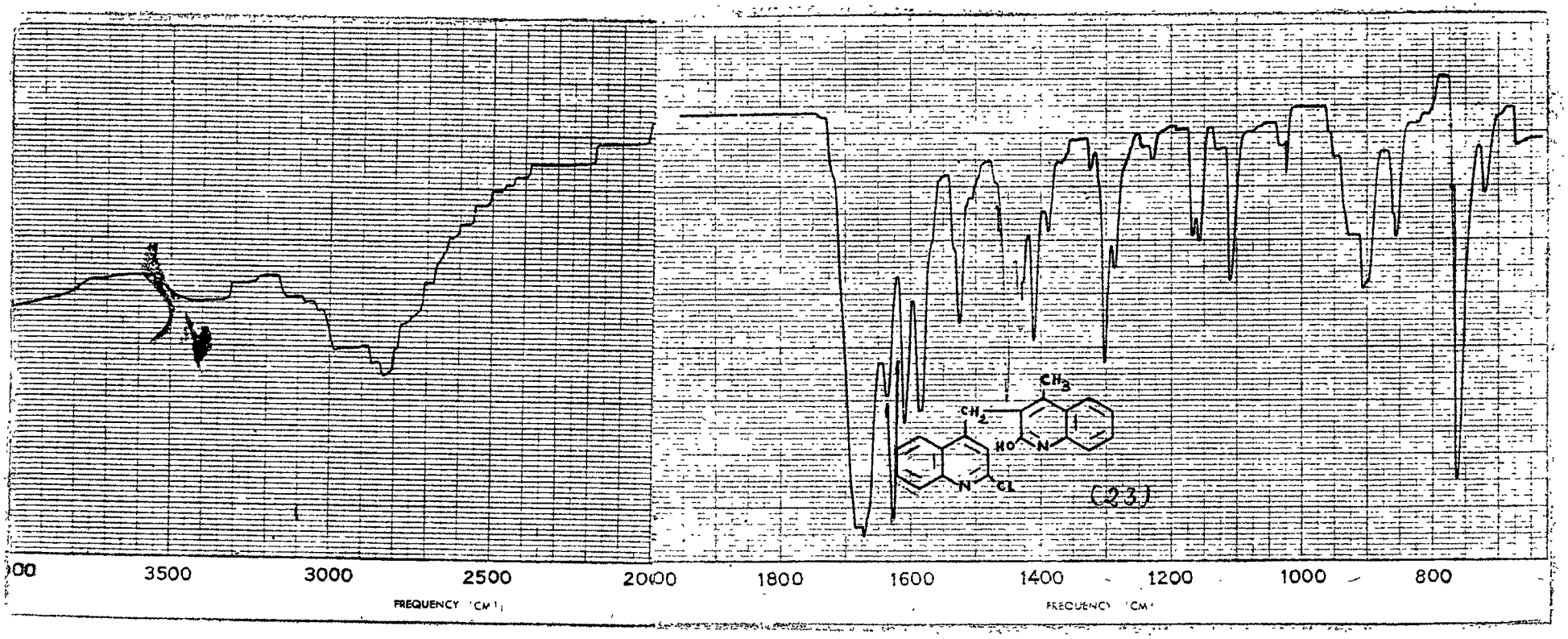


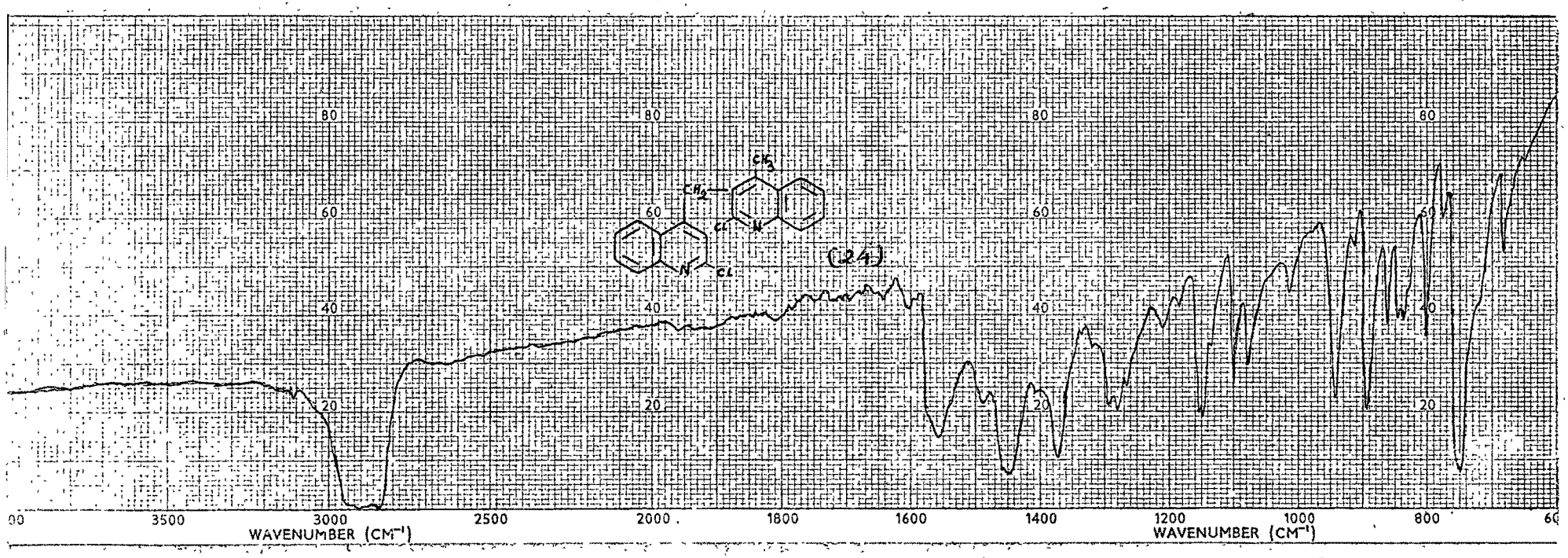
(27A)

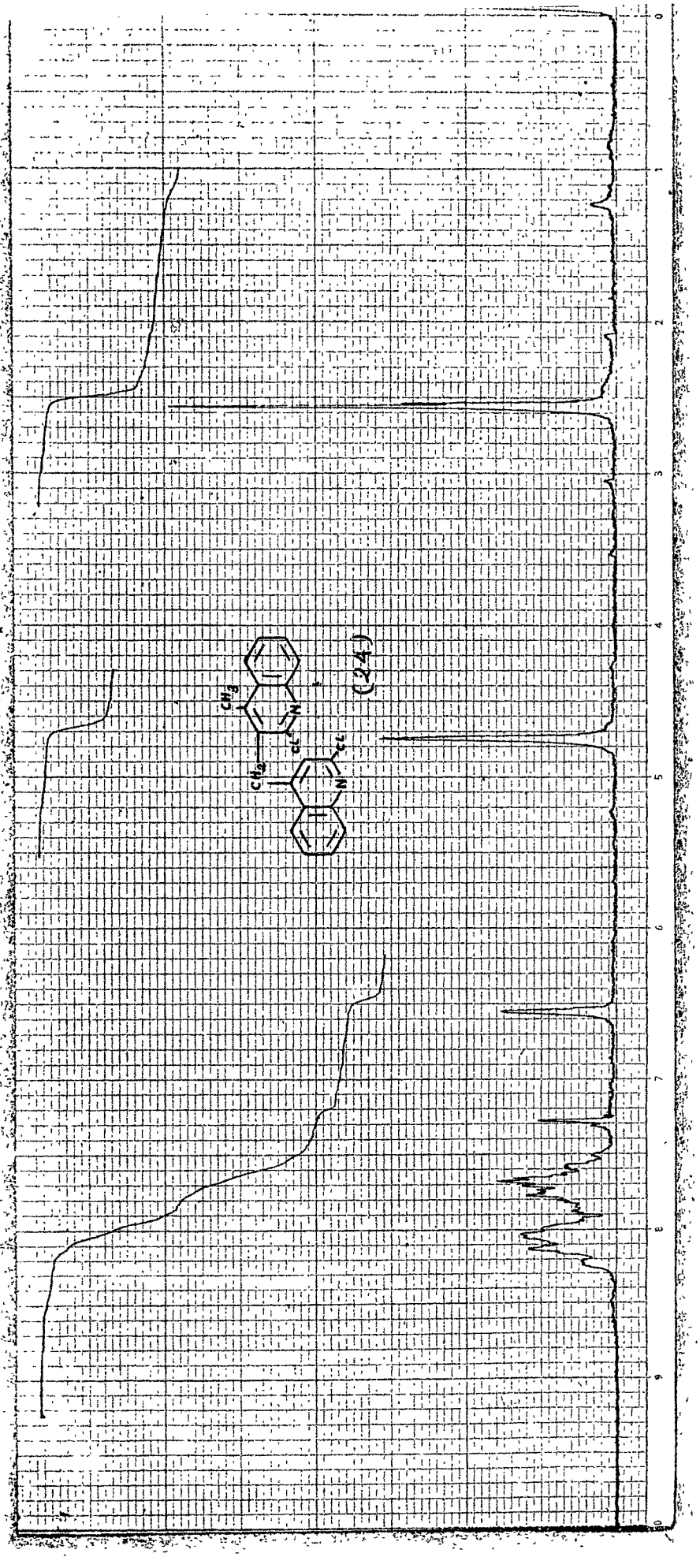
(28)

at 3400 cm^{-1} for OH group and at 760 cm^{-1} for C-Cl group. (23) was reacted with phosphorusoxychloride to give 4,3'-methylene bis (2,2'-dichloro-4'-methylquinoline) (24). The structure of (24) was confirmed by its NMR spectrum ($CDCl_3$) which showed signals at δ; 2.6, singlet, 3H, $-CH_3$ group at C_4' ; 4.8, singlet, 2H, $-CH_2$ group ; 6.6, singlet, 1H, aromatic and 7.3 - 8.2, multiplet, 8H, aromatic. The same compound (24) was obtained by another route also. Thus α-sodium salt of acetoacetanilide (20) condensed with 4-bromomethyl-2-hydroxyquinoline (27) in dry benzene in the presence of DMSO, gave α-(2-hydroxy-4-quinolyl methyl) acetoacetanilide (26), which was cyclised with sulphuric acid and followed by phosphorusoxychloride treatment, gave 4,3'-methylene bis (2,2'-dichloro-4'-methyl quinoline) (24). M.ps. and mixed m.p. were identical.

Similarly 4,3'-methylene bis (2,2'-dichloro-4', 8',8-trimethyl quinoline) (47), 4,3'-methylene bis


3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY (CM⁻¹)
CH3
CH2
HO
N
CL
N
(23)


(24)
80
60
40
20
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)


(24)

(2,2'-dichloro-4',8'-dimethylquinoline) (45), 4,3'-methyl bis (2,2'-7'-trichloro-4'-methyl quinoline) (46) and 4,3'-methylene bis (2,2'-dichloro-4'-methyl-benzo(h') quinoline) (48) were synthesised.

EXPERIMENTAL

General Method for Synthesis of 4,3'-Methylene-bis (2,2'-dichloro-4'-methyl quinoline) derivatives :

Synthesis of 2-chloro-4-chloromethyl quinoline derivatives:

A mixture of 2-hydroxy-4-bromomethyl quinoline derivative (0.02 M) and phosphorusoxychloride (0.1 M) was heated in an oil-bath at 110-120° for 2 hrs. The reaction mixture poured over crushed ice with stirring and the separated product were filtered and crystallised from benzene-petroleum ether mixture. Yield about 3-4 gm.

Synthesis of α-(2-chloro-4-quinolylmethyl)acetoacetanilide derivatives :

Acetoacetanilide derivative (0.01 M) was refluxed with pulverised sodium (0.01 M) in dry benzene at water-bath temperature for 6 hr. 2-chloro-4-chloro methyl quinoline derivative (0.01 M) and dimethyl sulphoxide (2 ml) were added to the above reaction mixture and continued refluxing for more 10 hrs. The solvent was removed and the pasty mass was dissolved in minimum quantity of glacial acetic acid and then poured into water with stirring. The separated product was filtered,

washed with water and crystallised from benzene, yield about 3-4 gm. The m.ps. and analytical results are reported in Table No.1 and spectral results are in Table No. 2.

Synthesis of 4,3'-methylene bis (2-chloro-2'-hydroxy-4'-methyl quinoline) derivatives :

α-(2-chloro-4-quinolylmethyl) acetoacetanilide derivative (0.01 m) was dissolved in conc. sulphuric acid (7 ml) and heated for 90 min. at 80-90° in water bath. The reaction mixture was poured in ice-cold water, separated product was filtered, washed with water and crystallised from acetic acid. Yield 2-3 gm. The m.ps. and analytical results are reported in Table No. 3 and spectral data are given in Table No. 4.

Synthesis of 4,3'-methylene bis (2,2'-dichloro-4'-methylquinoline) derivatives :

A mixture of 4,3'-methylene bis (2-chloro-2'-hydroxy-4'-methyl-quinoline) derivative (0.01 M) and phosphorusoxychloride was heated in an oil bath at 110-120° for 2 hrs. The reaction mixture was poured into ice water with stirring and the product was filtered, washed with water and crystallised from benzene. Yield, 1.0-1.5 gm. The m.ps. and analytical results are reported in Table No. 5 and spectral data in Table No. 4.

Synthesis of α-(2-hydroxy-4-quinolyl methyl) acetoacetanilide derivatives :

Acetoacetanilide derivative (0.01 M) was refluxed with pulverised sodium (0.01 M) in dry benzene at water bath temperature for 5-6 hrs. 2-Hydroxy-4-bromomethyl quinoline (0.01 M) and Dimethyl sulphoxide (2 ml) were added to the above reaction mixture and continued refluxing more 7-9 hrs. Solvent was removed and the pastymass was dissolved in minimum quantity of acetic acid (glacial) and then it was poured into water with constant stirring. The separated product was filtered, washed with water and crystallised from alcohol. Yield, 3-4 gm. The m.ps. and analytical results are reported in Table No. 6 and spectral data in Table No. 2.

Synthesis of 4,3'-methylene bis (2,2'-dihydroxy-4'-methyl quinoline) derivatives :

α-(2-hydroxy-4-quinolyl methyl) acetoacetanilide derivative (0.01 M) was dissolved in conc. sulphuric acid (7 ml) and heated for 90 min. at 80-90° in water bath. The reaction mixture was decomposed by pouring over crushed ice. The separated product was filtered, washed with water and crystallised from acetic acid. Yield, 2-3 gms The m.ps. and analytical results are reported in Table No. 7 and spectral data in Table No. 4.

Synthesis of 4,3'-methylene bis (2,2'-dichloro-4'-methyl quinoline) derivatives :

A mixture of 4,3'-methylene bis (2,2'-dihydroxy-4'-methyl quinoline) derivative (0.01 M) and phosphorus-oxychloride (0.05 M) was heated in oil-bath at 110-120° for 2 hr. The reaction mixture was poured into ice-water with constant stirring and separated product was filtered, washed with water and crystallised from benzene. Yield, 1.0-1.5 gm. The m.ps. and analytical results are reported in Table No. 5.

Table 1

α-(2-chloro-4-quinolylmethyl)acetoacetanilide derivatives

comp. No.	R	R_1	m.p.	Found %				Molecular formula	Required %			
				C	H	N	Cl		C	H	N	Cl
25	H	H	157	68.58	5.05	7.48	10.00	$C_{20}H_{17}N_2O_2Cl$	68.10	4.82	7.94	10.08
54	H	2-Me	199	68.36	5.48	7.15	10.10	$C_{21}H_{19}N_2O_2Cl$	68.75	5.18	7.64	9.68
56	H	4-MeO	189	65.33	5.11	7.80	9.00	$C_{21}H_{19}N_2O_3Cl$	65.88	4.96	7.32	9.28
55	H	2-MeO	178	65.95	4.91	7.76	9.11	$C_{21}H_{19}N_2O_3Cl$	65.88	4.96	7.32	9.28
57	H	3-Cl	166	61.70	4.54	7.71	18.55	$C_{20}H_{16}N_2O_2Cl_2$	62.01	4.13	7.23	18.35
58	H	4-Cl	185	61.90	4.53	7.06	18.29	$C_{20}H_{16}N_2O_2Cl_2$	62.01	4.13	7.23	18.35
59	H	4-Br	187	55.37	3.57	6.44	-	$C_{20}H_{16}N_2O_2ClBr$	55.61	3.70	6.49	-
61	H	Benzo (h)	200	72.05	4.99	6.92	8.54	$C_{24}H_{19}N_2O_2Cl$	71.57	4.72	6.96	8.82
53	CH_3	H	185	68.54	5.45	7.52	10.09	$C_{21}H_{19}N_2O_2Cl$	68.75	5.18	7.64	9.68
60	CH_3	2-CH_3	195	69.18	5.12	7.32	9.55	$C_{22}H_{21}N_2O_2Cl$	69.38	5.52	7.36	9.33

Table 2

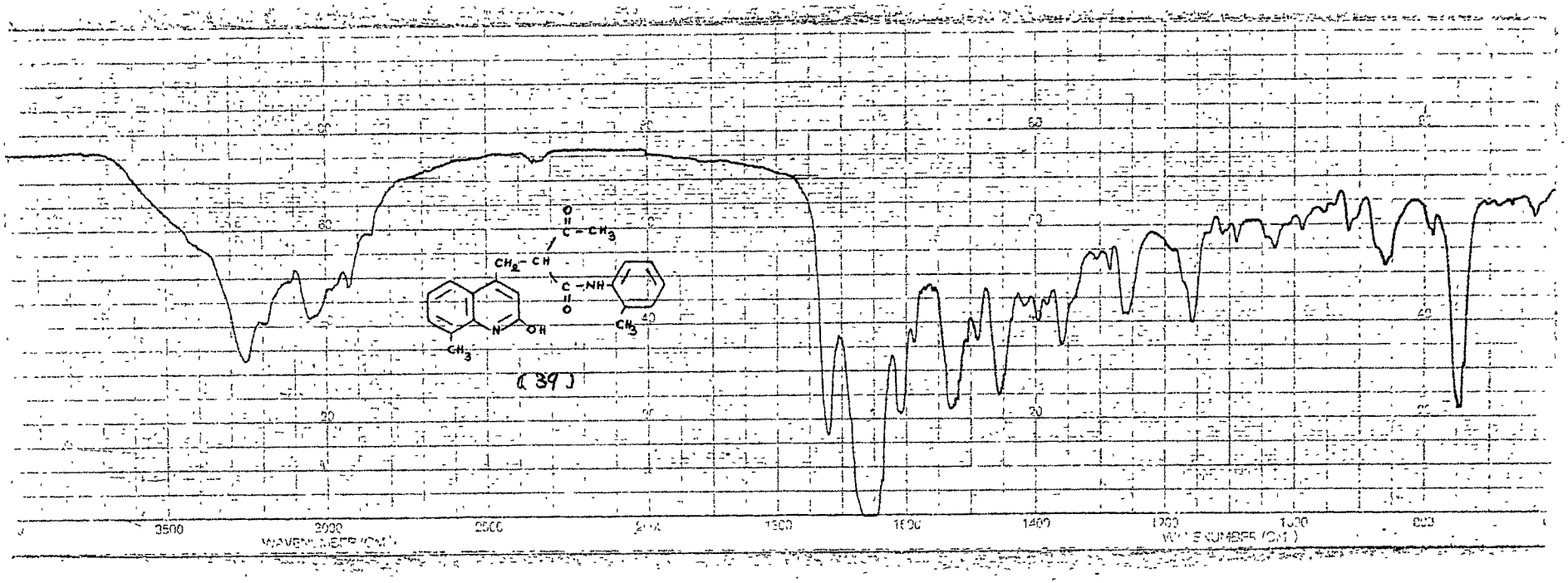
Results of IR spectrum

Comp.No.	IR bands (cm^{-1})					
	HO-C=C	NH	$-CO-CH_3$	-CO-NH	C-Cl	Ar-OH
25	1570	3250	1730	1660	760	-
57	1595	3260	1720	1650	760	-
39	1610	3260	1720	1660	-	3190
55	1600	3270	1720	1650	760	-

Table 2

Results of NMR spectra

Comp.No.	NMR Signals at δ						
	$-COCH_3$	-NH-	$-CH_2-$	-CH-	aromatic	enolic OH	$-ArCH_3$
25	S, 2.30	S, 8.80	d, J=8Hz, 3.65	t, J=8Hz, 4.25	m, 10H, 7.1-8.0	S, 10.0	-
57	S, 2.44	S, 8.65	d, J=8Hz, 4.02	t, J=8Hz, 4.25	m, 9H, 7.0-8.1	-	-
39	S, 1.90	S, 8.60	d, J=8Hz, 3.80	t, J=8Hz, 4.30	m, 8H, 6.95-7.8	-	S, 2.5 and S, 2.65
55	S, 2.44	S, 8.80	d, J=8Hz, 3.96	t, J=8Hz, 4.15	m, 9H, 7.8-8.5	-	-



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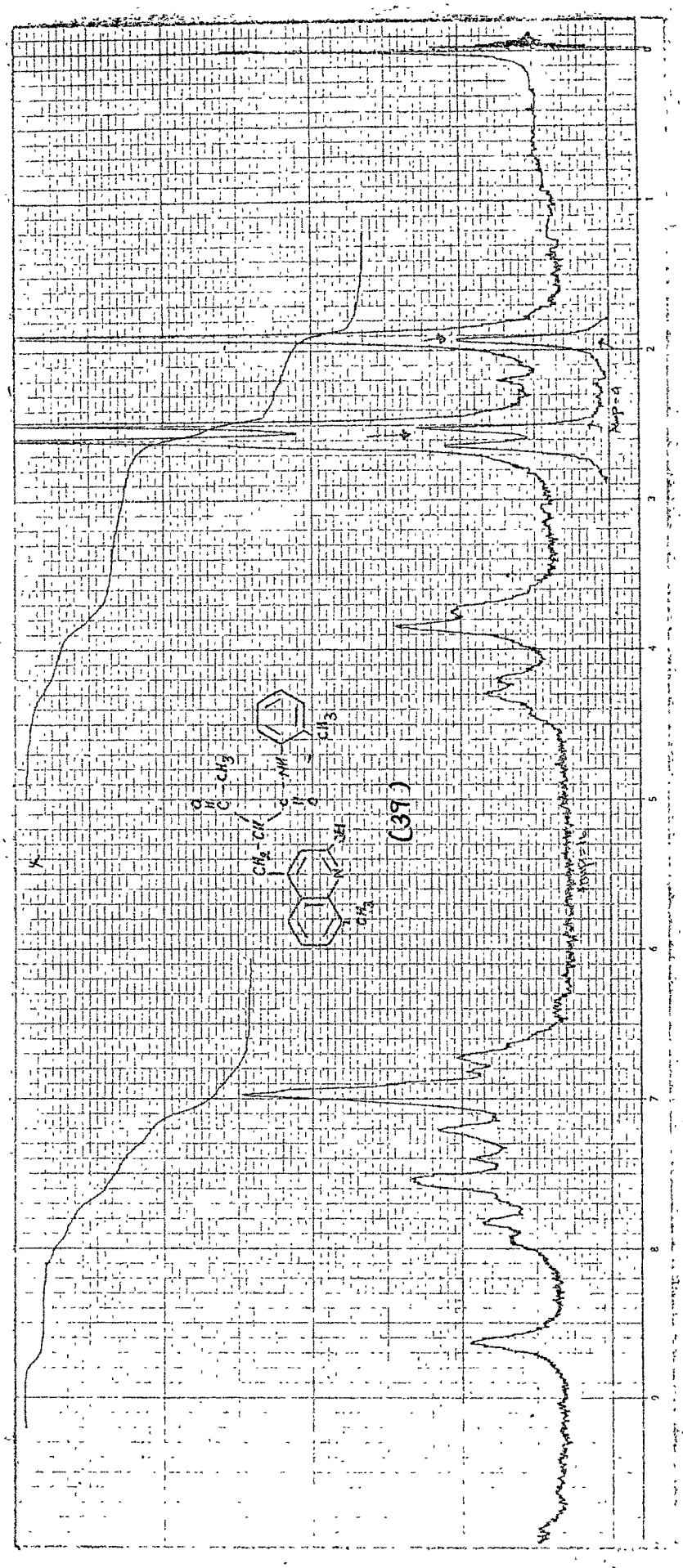
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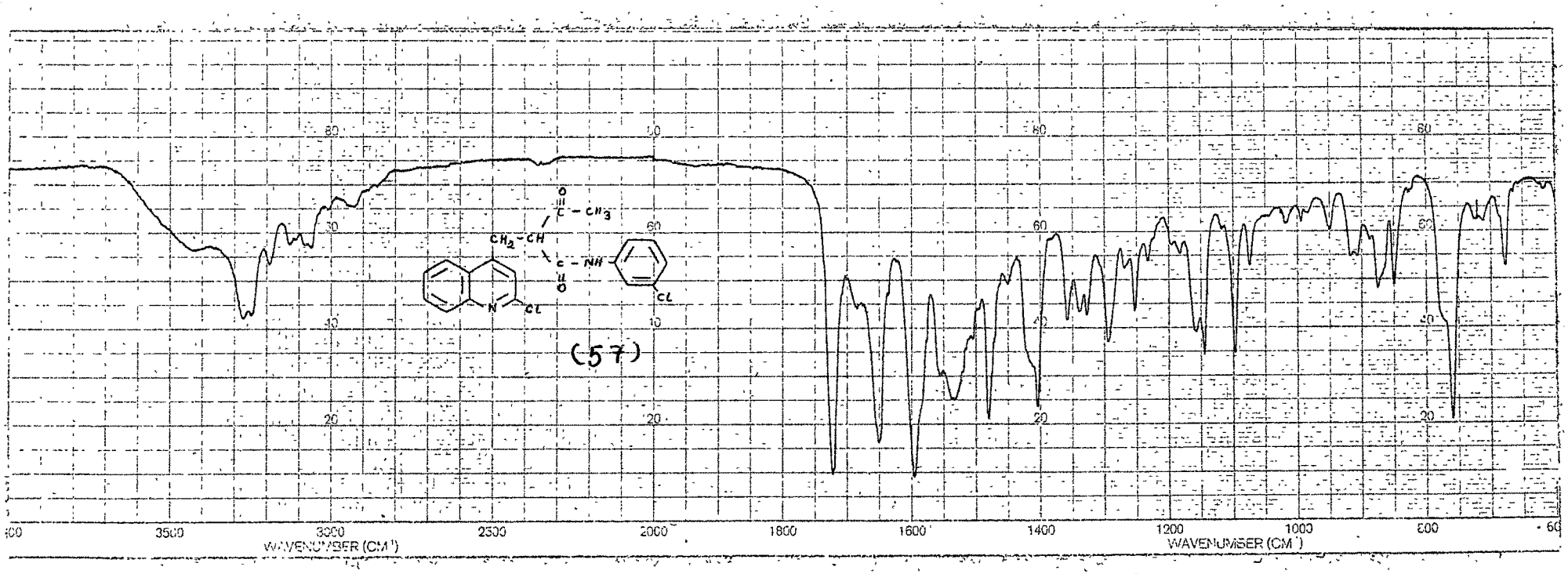
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WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)

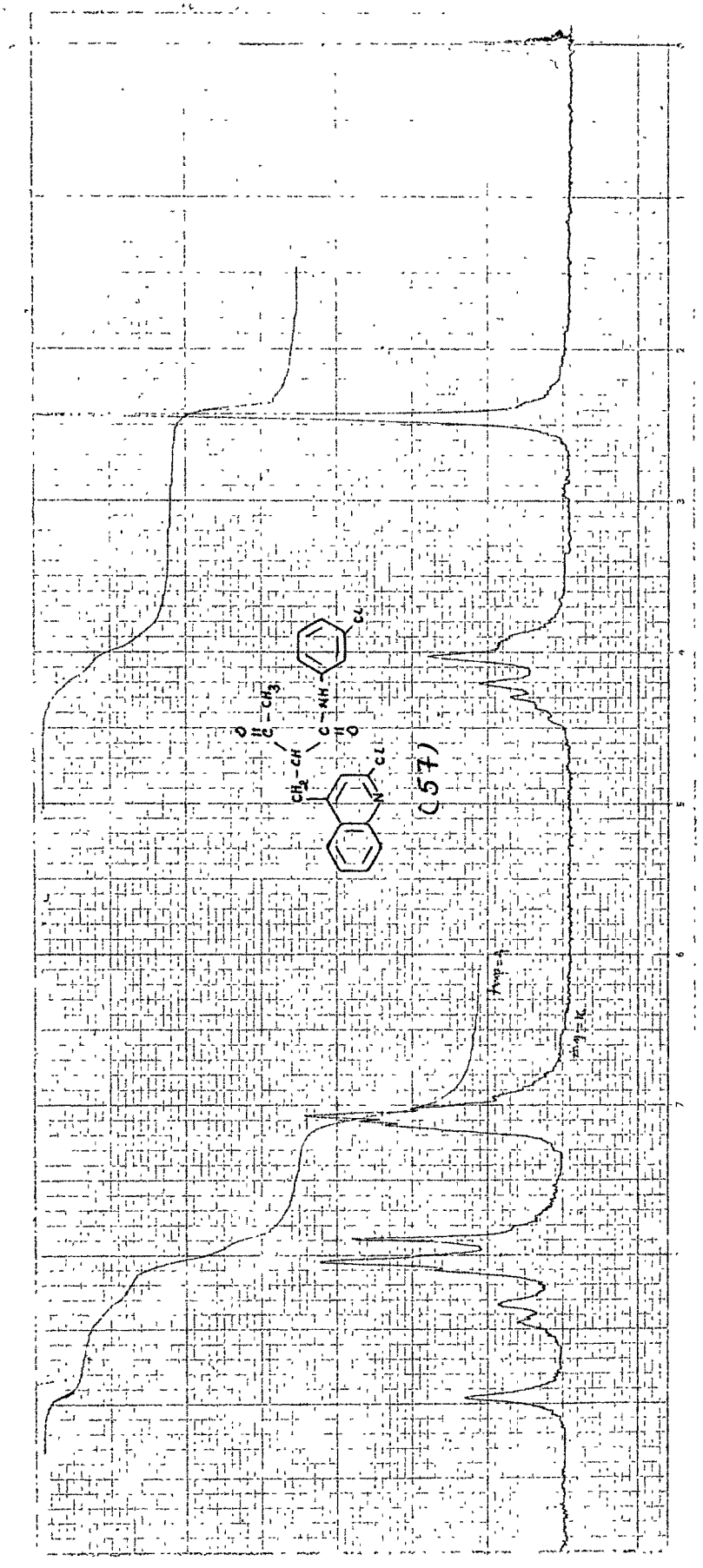
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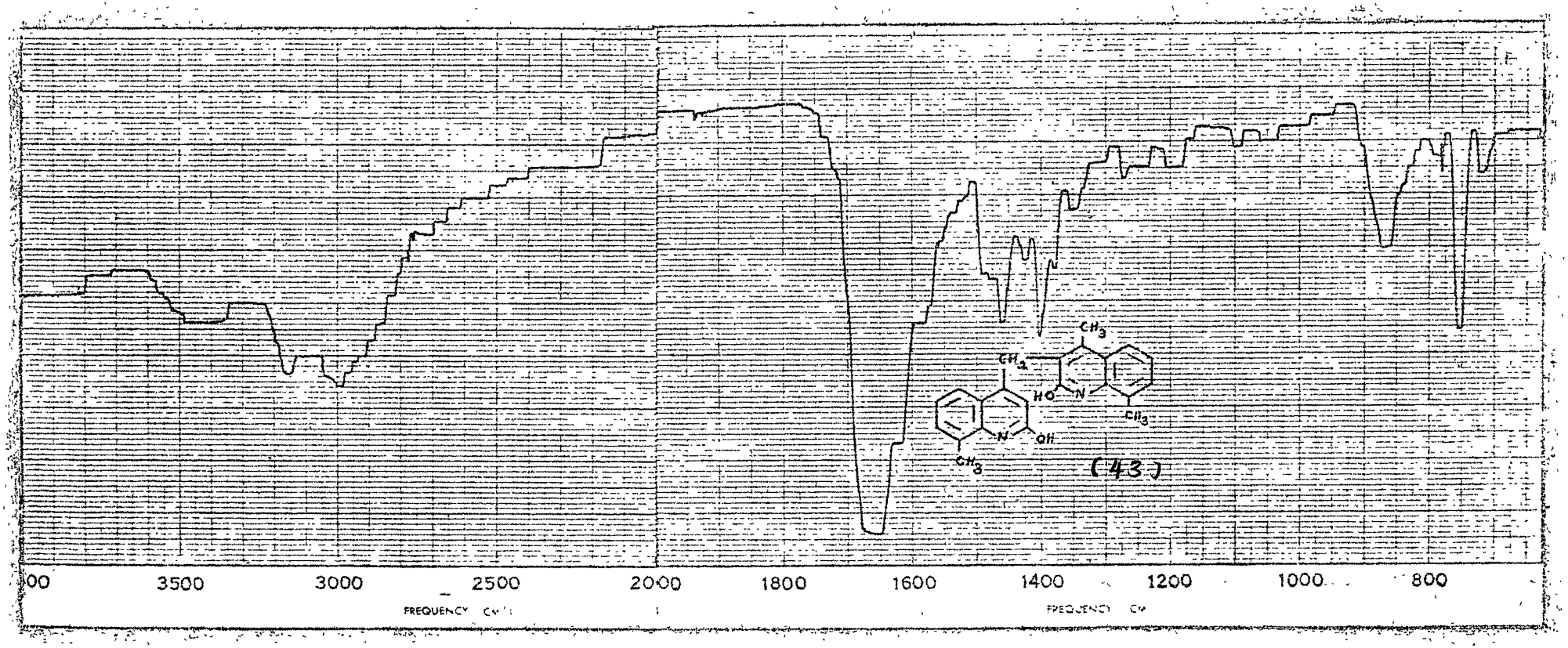
Table 3

4,3'-methylene bis(2-chloro-2'-hydroxy-4'-methyl quinoline)derivatives

Comp. No.	R	R_1	m.p.	Found %				Molecular formula	Required %			
				C	H	N	Cl		C	H	N	Cl
49	H	H	300	71.30	4.47	8.32	10.93	$C_{20}H_{16}N_2OCl$	7.176	4.48	8.37	10.62
51	H	6-MeO	291	68.89	5.07	7.32	9.51	$C_{21}H_{17}N_2O_2Cl$	69.13	4.66	7.68	9.47
63	H	8-MeO	296	59.63	4.58	8.01	9.39	$C_{21}H_{17}N_2O_2Cl$	69.13	4.66	7.68	9.47
50	H	7-Cl	315	64.87	4.41	7.84	19.70	$C_{20}H_{14}N_2OCl_2$	65.05	3.79	7.59	19.20
52	H	Benzo (h)	360	75.08	4.63	7.16	9.50	$C_{24}H_{17}N_2OCl$	74.90	4.42	7.28	9.23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3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY
FREQUENCY
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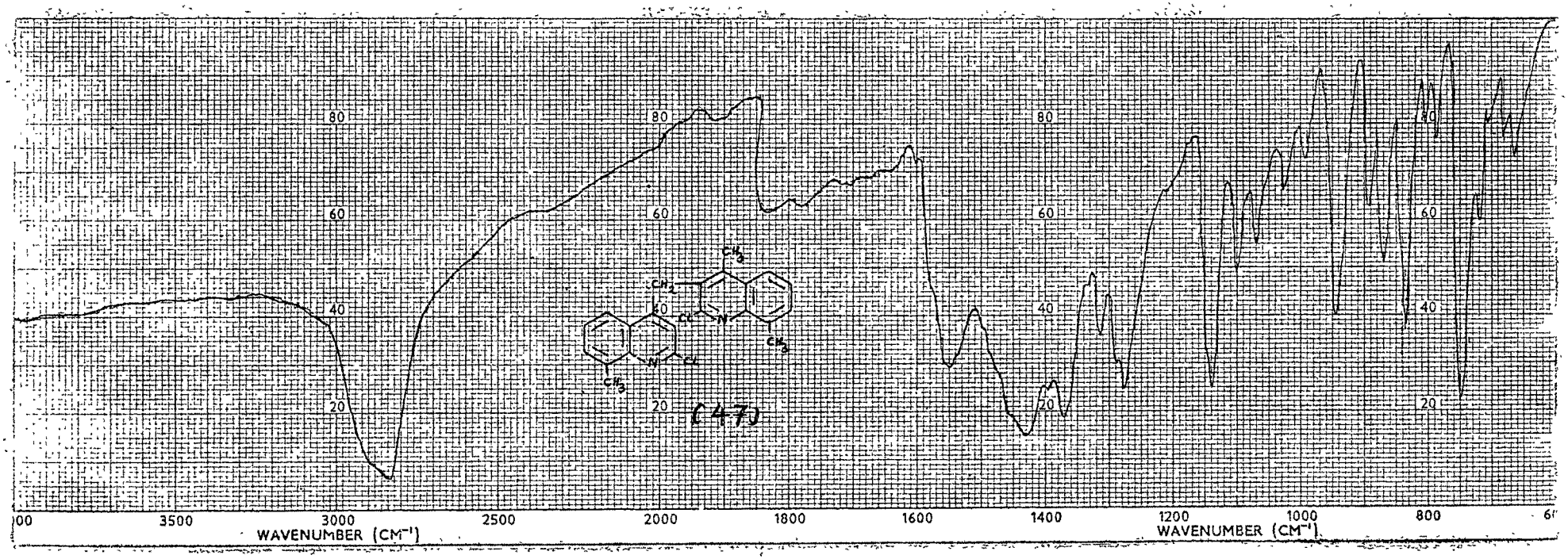
CH3
HO
N
N
OH
CH3
CH3
(43)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20
3500
3000
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2000
1800
1600
1400
1200
1000
800
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WAVENUMBER (CM⁻¹)
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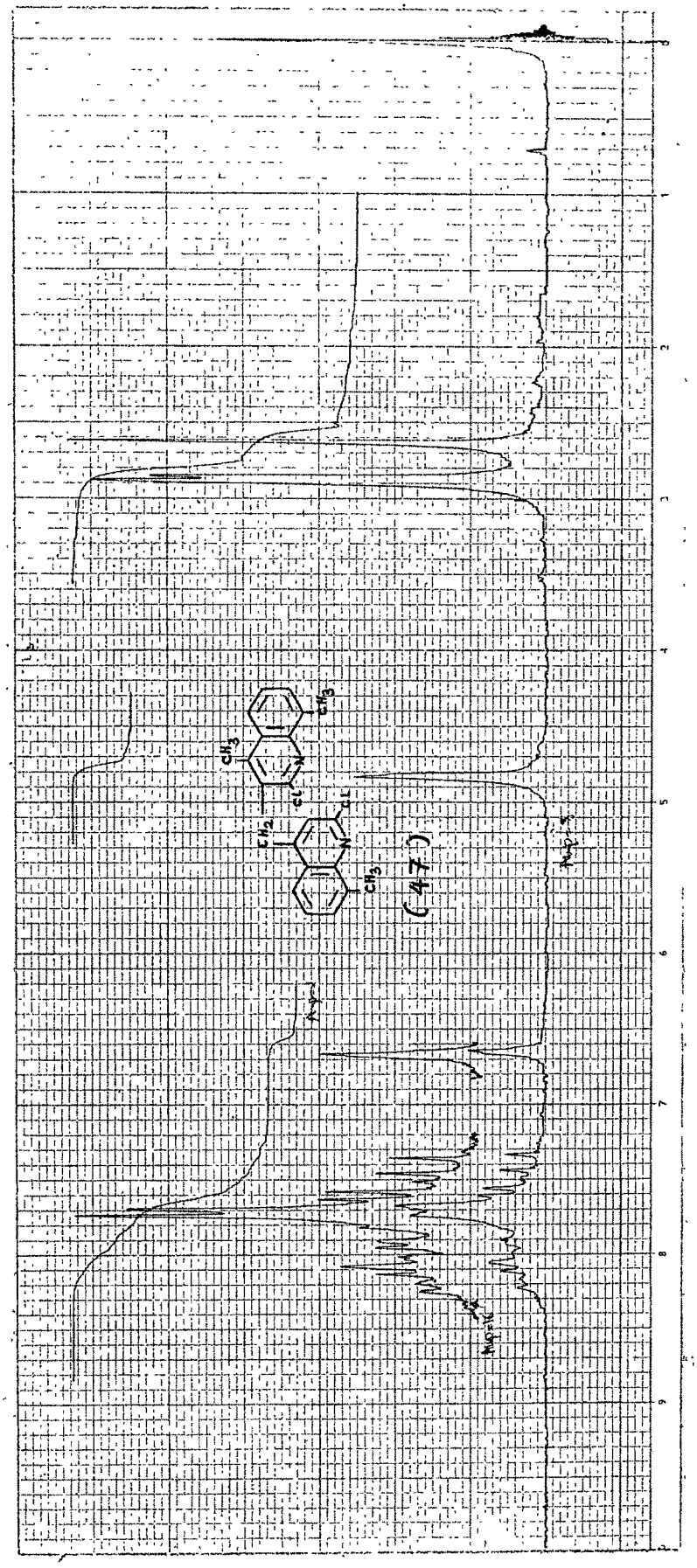
CH3
Cl
N
CH3
N
Cl
CH3

(47)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CH3
CH2
Cl
N
Cl
N
CH3
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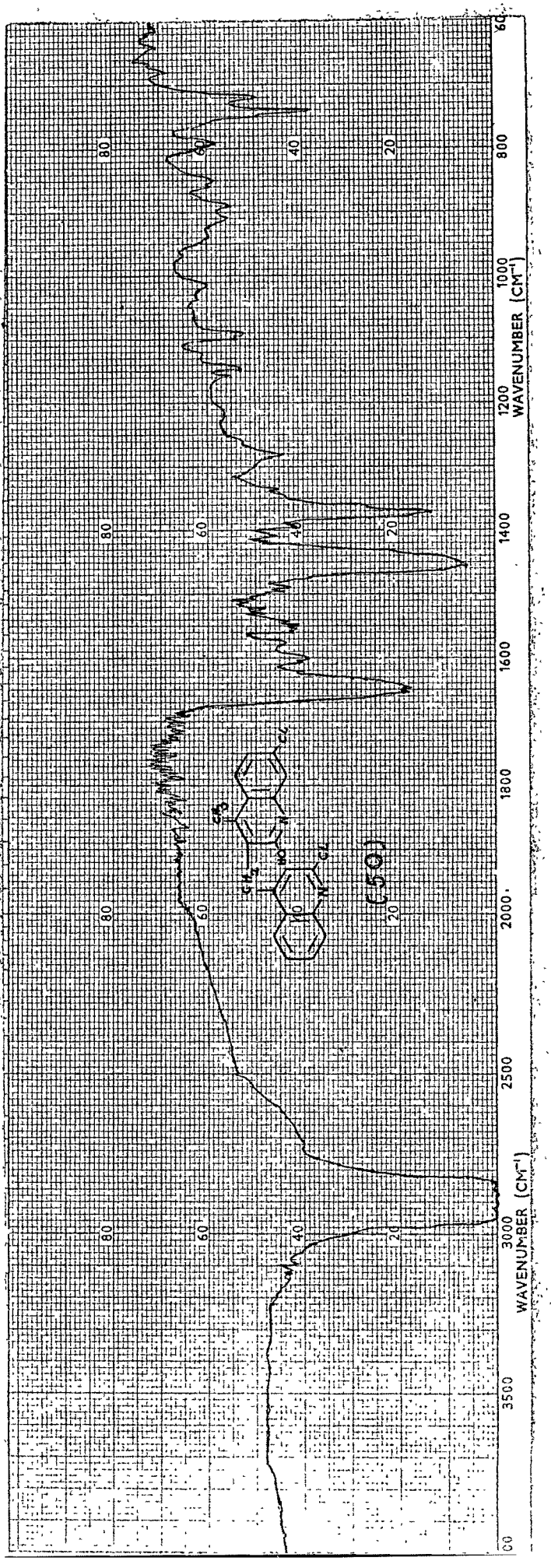
Ar-H
Ar-H
Ar-H
Ar-H
TMS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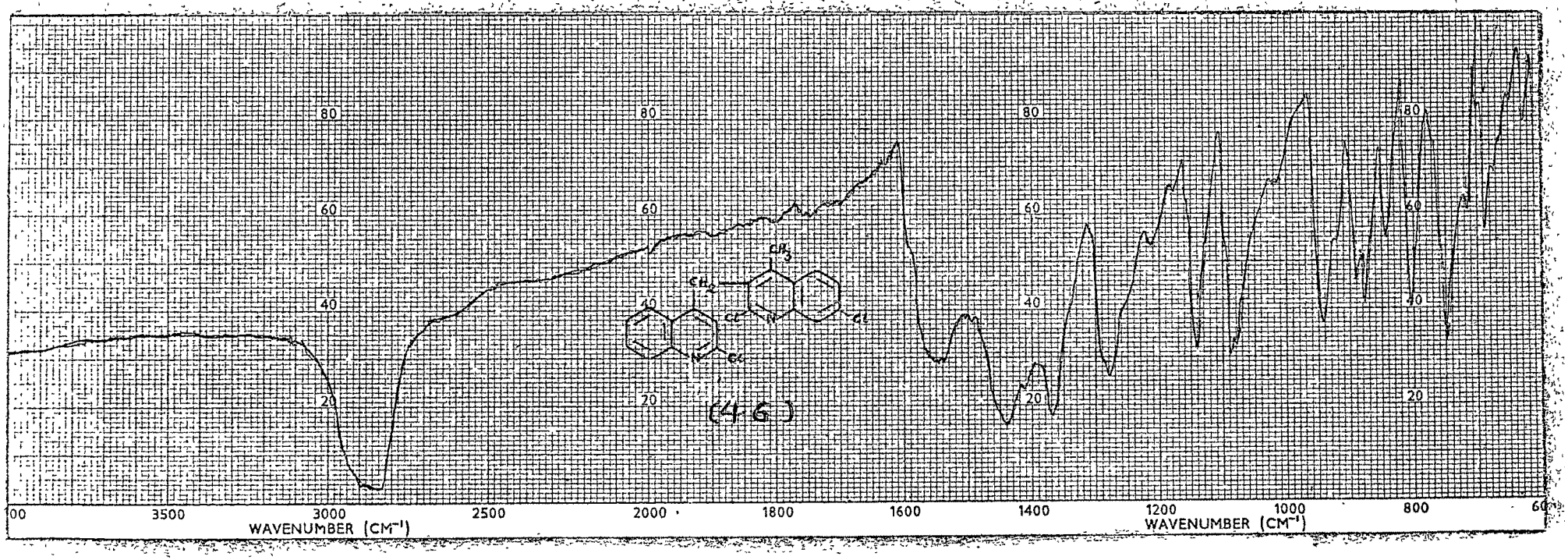
1400
1200
1000
800
600
100
80
60
40
20
(50)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3000
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2000
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1600
1400
1200
1000
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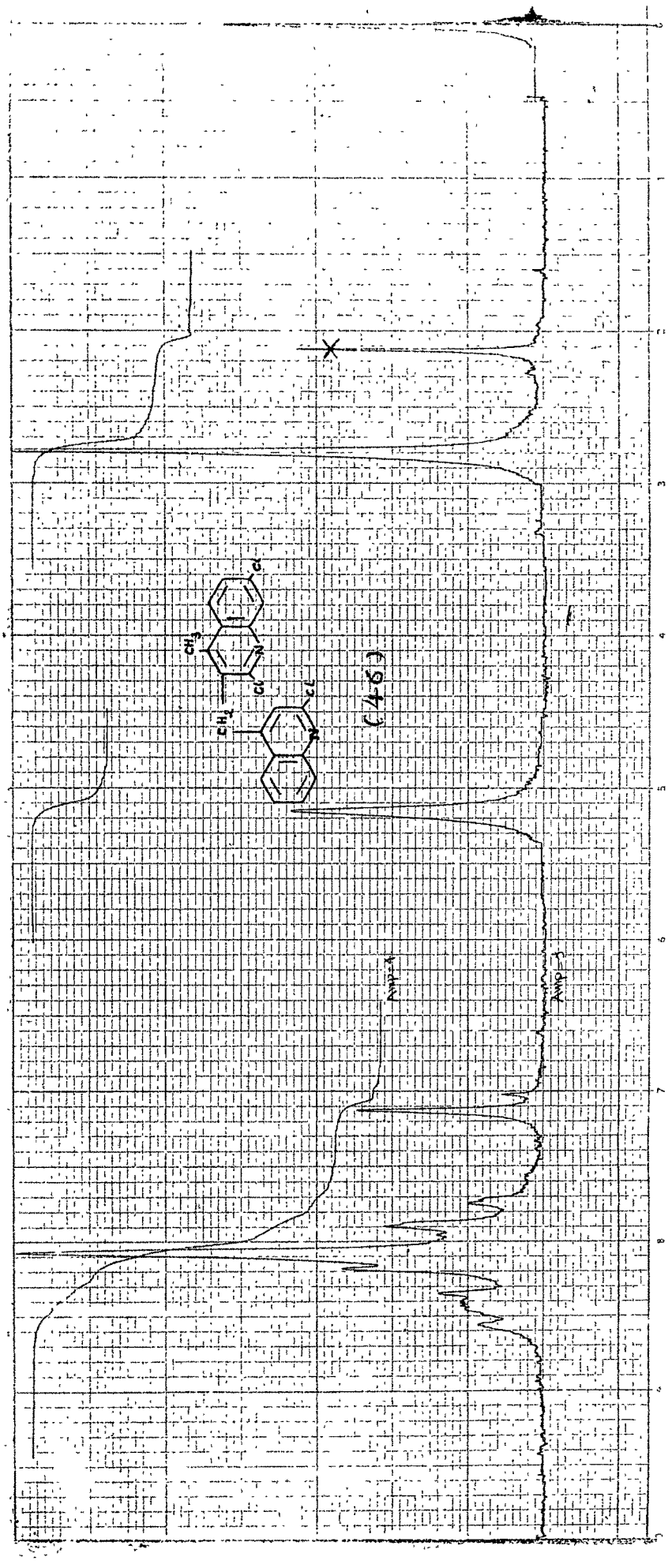
WAVENUMBER (CM⁻¹)
WAVENUMBER (CM⁻¹)
(46)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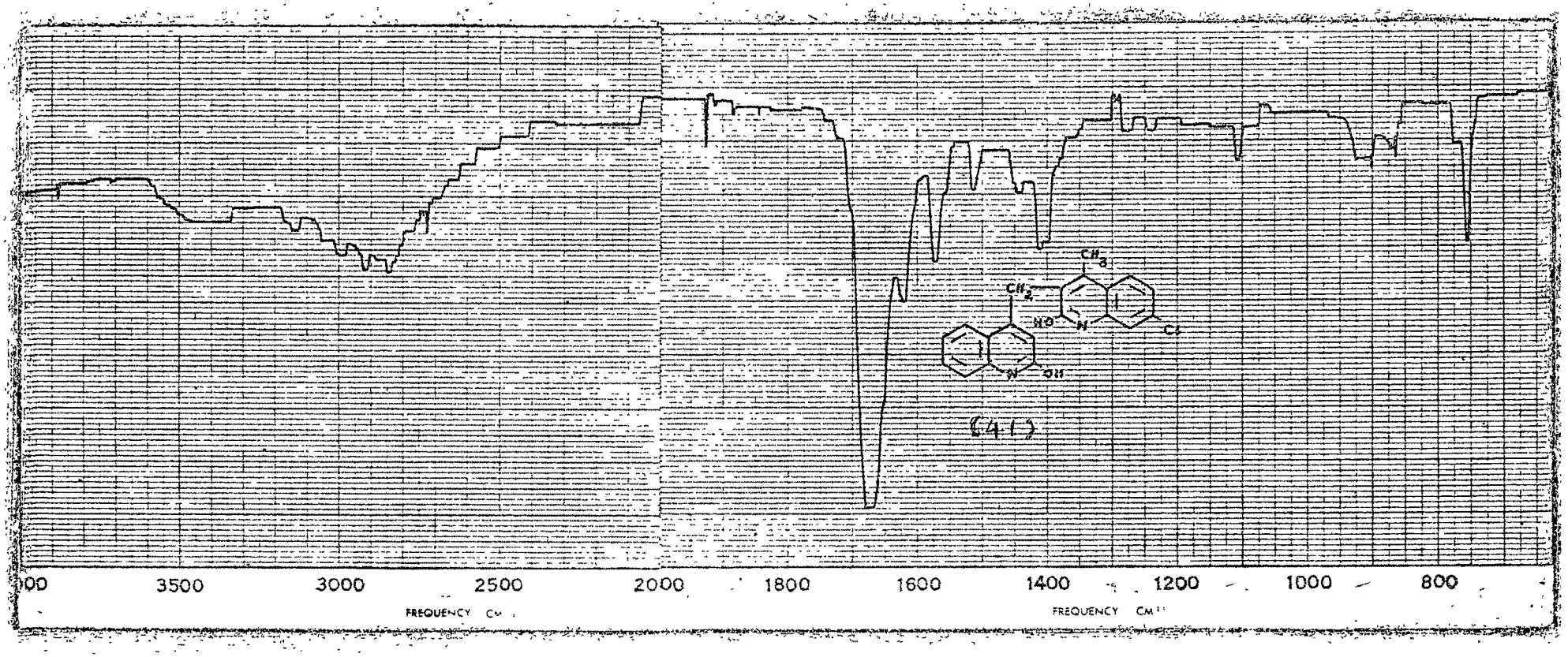
Cl
CH2
Cl
N
Area=A
Area=B


3500
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2000
1800
1600
1400
1200
1000
800
FREQUENCY
FREQUENCY
641

Table 4

Comp. No.	IR band (CM^{-1})		NMR Signals at				
	Ar-OH	Ar-Cl	$-CH_3$ at C_4'	$-CH_3$ at C_8	$-CH_3-$ at C_8'	$-CH_2-$	Aromatic C_3
49	3400	730	-	-	-	-	-
23	-	750	s, 2.55	-	s, 4.75	s, 4.75	m, 7.6-8.2 8H
43	3150	-	-	-	-	-	-
47	-	750	s, 2.62	s, 2185	s, 2.86	s, 4.82	m, 7.35-8.25 6H
41	3150	750	-	-	-	-	-
50	-	740	-	-	-	-	-
46	-	750	s, 2.8	-	-	s, 5.15	m, 7.7-8.55 8H

Table 5

4,3'-methylene bis (2,2'-dichloro-4'-methylquinoline)derivatives

Comp. No.	R	R_1	m.p.	Found % C	H	N	Cl	Molecular formula	Required % C	H	N	Cl
23	H	H	210	68.06	3.82	7.89	20.56	$C_{20}H_{14}N_2Cl_2$	68.00	3.96	7.93	20.11
46	H	7-Cl	249	61.51	3.55	7.25	27.10	$C_{20}H_{13}N_2Cl_3$	61.93	3.35	7.23	27.47
45	CH_3	H	228	68.72	4.68	7.88	19.55	$C_{21}H_{16}N_2Cl_2$	68.66	4.36	7.63	19.35
47	CH_3	8-Me	205	69.08	4.60	7.87	18.55	$C_{22}H_{18}N_2Cl_2$	69.30	4.73	7.35	18.64
48	H	Benzo (h)	271	71.74	4.23	6.92	17.55	$C_{24}H_{16}N_2Cl_2$	71.46	3.97	6.95	17.62

Table 6

α-(2-hydroxy-4-quinolymethyl)acetoacetanilide derivatives

Comp. No.	R	R_1	m.p.	Found % C	H	N	Cl	Molecular formula	Required % C	H	N	Cl
21	H	H	265	71.52	5.21	7.94	-	$C_{20}H_{18}N_2O_3$	71.86	5.39	8.39	-
35	H	4-MeO	240	69.64	5.49	7.84	-	$C_{21}H_{20}N_2O_4$	69.23	5.49	7.69	-
36	H	3-Cl	233	65.06	5.02	7.29	10.00	$C_{20}H_{17}N_2O_3Cl$	65.13	4.61	7.60	9.63
37	H	4-Cl	265	64.90	4.84	2.76	9.55	$C_{20}H_{17}N_2O_3Cl$	65.13	4.61	7.60	9.63
62	H	Benzo (h)	280	74.82	5.34	7.09	-	$C_{24}H_{20}N_2O_3$	75.00	5.21	7.29	-
38	CH_3	H	242	72.05	5.62	7.99	-	$C_{21}H_{20}N_2O_3$	72.42	5.74	8.05	-
39	CH_3	8-Me	274	72.69	6.26	6.98	-	$C_{22}H_{22}N_2O_3$	72.94	6.08	7.74	-

Table 7

4,3'-methylene bis(2,2'-dihydroxy-4'-methyl quinoline)derivatives

Comp. No.	R	R_1	m.p.	Found %				Molecular formula	Required %			
				C	H	N	Cl		C	H	N	Cl
22	H	H	360	75.56	5.18	8.22	-	$C_{20}H_{16}N_2O_2$	75.96	5.06	8.85	-
64	H	6-MeO	360	72.38	4.98	7.91	-	$C_{21}H_{18}N_2O_3$	72.84	5.20	8.09	-
41	H	7-Cl	360	68.69	4.04	7.64	10.50	$C_{20}H_{15}N_2O_2Cl$	68.47	4.28	7.99	10.13
42	H	6-Cl	360	68.60	4.56	7.59	10.56	$C_{20}H_{15}N_2O_2Cl$	68.47	4.28	7.99	10.13
40	CH_3	H	360	73.77	5.49	8.19	-	$C_{21}H_{18}N_2O_2$	73.37	5.45	8.49	-
43	CH_3	8-Me	360	76.35	5.65	8.00	-	$C_{22}H_{20}N_2O_2$	76.74	5.81	8.14	-
44	H	Benzo (h)	360	79.01	5.10	7.82	-	$C_{24}H_{18}N_2O_2$	78.69	4.92	7.65	-

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SUMMARY

Studies in the synthesis of quinoline derivatives :

Quinoline derivatives are found in nature in the form of alkaloids in coal-tar and in petroleum. Many furoquinoline and pyranoquinoline derivatives are isolated from different plant species. Quinine is one such naturally occuring quinoline derivatives, known to us since 300 to 400 years ; used for the remedy of Malaria. In recent years, considerable interest has been created in the antimalarial nitrogen mustards as potent chemotherapeutic agents for the cancer treatment.

The present work was undertaken with a view to synthesis pyranoquinoline derivatives and furoquinoline derivatives from substituted quinolines by prenylation, some of the anticancer compounds were synthesised from substituted quinoline derivatives to give nitrogen mustards. Similarly some bis quinoline derivatives were also prepared by the condensation of 4-halomethyl quinoline derivatives with α-sodio acetoacetanilides, followed by cyclization.

In chapter I, section I, the synthesis of pyrano(3,2-c) quinoline and pyrano (2,3-b)quinoline derivatives has been described.

2-Methyl-4-hydroxy quinoline was condensed with prenyl chloride (1-chloro-3-methyl-but-2-ene) in the presence

of potassium carbonate and potassium iodide using ethyl-methylketone at solvent, to give 2-methyl-4-(3-methyl-but-2-enyloxy)-quinoline which on Claisen rearrangement gave 2-methyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline. The migrated product was subjected to cyclization using conc. sulphuric acid, gave 2,2,5-trimethyl-3,4,7-dihydro pyrano (3,2-c)quinoline. The structure of prenyloxy migrated hydroxy derivative and cyclized product were confirmed on the basis of IR and NMR spectra.

2,2,5-Trimethyl-3,4-dihydro pyrano (3,2-c)quinoline failed to undergo dehydrogenation when it was reacted with DDQ in dry benzene to give 2,2,5-trimethyl pyrano(3,2-c) quinoline. Also on similar treatment, 2-methyl-3-(3-methyl-but-2-enyl)-4-hydroxy quinoline failed to under cyclodehydrogenation. To synthesise dehydrogenated product, 2,2,5-trimethyl quinoline derivatives, 2-methyl-4-hydroxy quinoline was condensed with 3-methyl-3-chloro-but-1-yne, in the presence of potassium carbonate and potassium iodide in ethylmethylketone gave directly cyclized product 2,2,5-trimethyl pyrano(3,2-c) quinoline instead of obtaining 4-(2-methyl-3-butynyl-2-oxy) quinoline or 2-methyl-3-(2-methyl-3-butyn-2-yl)-4-hydroxy quinoline. The structure of 2,2,5-trimethyl pyrano(3,2-c) quinoline derivative was confirmed on the basis of NMR spectra.

A mixture of α-sodium acetoacetanilide and prenyl chloride (1-chloro-3-methyl-but-2-ene) in dry benzene gave α-prenyl acetoacetanilide (α-(3-methyl-but-2-enyl)acetoacetanilide) which on cyclization using polyphosphoric acid gave 2,2,5-trimethyl 3,4-dihydro pyrano(2,3-b)quinoline. The

structure of this compound was assigned on the basis of its IR - NMR spectra.

In the section II, the synthesis of furo(3,2-c) quinoline derivatives has been described.

2-Methyl-4-hydroxyquinoline on condensation with cinnamyl chloride in the presence of potassium carbonate and potassium iodide in ethylmethylketone gave 2-methyl-4-cinnamyloxy quinoline which was subjected to Claisen rearrangement by pyrolysis without solvent at 200°C ; gave mixture of migrated products. All attempts to separate these two isomers failed, therefore, subjected to cyclization using polyphospheric acid gave again mixture of two cyclic products, which were separated by preparative thin-layer chromatography (Silica-gel). The structure of these two isomers were assigned as 2,4-dimethyl-3-phenyl-2,3-dihydro furo(3,2-c) quinoline and 3,4-dimethyl-2-phenyl-2,3-dihydro furo(3,2-c) quinoline, on the basis of NMR spectra.

Studies in the synthesis of furoquinoline derivatives by cinnamylation of 4-hydroxy quinolines, gave two isomers by abnormal Claisen rearrangement. It was thought of interest to study the cinnamylation on acetoacetanilide derivatives.

When α-sodium acetoacetanilide was condensed with cinnamyl chloride in dry benzene gave α-(cinnamyl)acetoacetanilide which on cyclization with 70 % sulphuric acid gave a novel product N-phenyl-2-phenyl-5-acetyl-6-hydroxy-3,4-dihydro pyridine. The structure of this novel product was assigned on the basis of its IR - NMR spectra.

In Section III, the synthesis of pyrano (3,2-c) quinoline derivatives by Perkin and Knoevenagel reaction has been described.

2-methyl-3-formyl-4-hydroxy quinoline on condensation with diethylmelonate in presence of pyridine and piperidine gave a novel product 3-carbethoxy 4-(N-piperidyl)-2-oxo-2H-pyrano (3,2-c)quinoline. The structure of this compound was confirmed on the basis of IR and NMR spectra. Similar series of reaction were carried out using ethyl acetoacetate and ethyl cyanoacetate to give 3-acetyl-4-(N-piperidyl)-2-oxo-2H-pyrano(3,2-c)quinoline and 3-cyano-4-(N-piperidyl)-2-oxo-2H-pyrano(3,2-c)quinoline, respectively.

Also on Perkin reaction 2-methyl-3-formyl-4-hydroxy quinoline gave 3-acetylamino-2-oxo-2H-pyrano(3,2-c)quinoline derivatives. Thus a mixture of 2-methyl-3-formyl-4-hydroxy quinoline, acetyl glycine, acetic anhydride and triethylamine was heated at 110° to give 3-acetylamino-2-oxo-2H-pyrano (3,2-c)quinoline which on hydrolysis with 50 % sulphuric acid and alcohol (1:1) mixture an inner atmosphere of Nitrogen gas gave 3-hydroxy-2-oxo-2H-pyrano(3,2-c)quinoline. It was observed that hydrolysis of 3-acetylamino derivative in an innert atmosphere of nitrogen gas gave good yield of pure product. The structure of 3-acetylamino derivatives and 3-hydroxy derivatives were assigned on the basis of IR spectrum.

Synthesis of nitrogen mustards has been described in the Chapter II. In Section I, synthesis of 2-methyl-4-

(p-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)carbhydrazide phenyl amino)quinoline derivatives, 2-(p-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)carbhydrazide phenyl amino)-4-methyl quinoline, 2-methyl-4-(o-(p-(N,N-bis(2-chloroethyl) amino)benzylidine)carbhydrazide phenylamine)quinoline and 2-(o-(p-(N,N-bis(2-chloroethyl)amino)benzylidine)carbhydrazide phenyl amino)-4-methyl quinoline has been described.

Thus 2-methyl-4-hydroxy quinoline on treatment with phosphorousoxychloride gave 2-methyl-4-chloroquinoline which on condensation with p-amino benzoic acid in 2N HCl, gave 2-methyl-4-(p-carboxy-phenyl amino)quinoline Hydrochloride. The latter was then converted to 2-methyl-4-(p-carbhydrazide phenyl amino)quinoline by converting, first, free acid into ester and then treating with Hydrazine Hydrate. 2-Methyl-4-(p-carbhydrazide phenyl amino)quinoline was condensed with p-(N,N-bis(2-chloroethyl)amino)benzaldehyde to give 2-methyl-4-(p-(p-(N,N-bis(2-chloroethyl)amino)benzylidine)carbhydrazide phenyl amino)quinoline. The structure of latter was confirmed on the basis of IR spectra and by analytical results.

In Section II, synthesis of 2-methyl-4-(p-(N,N-bis (2-chloroethyl)amino)benzylidine)carbhydrazide methoxy) quinoline has been described.

2-Methyl-4-hydroxy quinoline on treatment with ethyl bromoacetate in the presence of potassium carbonate and potassium iodide in ethylmethylketone gave 2-methyl-4-(carbethoxy-methoxy)quinoline, which on treatment with hydrazine hydrate gave 2-methyl-4-(carbhydrazide methoxy)quinoline.

The latter one was condensed with p-(N,N-bis(2-chloroethyl) amino)benzaldehyde gave 2-methyl-4-(p-(N,N-bis(2-chloroethyl) amino)benzylidine)carbhydrazide methoxy)quinoline. The structure of which was confirmed on the basis of IR spectra.

Synthesis of 2-methyl-4-(p-(N,N-bis(2-chloroethyl) amino)benzylidine)hydrazino quinoline and 2-(p-(N,N-bis(2-chloroethyl)amino)benzylidine)hydrazino-4-methyl quinoline has been described in section III.

2-Methyl-4-chloro quinoline on condensation with Hydrazine hydrate gave 2-methyl-4-hydrazino quinoline which on condensation with p-(N,N-bis(2-chloroethyl)amino) benzaldehyde gave 2-methyl-4-(p-(N,N-bis(2-chloroethyl) amino)benzylidine)hydrazino quinoline. The structure of latter one was confirmed on the basis of IR spectra and on the basis of analytical results.

In Chapter III, synthesis of 4,3'-methylene bis (2,2'-di chloro-4'-methyl quinoline)derivatives has been described.

2-Hydroxy-4-bromomethyl quinoline was converted into 2-chloro-4-chloromethyl quinoline by reacting former with phosphorousoxychloride. 2-chloro-4-chloromethyl quinoline was condensed with α-sodium salt of acetoacetanilide, in the presence of DMSO to give α-(2-chloro-4-quinolylmethyl)-acetoacetanilide. The structure of this latter compound was confirmed on the basis of IR and NMR spectra. α-(2-chloro-4-quinolymethyl) acetanilide was then cyclized with conc. sulphuric acid, gave 4,3'-methylene-bis (2-chloro-2'-hydroxy-

4'-methylquinoline) which was converted into 4,3'-methylene bis (2,2-dichloro-4'-methyl quinoline) by the treatment of phosphorusoxychloride. The structure of the methylene bis quinoline derivatives were assigned on the basis of IR and NMR spectra.

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Studies in the synthesis of Quinoline Derivatives Part VIII**. Synthesis of 4 : 3'-methylenebis-(2,2'-dichloro-4'-methylquinoline) Derivatives

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Baroda-390 002

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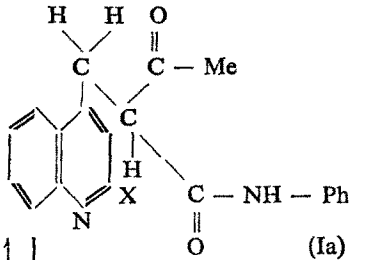
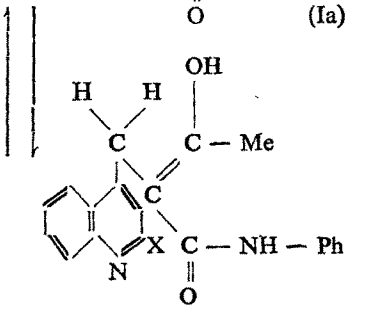
IN continuation of our work on reactivity of 4-Bromomethyl-2-hydroxy and 4-Chloromethyl-2-chloroquinoline derivatives[1,2,3], we report here the condensation of 4-chloromethyl-2-chloroquinoline and 4-bromomethyl-2-hydroxyquinoline with sodium salt of acetoacetanilide in the presence of Dimethyl sulphoxide, to give α-2-chlorolepidinyl acetoacetanilide (Ia) and α-2-hydroxylepidinyl acetoacetanilide (Ib), respectively. It was observed that the condensation did not occur in the absence of DMSO. The structure of (Ia) was confirmed by NMR spectrum (DMSO-d_6+acetone-d_6), δ, 2.3, singlet, 3H, for methyl group ; 3.65, doublet, J=8Hz, 2H, for $-CH_2-$group ; 4.25, triplet, J=8Hz., 1H, for -CH-group ; 3 25, singlet, 1H, for -NH-group, which disappears on D_2O-exchange ; 7.1 to 8.0, multiplet 9H, aromatic protons. It also shows the enolic proton at δ, 10.6 which disappears on D_2O-exchange, indicating that it partially exists in the enolic form (Ic). The lower value obtained for the methylene protons at δ, 3.65, in the spectrum is due to the additional deshielding effect of the carbonyl group as shown in the structure (Ia). On the basis of integration values of methyl, methylene and enolic protons, it is calculated that the percentage of enol content is 20%. This is supported by the IR of (Ia) which shows broad enolic band at 3250 cm^{-1} and broad ketonic band of enol at 1570 cm^{-1}. (Ia) and (Ib) underwent cyclization when reacted with conc. H_2SO_4 to give 4 : 3'-methylenebis-(2-chloro-2'-hydroxy-4'-methylquinoline) (IIa) and 4 : 3'-methylenebis-(2,2'-dihydroxy-4'-methylquinoline) (IIb) respectively. (IIa) and (IIb) when reacted with phosphorous oxychloride, gave the same 4 : 3'-methylenebis-(2,2'-dichloro-4'-methylquinoline), (IIc). The structure of (IIc) is also confirmed by NMR spectrum ($CDCl_3$), δ, 2.6, singlet. 3H, $-CH_3$-group , 4 8, singlet, 2H, $-CH_2$-group ; 6.6, singlet, 1H, aromatic proton of quinoline ring at 3-position, 7.3 to 8.2, multiplet 8H, for aromatic protons.

Experimental

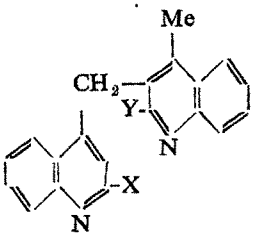
General method for the synthesis of α-2-chlorolepidinylacetoacetanilides : Pulverised sodium (0.23 g.) in dry benzene, was added acetoacetanilide (1.77 g.) and the mixture was refluxed for 5-6 hr. on water bath. 4-chloromethyl-2-chloroquinoline (2.2 g.) and Dimethyl sulphoxide (2.0 ml.) were added to the above reaction mixture. The whole reaction mixture was refluxed for 8-9 hrs. The reaction mixture was poured in water, the residue filtered off and washed with water and finally crystallized from benzene. The m. ps. and the analytical data are reported in Table 1. The yields of products varied from 70 – 80%.



(Ia) X=Cl
(Ib) X=OH



(Ic)



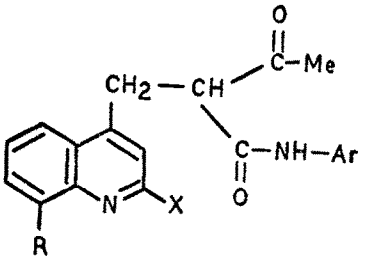
(IIa) X=Cl, Y=OH
(IIb) X=Y=OH
(IIc) X=Y=Cl

4 : 3'-Methylenebis-(2-chloro-2'-hydroxy-4'-methylquinoline) derivatives (IIa) : α-2-Chlorolepidinylacetoacetanilide (3.5g.) was dissolved in conc. H_2SO_4 (5. 0 ml.) and heated for 90 min. at 80-90° on water bath. The reaction mixture was poured on crushed ice, the residue was filtered off and crystallized from acetic acid. The m. ps. and the analytical data are reported in Table 2. The yields of products varied from 70-80%.

4 : 3'-Methylenebis-(2,2'-dichloro-4'-methylquinoline) derivatives (IIc) : The above (IIa), (1.0 g) was heated with phosphorus oxychloride (3.0 g.) on an oil-bath at 110-15° for 2 hrs. The reaction mixture was cooled and poured on crushed ice and the products crystallized from benzene. The m. ps. and analytical data are reported in Table 2. The yields of products varied from 40-50%.

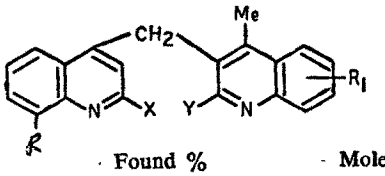
**R. J. CHUDGAR and K. N. TRIVEDI, *J. Indian Chem. Soc.*, 1972, 49, 49 (for the previous part VII).

TABLE I



Ar	R	X	m.p.	Found % C	H	N	Cl	Molecular Formula	Required % C	H	N	Cl
Ph	H	Cl	157	68.58	5.05	7.48	10.00	$C_{20}H_{17}N_2O_2Cl$	68.10	4.82	7.94	10.08
Ph	H	OH	265	71.52	5.21	7.94	—	$C_{20}H_{18}N_2O_3$	71.86	5.39	8.39	—
o-MeC_6H_4	H	Cl	199	68.36	5.48	7.15	10.10	$C_{21}H_{19}N_2O_2Cl$	68.75	5.18	7.64	9.68
o-$MeOC_6H_4$	H	Cl	178	65.95	4.91	7.76	9.17	$C_{21}H_{19}N_2O_3Cl$	65.88	4.96	7.32	9.28
p-$MeOC_6H_4$	H	Cl	189	65.73	5.11	7.80	9.00	$C_{21}H_{19}N_2O_3Cl$	65.88	4.96	7.32	9.28
p-$MeOC_6H_4$	H	OH	240	69.64	5.49	7.84	—	$C_{21}H_{20}N_2O_4$	69.23	5.49	7.69	—
m-ClC_6H_4	H	Cl	166	61.70	4.54	7.71	18.55	$C_{20}H_{16}N_2O_2Cl_2$	62.01	4.13	7.23	18.35
m-ClC_6H_4	H	OH	233	65.06	5.02	7.29	10.00	$C_{20}H_{17}N_2O_3Cl$	65.13	4.61	7.60	9.63
p-ClC_6H_4	H	Cl	185	61.90	4.53	7.06	17.29	$C_{20}H_{16}N_2O_2Cl_2$	62.01	4.13	7.23	18.35
p-ClC_6H_4	H	OH	265	64.90	4.84	7.26	9.55	$C_{20}H_{17}N_2O_3Cl$	65.13	4.61	7.60	9.64
p-Br_6H_4	H	Cl	187	55.37	3.57	6.44	—	$C_{20}H_{16}N_2O_2BrCl$	55.61	3.70	6.49	—
α-$C_{10}H_7$	H	Cl	200	72.05	4.99	6.92	8.54	$C_{24}H_{19}N_2O_2Cl$	71.57	4.72	6.96	8.82
α-$C_{10}H_7$	H	OH	280	74.82	5.34	7.09	—	$C_{24}H_{20}N_2O_3$	75.00	5.21	7.29	—
Ph	CH_3	OH	242	72.05	5.62	7.99	—	$C_{21}H_{20}N_2O_3$	72.42	5.74	8.05	—
Ph	CH_3	Cl	185	68.54	5.45	7.52	10.09	$C_{21}H_{19}N_2Cl$	68.75	5.18	7.64	9.68
o-MeC_6H_4	CH_3	Cl	195	69.18	5.12	7.32	9.55	$C_{22}H_{21}N_2O_2Cl$	69.38	5.52	7.36	9.33
o-MeC_6H_4	CH_3	OH	274	72.69	6.26	6.98	—	$C_{22}H_{22}N_2O_3$	72.94	6.08	7.74	—

TABLE 2



R_1	R	X	Y	m. p.	Found %				Molecular formula	Required %			
					C	H	N	Cl		C	H	N	Cl
H	H	OH	OH	>360	75.56	5.18	8.22	—	$C_{20}H_{16}N_2O_2$	75.96	5.06	8.85	—
H	H	Cl	OH	300	71.30	4.47	8.32	10.93	$C_{20}H_{15}N_2OCl$	71.76	4.48	8.37	10.62
H	H	Cl	Cl	210	68.06	3.82	7.89	20.56	$C_{20}H_{14}N_2Cl_2$	68.00	3.96	7.93	20.11
6-MeO	H	OH	OH	>360	72.38	4.98	7.91	—	$C_{21}H_{18}N_2O_3$	72.84	5.20	8.09	—
6-MeO	H	Cl	OH	291	68.89	5.07	7.32	9.51	$C_{21}H_{17}N_2O_2Cl$	69.13	4.66	7.68	9.47
8-MeO	H	Cl	OH	296	69.63	4.58	8,01	9.39	$C_{21}H_{17}N_2O_2Cl$	69.13	4.66	7.68	9.74
7-Cl	H	OH	OH	>360	68.69	4.04	7.64	10.50	$C_{20}H_{15}N_2O_2Cl$	68.47	4.28	7.99	10.13
7-Cl	H	Cl	OH	315	64.87	4.41	7.84	19.70	$C_{20}H_{14}N_2OCl_2$	65.05	3.79	7.59	19.20
7-Cl	H	Cl	Cl	249	61.51	3.55	7.25	27.10	$C_{20}H_{13}N_2Cl_3$	61.93	3.35	7.23	27.47
6-Cl	H	OH	OH	>330	68.60	4.56	7.59	10.56	$C_{20}H_{15}N_2O_2Cl$	68.47	4.28	7.99	10.13
H	CH_3	OH	OH	>360	73.77	5.49	8.19	—	$C_{21}H_{18}N_2O_2$	73.37	5.45	8.49	—
H	CH_3	Cl	Cl	228	68.72	4.68	7.88	19.55	$C_{21}H_{16}N_2Cl_2$	68.66	4.36	7.63	19.35
8-Me	CH_3	OH	OH	>360	76.35	5.65	8.00	—	$C_{22}H_{20}N_2O_2$	76.74	5.81	8.14	—
8-Me	CH_3	Cl	Cl	205	69.08	4.60	7.87	18.55	$C_{22}H_{18}N_2Cl_2$	69.30	4.73	7.35	18.64
Benzo (h)	H	OH	OH	>360	79.01	5.10	7.82	—	$C_{24}H_{18}N_2O_2$	78.69	4.92	7.65	—
Benzo (h)	H	Cl	OH	>360	75.08	4.63	7.16	9.50	$C_{24}H_{17}N_2OCl$	74.90	4.42	7.28	9.23
Benzo (h)	H	Cl	Cl	271	71.74	4.23	6.92	17.55	$C_{24}H_{16}N_2Cl_2$	71.46	3.97	6.95	17.62

Acknowledgement

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