CHAPTER-II

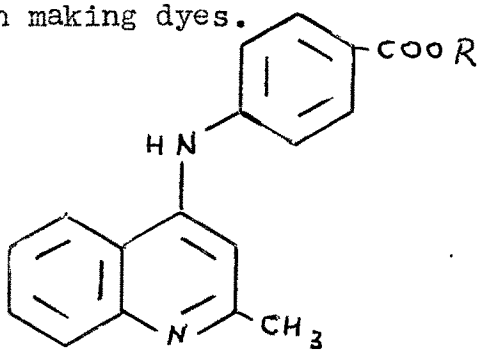
SECTION-I

Synthesis of Quinolyl aminobenzoic acid derivatives :-

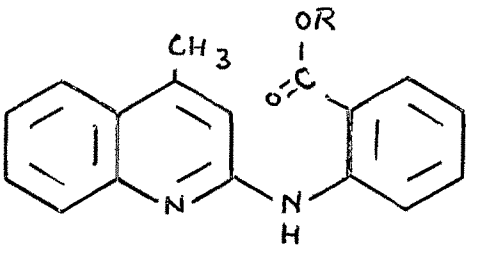
In recent years anticarcinogenic compounds have received considerable importance. Considerable amount of work had been carried out in early days and in recent years nitrogen mustards and their compounds have great importance, as they may be the remedy for cancer. In present work the quinolylamino benzoic acid derivatives are selected as carrier moiety for nitrogen mustards functional group. p(4-quinolylamino)benzoic acid, o-(4-quinolylamino) benzoic acid, p-(2-quinolylamino)benzoic acid and o-(2-quinolylamino)benzoic acid and their hydrazides are used as the carrier moiety for the nitrogen mustards.

Farbenind[1], synthesised 2-methyl-4-phenylamino quinoline-4'-carboxylic acid (1) by heating 4-chloro-2-methyl quinoline with p-amino benzoic acid ethyl ester in dichlorobenzene solution. 4-Methyl-2-phenylamino quinoline-2'-carboxylic acid (2) and its ethyl ester was

prepared by heating in $PhNO_2$ or by fusing 2-chloro-4-methylquinoline with o-amino benzoic acid or its ethyl ester. These compounds were synthesised with a view to use them as new therapeutic agents or as intermediates in making dyes.



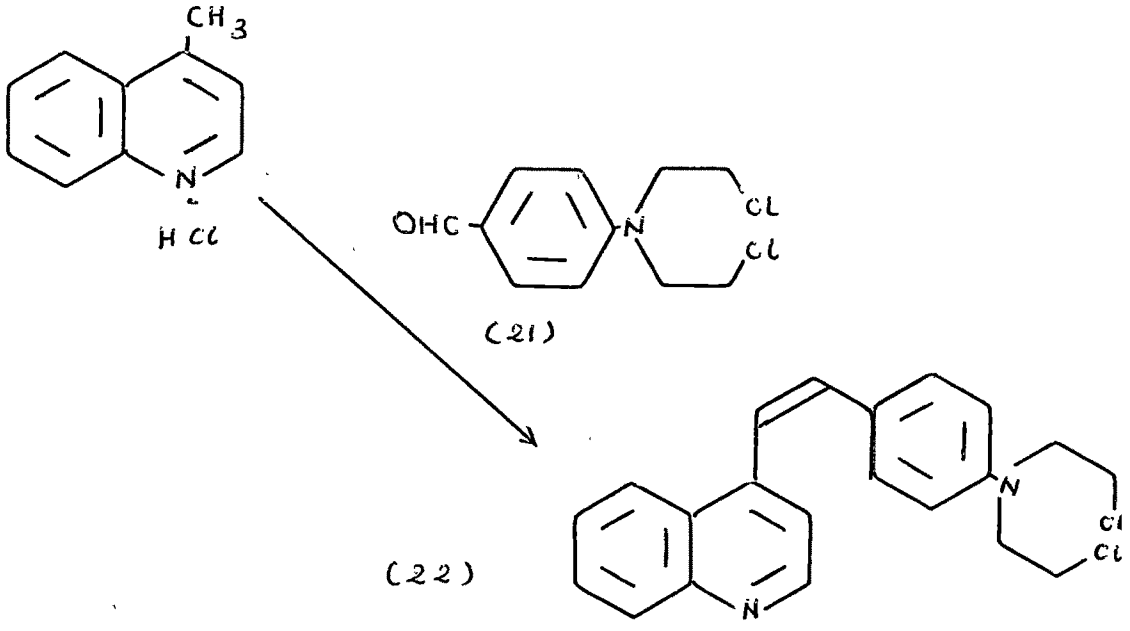
(I)



(2)

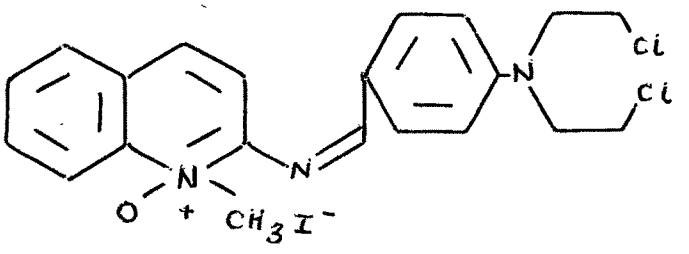
Kurt Desamari[2], reported condensation of p-amino--benzoic acid ethylester or m-aminobenzoic acid ethylester or methyl anthranilate with 4-alkyl-2-haloquinoline derivatives to afforded similar type of compounds. 4-chloroquinoline and p-aminobenzoic acid in acetic acid was refluxed to obtained p-(4-quinolylamino)benzoic acid by Fuller, et. al[3]. Stephen and Stephen[4] found that if equimolar proportion of the 2-chlorolepidine and methylanthranilate were used for the condensation, the yield was found to be 10-30 % lower than if one molar excess of methyl anthranilate was used. In literature, o-(4-quinolyl)amino benzoic acid derivatives were generally reported as anti inflamatory and analgesic agents[4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20]

Moreover Bahner and coworkers[21] condensed lepidine and its derivatives with p-(N,N-bis(2-chloroethyl) amino)benzaldehyde (21) to obtain 4-(p-(N,N-bis(2-chloroethyl)amino)styryl)quinoline ; as follows :



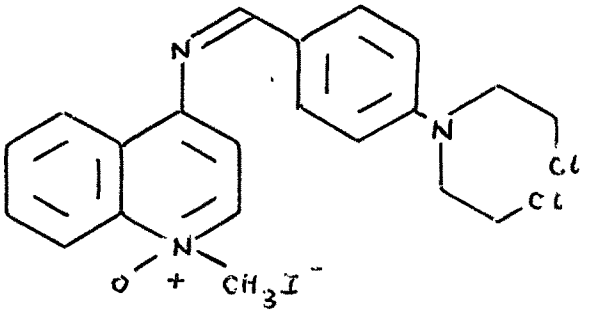
Similarly by using aldehyde (21), Schulze and Jungstand[22] synthesised some new Schiff bases and tried to establish the correlation between chemical structure and biological activity against the Ehrlich ascites tumour of azomethines containing the nitrogen mustard group. Thus they have prepared 4-(n-(p-(bis-(2-chloroethyl)amino)phenyl) formimidoyl)-1-methyl-quinolinium iodide oxide (23) and observed that it is most strongly active against Ehrlich ascites carcinoma in AB/Jenamice and survived the mice for more than 30 days. Also 2-(N-(p-(bis-(2-chloroethyl) amino)phenyl)formimidoyl)-1-methyl quinolinium iodide (24)

was moderately inhibitory and the animals survived for 21-30 days after tumour inoculation. But they reported none of the other compounds, which they prepared similar type, produced significant antitumour effects.



(23)

(24)

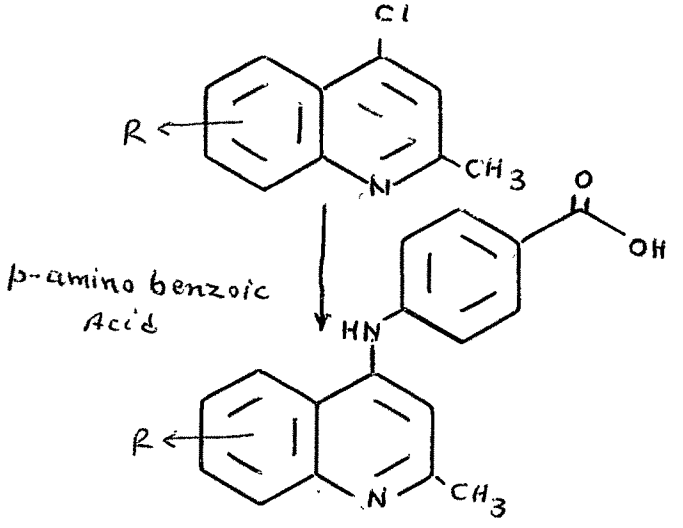


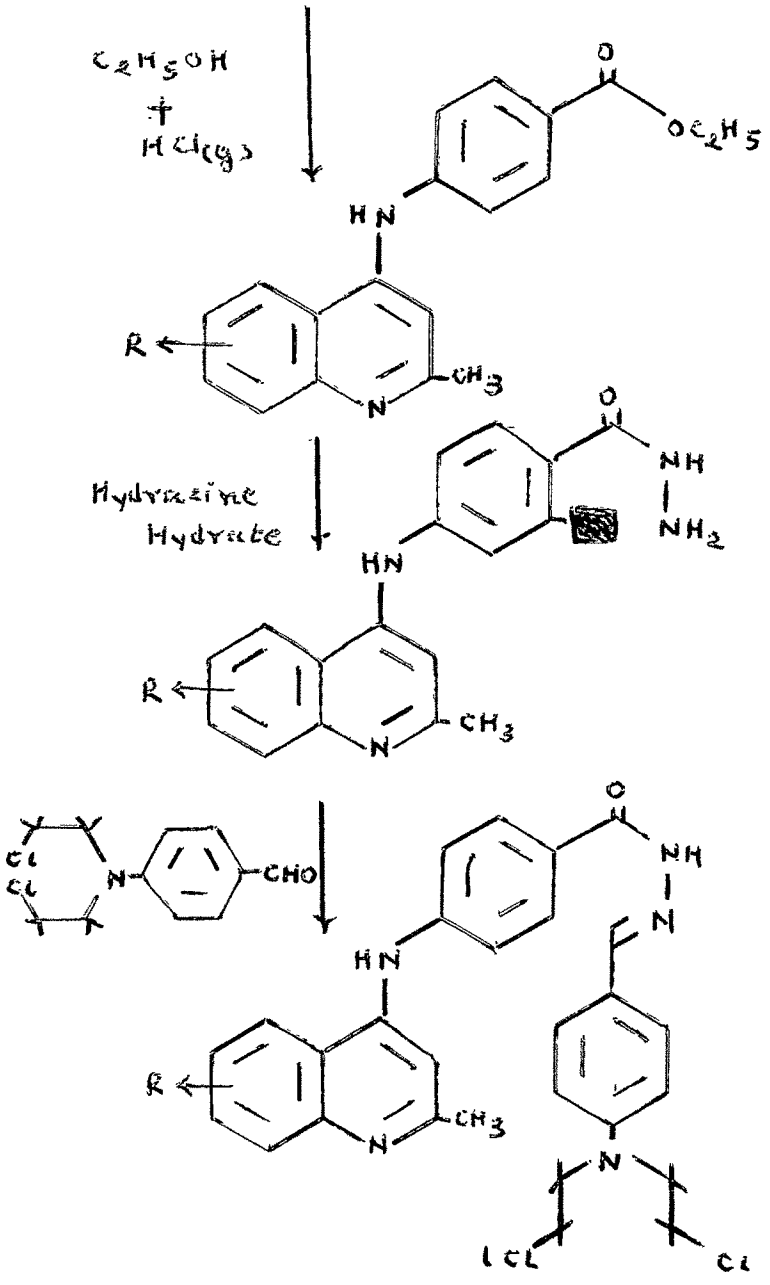
On reviewing literature it was observed that all the esters of carbonylphenyl amino quinoline derivatives were more or less good analgesic, anti inflammatory agents and some of them were hypotensive or hypertensive agents. In continuation of the work on anti-cancer agents, nitrogen mustards from the 4-(p-hydrazino-carbonyl phenyl amino) quinoline derivatives, 2-(p-hydrazino carbonyl phenyl amino) quinoline derivatives, 4-(o-hydrazino carbonyl phenyl amino) quinoline derivatives and 2-(o-hydrazino carbonyl phenyl amino)quinoline derivatives were prepared by condensation of corresponding hydrazino derivatives with p-(N,N-bis(2-chloroethyl)amino)benzaldehyde (21), to test them for anti-cancer activities.

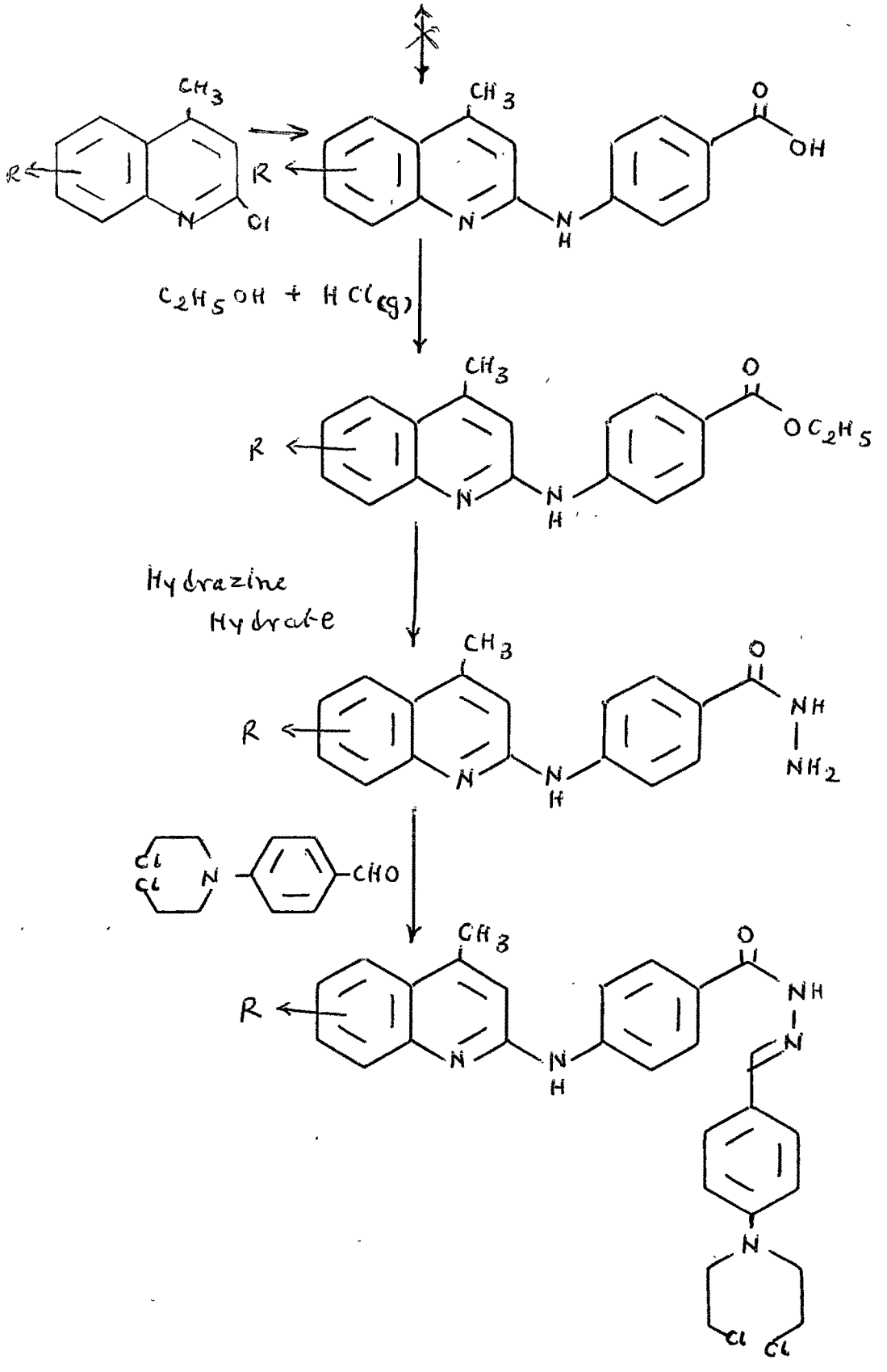
General Procedure for preparation of 4-(4-(2)-hydrazino carbonyl phenyl amino)-2-methyl quinoline derivatives :

4-Chloro-2-methylquinoline derivative was treated with p-aminobenzoic acid or anthranilic acid in 2N HCl to give 4-(carboxy phenyl amino)-2-methyl quinoline derivative which was esterified by reacting free acid with absolute ethanol and dry hydrochloric acid gas. The ester was then refluxed with Hydrazine hydrate in ethanol to give 4-(hydrazino carbonyl phenyl amino)-2-methyl quinoline derivative, which was further treated with aldehyde (32) in ethanol to give hydrazones, structure of which were assigned on the basis of their analytical results and IR spectra.

Similar series of reactions were carried out on 2-chloro-4-methyl quinoline derivatives by condensing with p-aminobenzoic acid and o-aminobenzoic acid. The structure of these compounds were also assigned on the basis of analytical results and IR spectra.




C2H5OH
+
HCl(g)
HN
O
OC2H5
R
CH3
N
Hydrazine
Hydrate
NH
NH2
Cl
Cl
CHO


CH3
R
Cl
N
OH
NH
$C_2H_5OH + HCl_{(g)}$
OC_2H_5
Hydrazine
Hydrate
NH_2
Cl
CHO

EXPERIMENTAL

General method for the synthesis of 4-(p-(p-(N,N-bis-(2-chloroethyl)amino)benzylidine)carbhydrazide phenyl amino)-2-methyl quinoline derivative (9) :

4-(p-carbethoxy phenyl amino)-2-methyl quinoline derivative (7) :

A mixture of 2-methyl-4-chloro quinoline derivative (0.01 M), p-aminobenzoic acid (0.01 M) and 2N HCl (10 ml) was refluxed on sand bath for 5 hr. The solid, 4-(p-carboxy phenyl amino)-2-methyl quinoline hydrochloride was separated on cooling, which was filtered and dried. The latter one (3.0 g) was added to the absolute ethanol (30 ml) made saturated with hydrochloric acid by passing hydrochloric acid gas and reaction mixture was then refluxed in water bath for 5-6 hr. The reaction mixture was poured into excess of water and was treated with $NaHCO_3$ (20 %) solution. The separated product was filtered and crystallised from ethanol. Yield about 2.0-3.0 gm. The m.ps. and analytical results are reported in Table 1.

4-(p-carbhydrazide phenyl amino)-2-methyl quinoline derivatives (8) :

A mixture of Hydrazine hydrate (5.0 ml 80 %) and 4-(p-carbethoxy phenyl amino)-2-methyl quinoline (0.01 M) in 25 ml. ethanol was refluxed in water bath for 6-7 hr. The solvent was removed and solid product crystallised from ethanol. Yield about 1.0 gm. The m.ps. and analytical results are reported in Table 2.

4-(p-(p-(N,N-bis(2-chloroethyl)amino)benzylidene) carbhydrazide phenyl amino)-2-methyl quinoline derivative (9) :

4-(p-carbhydrazide phenyl amino)-2-methyl quinoline (0.01 M), p-(N,N-bis(2-chloroethyl)amino)benzaldehyde (0.01 M) and ethanol (25 ml) were refluxed for 60-90 min. in the water bath and reaction mixture was left at room temperature for few hours and separated product was filtered. It was crystallised from ethanol. Yield about 2 gm. The m.ps. and analytical results are reported in Table 3 and spectral results are in Table 4.

Similar series of reaction were carried out by using differently substituted 4-chloro-2-methyl quinolines derivatives and anthranilic acid. The m.ps. and analytical

results of 4-(o-(p-(N,N-bis(2-chloroethyl)amino) benzylidine carbhydrazide phenyl amino)-2-methyl quinoline derivative are reported in Table 5, 6 and 7. The spectral result of above prepared compounds are reported in Table 4. Also similar series of reactions were carried out by using substituted 2-chloro-4-methyl quinoline derivative and p-aminobenzoic acid. The m.ps. and analytical results of carbethoxy derivatives, carbhydrazide derivatives and 2-(p-(N,N-bis(2-chloroethyl)amino)benzylidine)carbhydrazide phenyl amino)-4-methyl quinoline derivatives are reported in Table 8, 9 and 10 respectively. The spectral results are in Table 4. Also by using 2-chloro-4-methyl quinoline derivatives and anthranilic acid, 2(o-(p-(N,N-bis(2-chloroethyl)amino)benzylidine)carbhydrazide phenyl amino) 4-methyl quinoline derivative were obtained. The m.ps. and analytical results of carbethoxy derivatives, carbhydrazide derivatives and hydrozone derivatives are reported in Table 11, 12 and 13 respectively. The spectral results are reported in Table 4.

Table 1

4-(p-carbethoxy phenyl amino)-2-methyl quinoline derivative

Comp. No.	R	m.p.	Found %			Molecular formula	Required %		
			C	H	N		C	H	N
7	H	170	74.20	5.55	9.00	$C_{19}H_{18}N_2O_2$	74.50	5.88	9.15
10	6-Me	208	74.66	6.15	7.99	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75
13	8-Me	225(d)	74.75	6.02	8.88	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75
16	6-MeO	262	71.02	5.59	8.00	$C_{20}H_{20}N_2O_3$	71.44	5.95	8.34
19	6-EtO	277	71.75	6.17	7.88	$C_{21}H_{22}N_2O_3$	72.00	6.28	8.00

Table 2

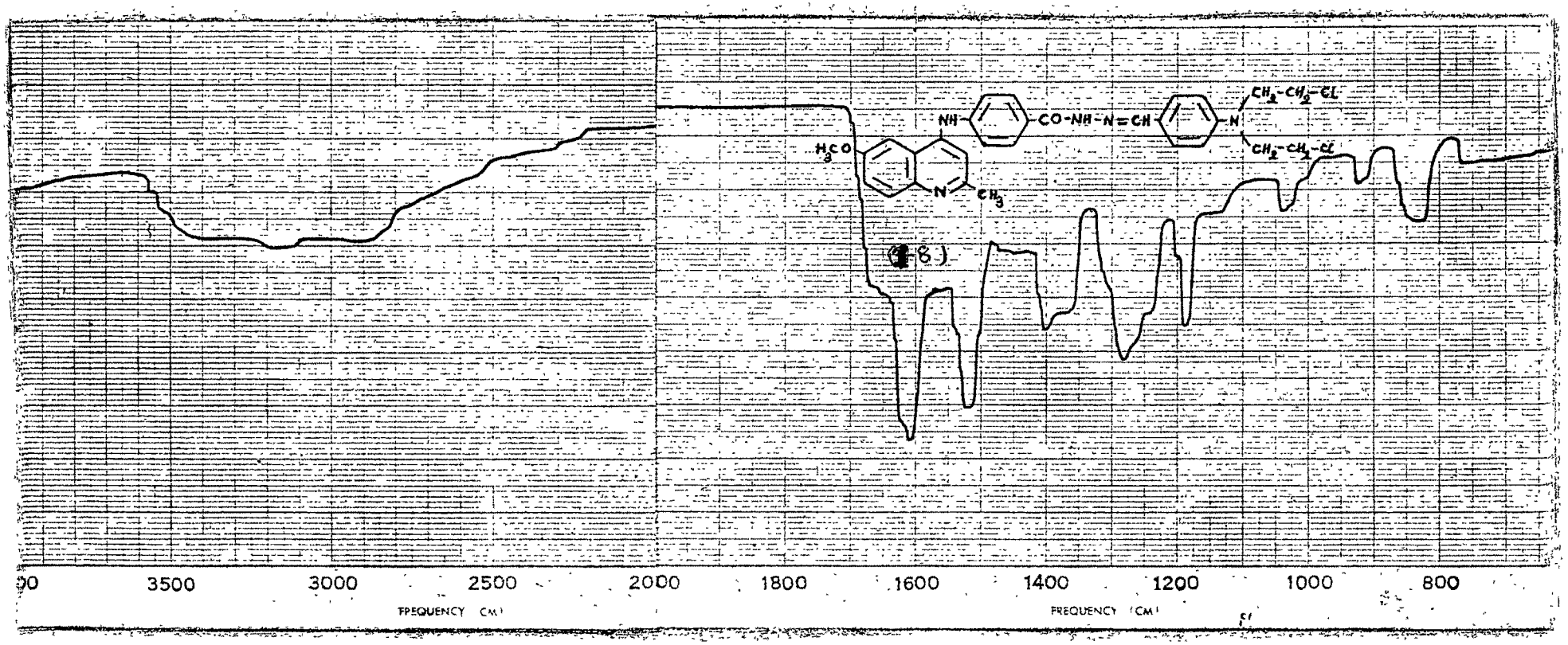
4-(p-carbhydrazide phenyl amino)-2-methyl quinoline derivative

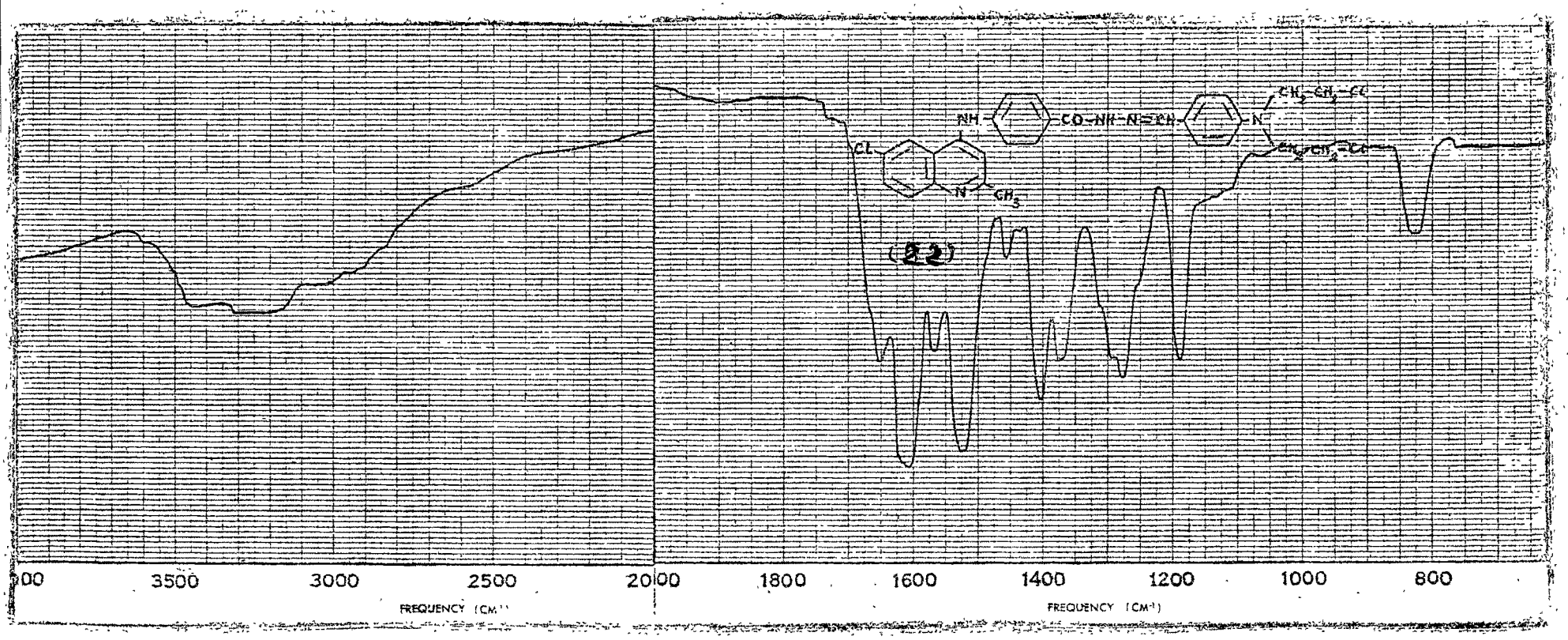
Comp. No.	R	m.p.	Found %			Molecular formula	Required %		
			C	H	N		C	H	N
8	H	268	69.35	5.63	18.70	$C_{17}H_{16}N_4O$	69.85	5.48	19.18
11	6-Me	245	70.10	6.08	18.04	$C_{18}H_{18}N_4O$	70.60	5.88	18.30
14	8-Me	273(d)	70.11	6.20	18.25	$C_{18}H_{18}N_4O$	70.60	5.88	18.30
17	6-MeO	245	66.88	5.70	17.51	$C_{18}H_{18}N_4O_2$	67.10	5.59	17.40
18	6-EtO	264	68.00	6.12	16.78	$C_{19}H_{20}N_4O_2$	67.86	5.95	16.67

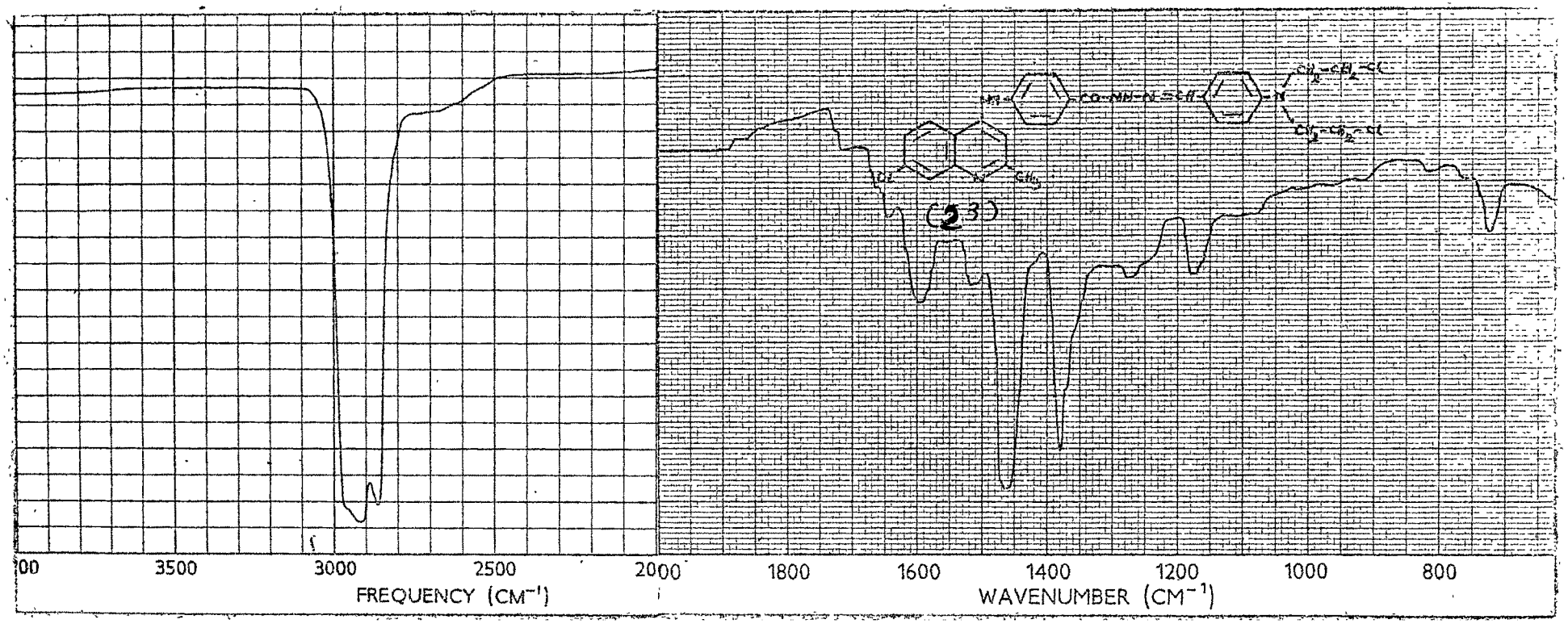
Table 3

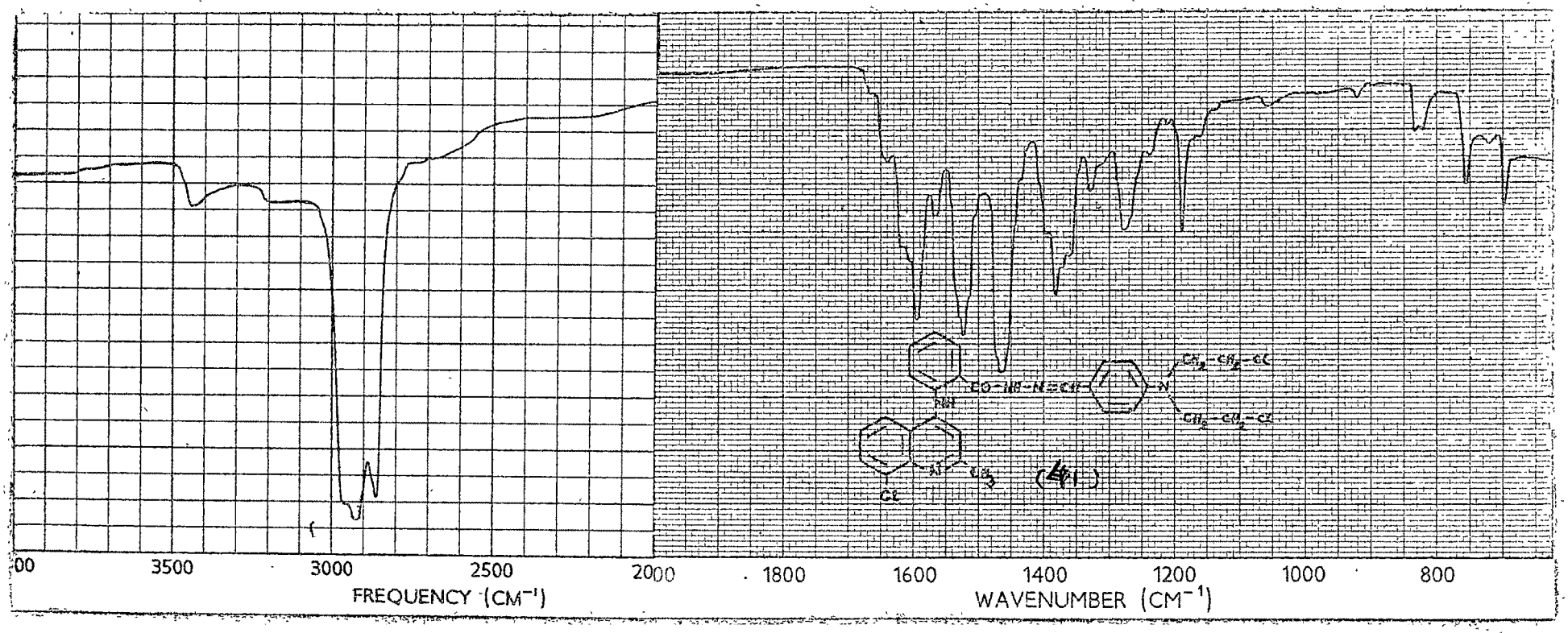
4-(p-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)carbhydraside phenyl amino)-2-methyl quinoline derivative

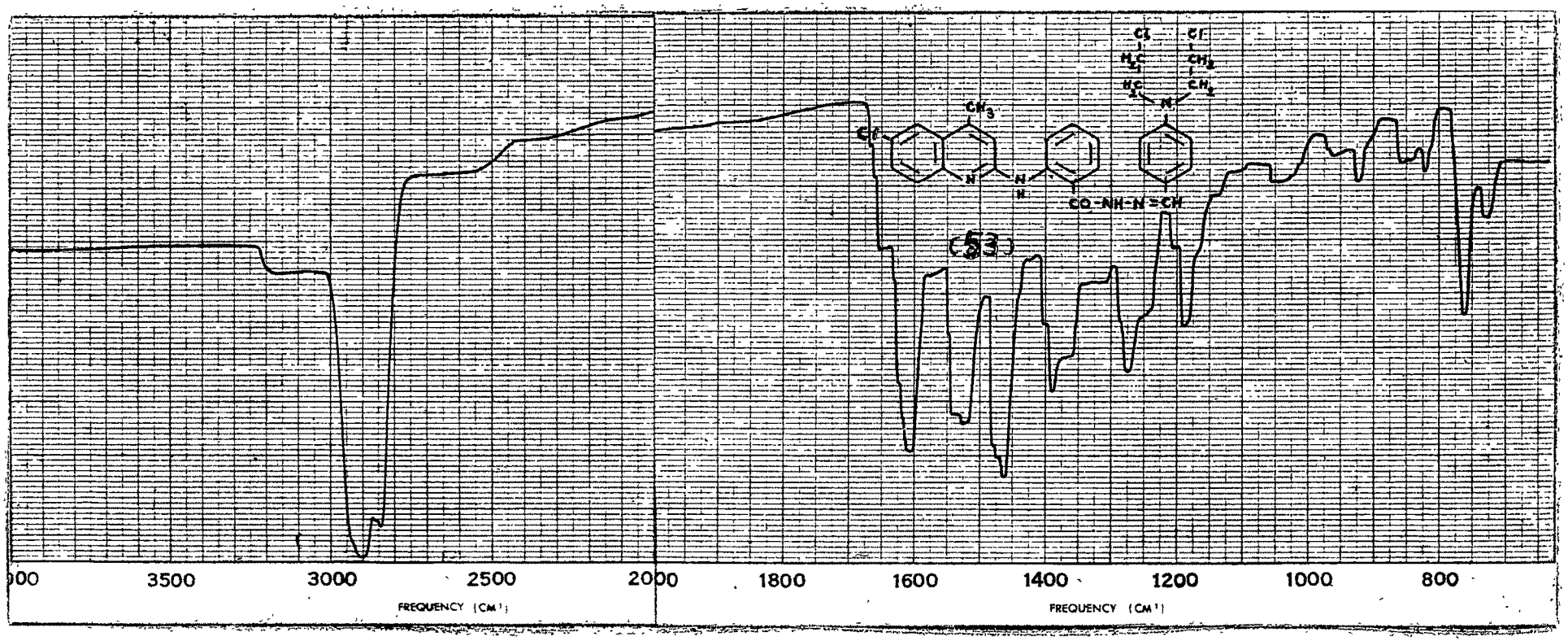
Comp. No.	R	m.p.	Found %				Molecular formula	Reauired %			
			C	H	N	Cl		C	H	N	Cl
9	H	185	64.23	5.54	13.04	13.42	$C_{28}H_{27}N_5OCl_2$	64.62	5.19	13.46	13.66
12	6-Me	153(d)	65.10	5.95	12.74	13.12	$C_{29}H_{29}N_5OCl_2$	65.20	5.43	13.11	13.30
15	8-Me	207	65.28	5.56	13.00	12.98	$C_{29}H_{29}N_5OCl_2$	65.20	5.43	13.11	13.30
18	6-MeO	190(d)	63.09	5.55	12.57	13.08	$C_{29}H_{29}N_5O_2Cl_2$	63.28	5.27	12.73	12.91
21	6-EtO	160(d)	63.50	6.06	12.10	12.73	$C_{30}H_{31}N_5O_2Cl_2$	63.83	5.49	12.41	12.60
22	6-Cl	192(d)	60.28	5.02	12.57	19.15	$C_{28}H_{26}N_5OCl_3$	60.60	4.69	12.62	19.20
23	7-Cl	132(d)	60.12	5.00	12.25	19.00	$C_{28}H_{26}N_5OCl_3$	60.60	4.69	12.62	19.20
24	8-Cl	147(d)	60.47	5.00	12.37	18.97	$C_{28}H_{26}N_5OCl_3$	60.60	4.69	12.62	19.20

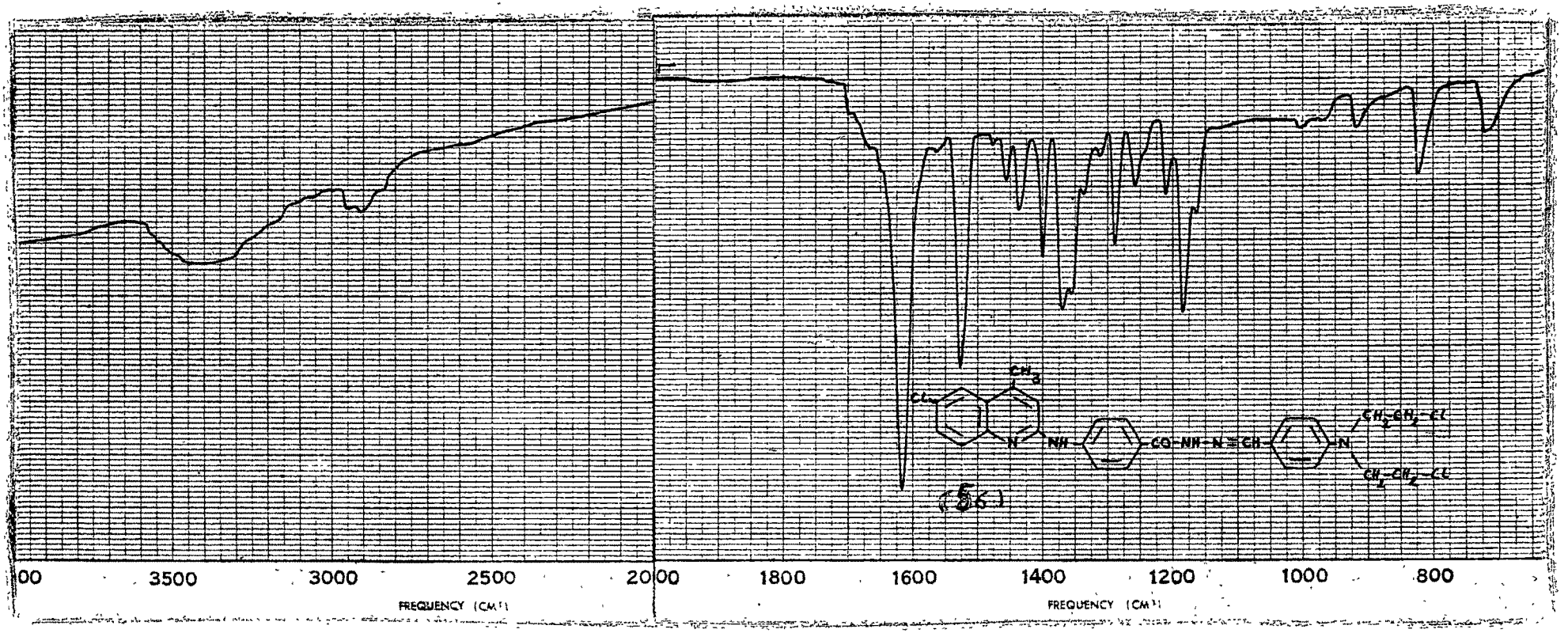

NH
CO-NH-N=CH
N
CH_2-CH_2-Cl
CH_2-CH_2-Cl
H_3CO
N
CH_3
(8)
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM)
FREQUENCY (CM)


NH
CO-NH-N=CH
N
Cl
N
CH3
(22)
3500
3000
2500
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY (CM⁻¹)


(23)
00
3500
3000
2500
2000
FREQUENCY (CM⁻¹)
1800
1600
1400
1200
1000
800
WAVENUMBER (CM⁻¹)


00
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
WAVENUMBER (CM⁻¹)
(41)


3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
FREQUENCY (CM⁻¹)
CH3
Cl
N
N
H
CO-NH-N=CH
Cl
H2C
H2C
N
CH2
CH2
Cl


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

(56)

Table 4

Results of IR spectra

Comp.No.	IR band (cm^{-1})			
	C=N	-CO-NH	-NH-	C-Cl
18	1625	1675	3300	775
32	1620	1655	3200	725
33	1650	1720	3200	725
41	1620	1640	3440	755
53	1620	1660	3400	725
56	1620	1660	3200	760

Table 5

4-(o-carbethoxy phenyl amino)-2-methyl quinoline derivative

Comp. No.	R	m.p.	Found %			Molecular formula	Required %		
			C	H	N		C	H	N
25	H	107	74.68	6.07	8.77	$C_{19}H_{18}N_2O_2$	74.50	5.88	9.15
28	6-Me	125	75.28	6.66	8.80	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75
31	8-Me	110	75.12	6.36	8.50	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75
34	6-MeO	205	70.98	6.00	8.50	$C_{20}H_{20}N_2O_3$	71.44	5.95	8.34
36	6-EtO	134	72.50	6.78	8.37	$C_{21}H_{22}N_2O_3$	72.00	6.28	8.00

Table 6

4-(p-carbhydrazide phenyl amino)-2-methyl quinoline derivative

Comp. No.	R	m.p.	Found %			Molecular formula	Required %		
			C	H	N		C	H	N
26	H	228	69.60	5.69	19.02	$C_{17}H_{16}N_4O$	69.85	5.48	19.18
29	6-Me	265	71.10	5.90	18.18	$C_{18}H_{18}N_4O$	70.60	5.88	18.30
32	8-Me	222	70.50	5.78	18.14	$C_{18}H_{18}N_4O$	70.60	5.88	18.30
35	6-MeO	216	67.18	5.84	17.20	$C_{18}H_{18}N_4O_2$	67.10	5.59	17.40
38	6-EtO	208	67.31	6.32	16.47	$C_{19}H_{20}N_4O_2$	67.86	5.59	16.67

Table 7

4-(o-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)carbhydraside phenyl amino)-2-methyl quinoline derivative

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
27	H	223	64.12	5.32	13.29	13.13	$C_{28}H_{27}N_5OCl_2$	64.62	5.19	13.46	13.66
30	6-Me	147(d)	65.34	5.79	12.61	13.19	$C_{29}H_{29}N_5OCl_2$	65.20	5.43	13.11	13.30
33	8-Me	195	65.00	5.55	13.19	13.93	$C_{29}H_{29}N_5OCl_2$	65.20	5.43	13.11	13.30
36	6-MeO	135	63.40	5.12	12.50	12.98	$C_{29}H_{29}N_5O_2Cl_2$	63.28	5.27	12.73	12.91
39	6-EtO	170	63.50	5.95	11.98	12.22	$C_{30}H_{31}N_5O_2Cl_2$	63.83	5.49	12.41	12.60
40	6-Cl	140(d)	60.26	5.15	12.18	19.12	$C_{28}H_{26}N_5OCl_3$	60.60	4.69	12.62	19.20
41	8-Cl	162(d)	60.42	5.02	12.20	19.00	$C_{28}H_{26}N_5OCl_3$	60.60	4.69	12.62	19.20

Table 8

2-(p-carbethoxy phenyl amino)-4-methyl quinoline derivative

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
42	H	182	74.60	6.35	9.11	-	$C_{19}H_{18}N_2O_2$	74.50	5.88	9.15	-
45	6-Me	222	74.50	6.68	8.82	-	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75	-
48	8-Me	199	74.50	6.42	8.75	-	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75	-
51	6-Cl	110	66.52	4.39	8.75	9.95	$C_{17}H_{17}N_2O_2Cl$	66.69	4.99	8.22	10.43

Table 9

2-(p-carbhydriazide phenyl amino)-4-methyl quinoline derivative

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
43	H	254	69.57	5.13	19.40	-	$C_{17}H_{16}N_4O$	69.85	5.48	19.18	-
46	6-Me	261	70.26	6.39	17.95	-	$C_{18}H_{18}N_4O$	70.50	5.88	18.30	-
49	8-Me	286	70.42	6.20	18.00	-	$C_{18}H_{18}N_4O$	70.50	5.88	18.30	-
52	6-Cl	220	62.18	4.77	17.10	10.57	$C_{17}H_{15}N_4OCl$	62.20	4.57	17.07	10.82

Table 10

2-(p-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)carbhydrazine phenyl amino)-4-methyl quinoline derivative

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
44	H	220	65.04	5.19	12.97	14.16	$C_{28}H_{27}N_5OCl_2$	64.62	5.19	13.46	13.66
47	6-Me	220	64.90	5.27	12.74	13.73	$C_{29}H_{29}N_5OCl_2$	65.20	5.43	13.11	13.30
50	8-Me	230	65.70	5.87	12.67	13.68	$C_{29}H_{29}N_5OCl_2$	66.20	5.43	13.11	13.30
53	6-Cl	162	60.40	4.25	12.98	19.37	$C_{28}H_{26}N_5OCl_3$	60.60	4.64	12.62	19.20

Table 11

2-(o-carbethoxy phenyl amino)-4-methyl quinoline derivative

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
54	H	130	74.33	5.73	9.07	-	$C_{19}H_{18}N_2O_2$	74.50	5.88	9.15	-
57	6-Me	173	74.57	6.57	8.43	-	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75	-
60	8-Me	132	74.50	6.42	8.75	-	$C_{20}H_{20}N_2O_2$	75.00	6.25	8.75	-
63	6-Cl	168	66.53	4.72	8.00	10.78	$C_{19}H_{17}N_4OCl$	66.96	4.99	8.22	10.42

Table 12

2-(o-carbhydriazide phenyl amino)-4-methyl quinoline derivative

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
55	H	222	69.44	5.94	19.12	-	$C_{17}H_{16}N_4O$	69.85	5.48	19.18	-
58	6-Me	241	70.18	6.38	18.41	-	$C_{18}H_{18}N_4O$	70.50	5.88	18.30	-
61	8-Me	178	71.20	6.39	18.14	-	$C_{18}H_{18}N_4O$	70.50	5.88	18.30	-
64	6-Cl	225	62.40	4.55	17.00	10.75	$C_{17}H_{15}N_4OCl$	66.20	4.57	17.07	10.82

Table 13

2-(o-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)carbhydrazide phenyl amino)-4-methyl quinoline derivative

Comp. No.	R	m.p. °C	Found % C	H	N	Cl	Molecular formula	Required % C	H	N	Cl
56	H	101	65.01	5.65	13.12	14.10	$C_{28}H_{27}N_5OCl_2$	64.62	5.19	13.46	13.66
59	6-Me	200	65.70	5.85	12.79	13.59	$C_{29}H_{29}N_5OCl_2$	65.20	5.43	13.11	13.30
62	8-Me	191	65.70	5.87	12.76	13.68	$C_{29}H_{29}N_5OCl_2$	65.20	5.43	13.11	13.30
65	6-Cl	158	60.38	4.29	12.90	19.57	$C_{28}H_{26}N_5OCl_3$	60.60	4.69	12.62	19.20

References :

1. I.G. Farbenind ; A.G. Brit. 321738. C.A., 24, 2837, 1930.

2. Kurt Desamari ; U.S. 1810267. C.A., 25, 4663, 1931.

3. A.T. Fuller, G.R. Harington, Rosalind Pitt River and Joan M.L. Stephen ; J.Chem.Soc., 241, 1948.

4. T. Stephen and Henry Stephen ; J.Chem.Soc., 4173-7, 1956.

5. Laboratories Francis de Chimiotherapie ; Fr. M. 1399. C.A., 58, 1320 c, 1963.

6. Rousel - UCLAF ; Fr. M. 1773. C.A., 59, 11450 b, 1963.

7. Roussel - UCLAF ; Fr.M. 1877. C.A., 60, 2959, 1965.

8. Roussel - UCLAF ; Neth.Appl. 6603870. C.A., 66, 85704 t, 1967.

9. Avies Robert ; Fr. 1543448. C.A., 72, 21620 d, 1970.

10. Allais Ander and Girault Pierre ; Fr. M. 6091. C.A., 72, 66847 z, 1970.

11. Allais Ander and Meier Jean ; Ger.Offen. 1925607. C.A., 74, 76341 k, 1971.

12. Soviete d' Etudes Scientifiques et Industrielles de I'Ille de- France ; Fr. 1600535. C.A., 74, 99905 m, 1971.

13. Theriault Robert John, Wideburg Normal Earl, and Karwowski James Paul ; Ger.Offen 2251054. C.A., 79, 16926 y, 1973.

14. Bertrand Francois R., U.S. 3769410. C.A., 80, 37020 j, 1974.

15. Najer Henry, Manoury Philippe M.J., Dumas Andre P.F., Lefevre Francoise M., Giicelli Don P.R. ; Ger.Offen 2338260. C.A., 80, 120999 f, 1974.

16. Allis Ander and Girault Pierre ; Fr.M. 6195. C.A., 72, 43490 p, 1970.

17. Coverdale Charles E., Skaletzky Louis L. ; Ger. Offen 2428194. C.A., 82, 171059 y, 1975.

18. Atwell Grahm J. and Cain Bruce F., J.Med.Chem., 17(9), 930-4, 1974. C.A., 81, 163225 p, 1974.

19. Coverdale Charles E., Skaletzky Louis L. ; Ger. Offen 2428190. C.A., 84, 44147 s, 1976.

20. El. Agmy A.A., El-Kerdawy M.M. and ouf A.A. J.Drug.Res. 6(2), 131-34, 1974. C.A., 84, 17101 r, 1976.

21. Carl Tabb Bahner, Lydia Moore Rives, Emma Bettis Bales, Ered Hannan, Bobby Pettyjohn, Lovely Free and Hugh Free ; J.Org.Chem., 27, 2233-6, 1962. C.A., 57, 5890, 1962.

22. W. Schulze, W. Gutsche and W. Jungstand ;
Arzneimittel-Forsch. 15(10), 1235-8, 1965.
C.A., 64, 7229, 1966.

CHAPTER-II

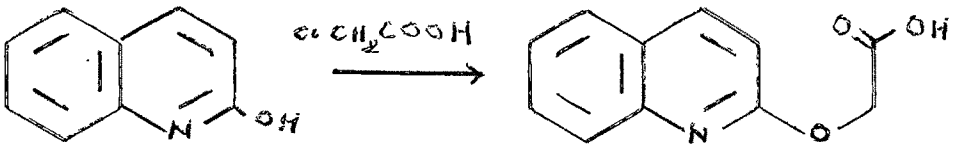
SECTION-II

Synthesis of Nitrogen Mustards from 4-quinolyloxy acetic acid derivatives :

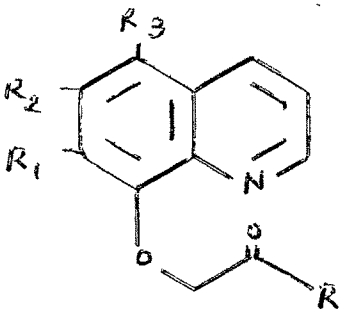
Quinolyloxy acetic acid derivatives are therapeutically active compounds e.g. 6-(8)-quinolinyloxy acetic acid derivatives were used as plant growth regulators, hypnotics, herbicides and growth stimulators. Also some of the 8-quinolinyloxy acetamide derivatives are used as feed additives. Moszew and Mirek[1] have prepared some derivatives of 6- and 8-quinolyloxy acetic acid as synthetic plant growth regulators. 7-chloro-8-quinolyloxy acetic acids were prepared by Skraup synthesis using 2-chloro-4-amino phenoxy acetic acid. Also unsuccessful attempts were made by Major and Ohly[2] to prepare N-alkoxy-N-alkyl 8-quinolyloxy acetamides to test them for their hypnotic activity by converting ethyl-8-quinolyloxy acetate to amides (1) and hydrazides (2).

In search for new herbicides and growth stimulators, 2-quinolyloxy acetic acid (3), 8-quinolyloxy acetic acid (4), 5,7-dichloro-8-quinolyloxy acetic acid (5) and 5,7-dibromo 8-quinolyloxy acetic acid (6) were synthesised by

Morgun and Volga[3]. 2-Hydroxyquinoline was condensed with chloro acetic acid in alkaline condition to give 2-quinolyloxy acetic acid (3).



(3)



(1) $R = NH_2$, $R_1 = R_3 = R_2 = H$

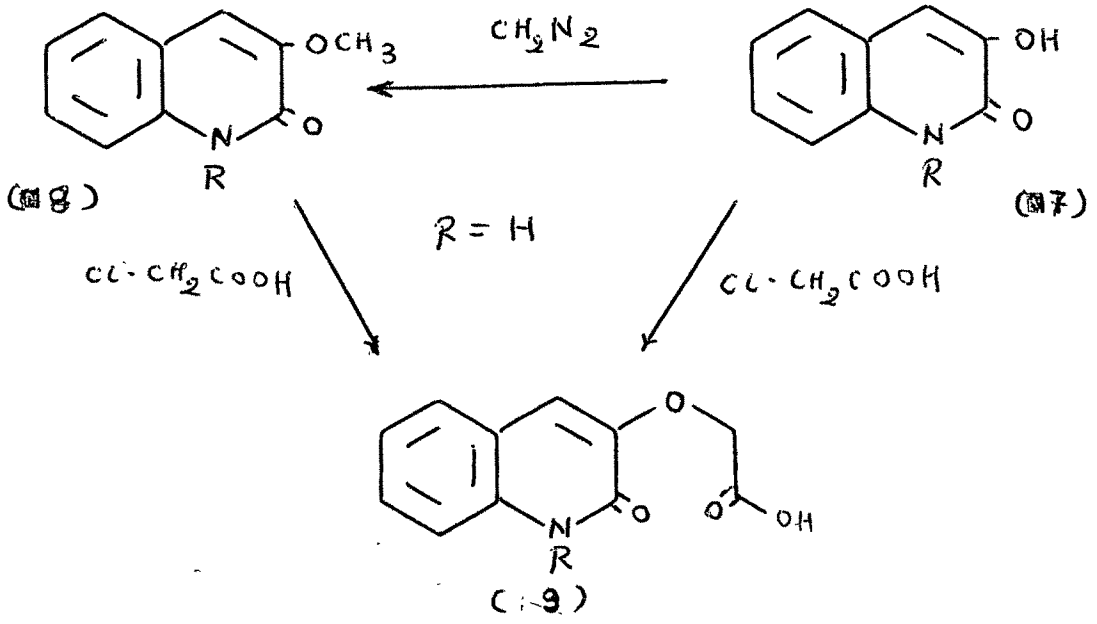
(2) $R = NH\text{-}NH_2$, $R_1 = R_2 = R_3 = H$

(3) $R = OH$, $R_1 = R_2 = R_3 = H$

(5) $R_1 = R_3 = Cl$, $R_2 = H$, $R = OH$

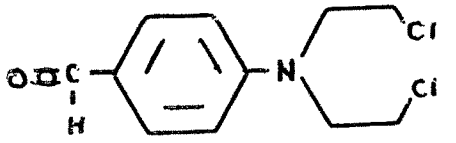
(6) $R_1 = R_3 = Br$, $R_2 = H$, $R = OH$

Makoto and Ykio[7] synthesised (2-hydroxy-3-quinolyloxy) acetic acid derivative (9) by condensing 2,3-dihydroxy quinoline with chloro acetic acid and observed that (7) had antimicrobial activity which was lost by N-methylation. Also (8) and (9) displayed a promoting effect on the root growth of young plants which was lost by N-methylation.



Pope[8] reported that p-(N,N-bis(2-chloroethyl)amino) benzaldehyde (10) and its derivatives are good synthetic potential anticancer agents. He prepared p-(chloroethyl)$_2$ -N-C_6H_4-CH=CRR, by condensing aldehyde (10) with the compound containing reactive methylene group such as malono nitrile, malonic ester, ethyl cyanoacetate, ethyl aceto--acetate by Knoevenagal reaction. He also observed that on preliminery screening test the compounds obtained from

malon nitrile and cyanoacetamide were active against the Dunning leukemia in rats. Also Hydrazono derivative of the same aldehyde (10) were synthesised by Koppec and Springer [9].



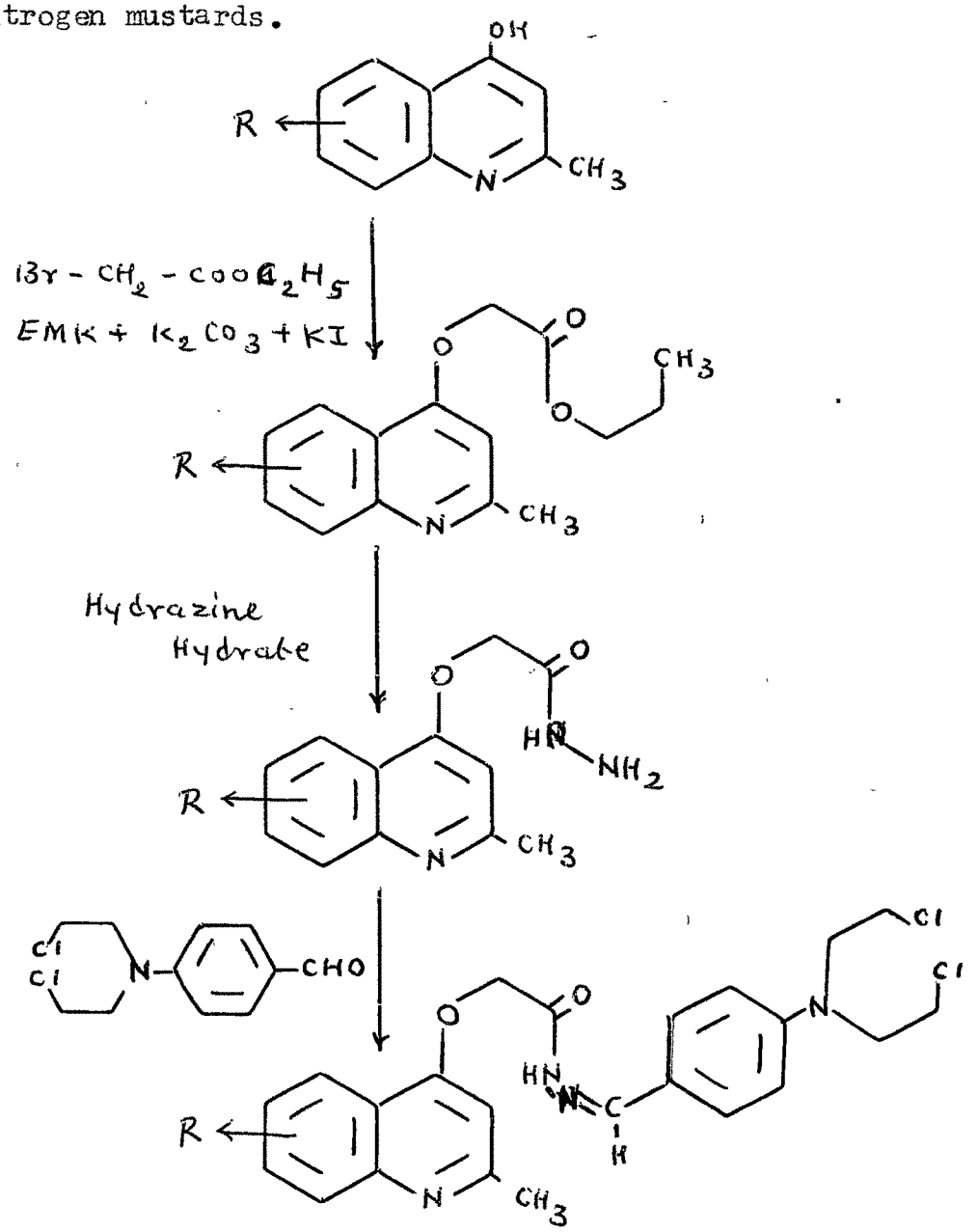
(10)

In the present work, 2-methyl-4-hydroxy quinoline derivatives converted to ethyl ester of 2-methyl-4-quinolyloxy acetic acid which on treatment with hydrazine hydrate gave the corresponding hydrazide derivative. These hydrazide derivatives were condensed with aldehyde (10) to give the nitrogen mustards, 4-(-(p-(N,N-bis(2-chloro--ethyl)amino)benzylidene)hydrazino carbonyl methoxy)-2-methyl quinoline derivatives.

Thus by condensing 2-methyl-4-hydroxy quinoline derivative with ethyl bromoacetate (11) in the presence of potassium carbonate and potassium iodide in ethylmethyl-ketone as solvent, 2-methyl-4-(ethoxy carbonylmethoxy)-6-quinoline derivative (12) were obtained which was further reacted with hydrazine hydrate to give 2-methyl-4-(hydrazino carbonyl methoxy)quinoline derivative (13). The latter one was condensed with p-(N,N-bis(2-chloroethyl)amino)benzaldehyde (10) to get nitrogen mustards, 4-(-(p-(N,N-bis(2-chloroethyl)

amino)benzylidene)hydrazino carbonylmethoxy)-2-methyl quinoline derivative (14).

A similar series of reaction were carried out by using different quinoline derivatives, to synthesise nitrogen mustards.



EXPERIMENTAL

General method for synthesis of 2-methyl-4-(-(p-(N,N-bis-(2-chloroethyl)amino)benzylidene)hydrazino carbonylmethoxy) quinoline derivatives :

2-Methyl-4-(hydrazino carbonylmethoxy)quinoline derivative :

A mixture of 2-methyl-4-hydroxy quinoline derivative (0.01 M) and ethylbromoacetate (0.01 M) was refluxed in the presence of potassium carbonate (5.0 g) and potassium iodide (1.0 g) in ethylmethylketone as a solvent on water bath for 20 hrs. The solvent was removed and reaction mass was poured into water. The obtained product was collected and dissolved in ethanol (25 ml) and refluxed with hydrazine hydrate (80 % 10 ml) for 5 hrs. The reaction mixture was poured into excess amount of water. The separated product was filtered washed with water and crystallised from ethanol. The m.ps. and analytical results are reported in Table 1.

2-Methyl-4-(-(p-(N,N-bis-(2-chloroethyl)amino)benzylidene) hydrazino-carbonylmethoxy)quinoline derivatives :

A mixture of 2-methyl-4-(hydrazino carbonylmethoxy)

quinoline derivative (0.01 M) and p-(N,N-bis-(2-chloro--ethyl)amino)benzaldehyde (0.01 M) in ethanol (25 ml) was refluxed for 30 min. to 1 hr. The reaction mixture was kept for some times at room temperature and obtained product was filtered, and crystallised from ethanol. The m.ps. and analytical results are reported in Table 2 and spectral results are in Table 3.

Table 1

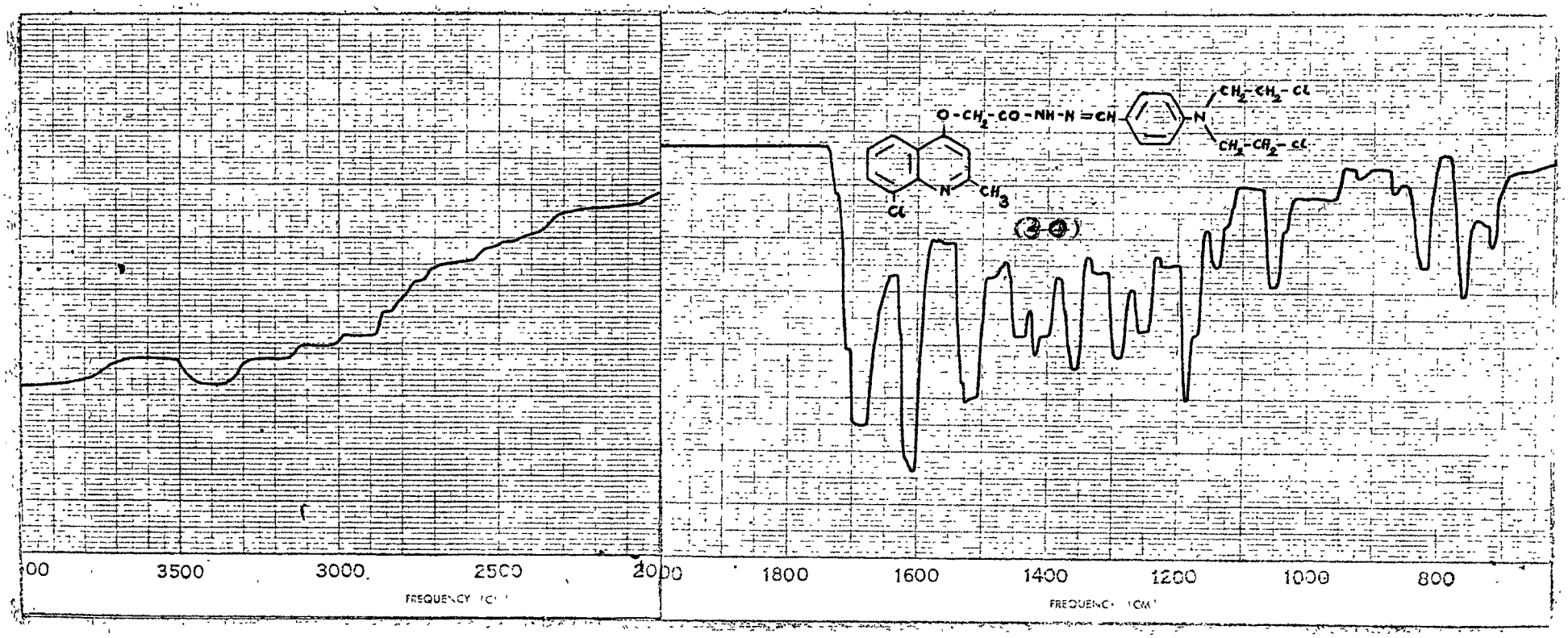
2-Methyl-4-(hydrazino carbonylmethoxy)quinoline derivatives

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
15	H	190	62.53	6.07	17.84	-	$C_{12}H_{13}N_3O_2$	62.35	5.63	18.18	-
16	6-Me	211	63.75	6.59	16.40	-	$C_{13}H_{15}N_3O_2$	63.66	6.12	17.14	-
17	8-Me	198	63.60	6.35	17.64	-	$C_{13}H_{15}N_3O_2$	63.66	6.12	17.14	-
18	6-MeO	208	59.57	5.79	16.22	-	$C_{13}H_{15}N_3O_3$	59.77	5.75	16.09	-
19	6-EtO	178(d)	61.45	6.52	15.30	-	$C_{14}H_{17}N_3O_3$	61.10	6.18	15.27	-
20	6-Cl	222(d)	54.87	4.60	15.13	13.12	$C_{12}H_{12}N_3O_2Cl$	54.25	4.52	15.82	13.37
21	7-Cl	200(d)	54.75	5.06	15.55	13.07	$C_{12}H_{12}N_3O_2Cl$	54.25	4.52	15.82	13.37
22	8-Cl	214(d)	54.58	4.62	15.90	13.12	$C_{12}H_{12}N_3O_2Cl$	54.25	4.52	15.82	13.37

Table 2

2-Methyl-4-(-(p-(N,N-bis-(2-chloroethyl)amino)benzylidene)-hydrazino carbonyl methoxy) quinoline derivatives

Comp. No.	R	m.p. °C	Found %				Molecular formula	Required %			
			C	H	N	Cl		C	H	N	Cl
23	H	122	60.37	5.85	11.78	15.30	$C_{23}H_{24}N_4O_2Cl_2$	60.13	5.23	12.20	15.47
24	6-Me	145(d)	60.73	5.57	11.45	14.88	$C_{24}H_{26}N_4O_2Cl_2$	60.90	5.50	11.84	15.01
25	8-Me	150	60.63	5.74	11.34	14.90	$C_{24}H_{26}N_4O_2Cl_2$	60.90	5.50	11.84	15.01
26	6-MeO	178	58.55	5.47	11.37	14.55	$C_{24}H_{26}N_4O_3Cl_2$	58.90	5.32	11.45	14.51
27	6-EtO	174	59.48	5.74	11.08	14.00	$C_{25}H_{28}N_4O_3Cl_2$	59.64	5.57	11.13	14.12
28	6-Cl	132	55.58	4.78	11.48	21.70	$C_{23}H_{23}N_4O_2Cl_3$	55.94	4.66	11.35	21.58
29	7-Cl	134	55.45	4.86	11.28	21.38	$C_{23}H_{23}N_4O_2Cl_3$	55.94	4.66	11.35	21.58
30	8-Cl	140	55.71	4.63	11.69	21.60	$C_{23}H_{23}N_4O_2Cl_3$	55.94	4.66	11.35	21.58


O-CH2-CO-NH-N=CH
CH2-CH2-Cl
CH2-CH2-Cl
N
Cl
N
CH3
(30)
00
3500
3000
2500
2000
1800
1600
1400
1200
1000
800

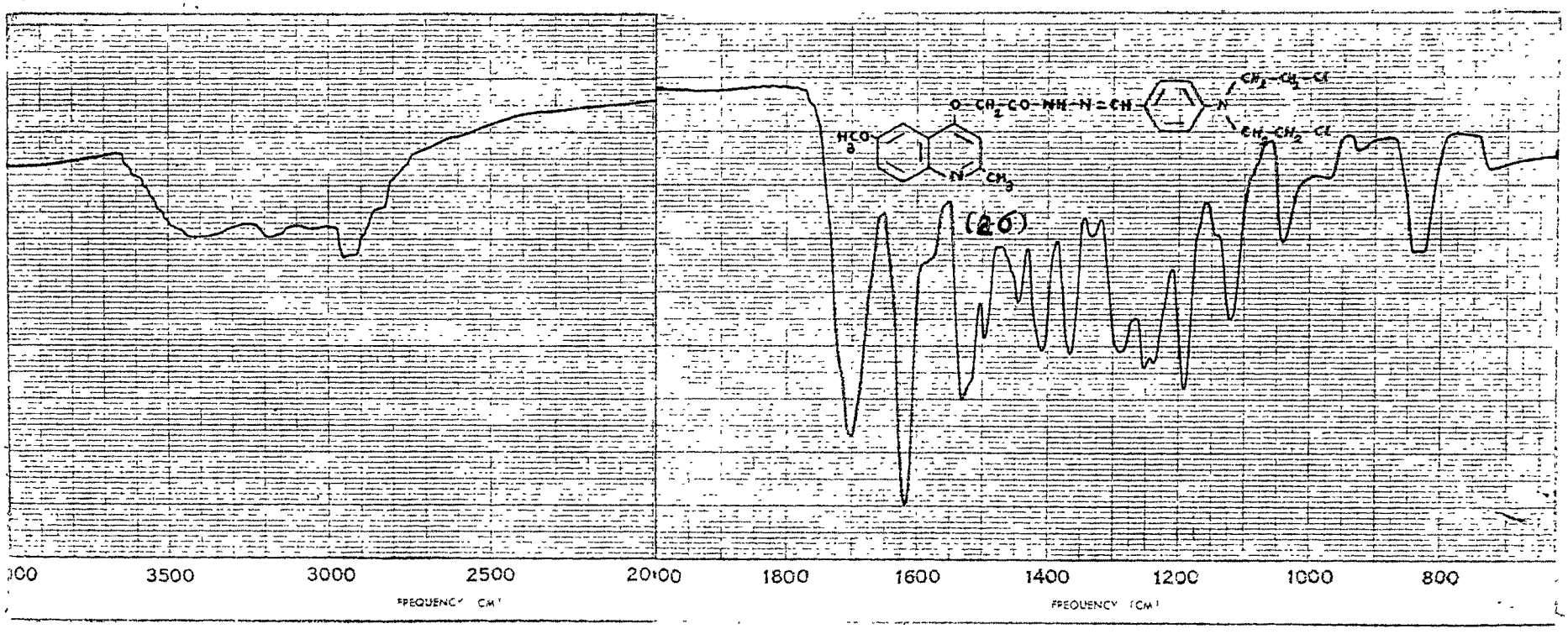

O-CH2-CO-NH-N=CH-
CH2-CH2-Cl
CH2-CH2-Cl
N
HCO
N
CH3
(20)
3500
3000
2500
1800
1600
1400
1200
1000
800
FREQUENCY (CM)
FREQUENCY (CM)

Table 3

Results of IR spectra

Comp.No.	IR bands (cm^{-1})			
	C=N	CO-NH	-NH-	C-Cl
26	1620	1700	3200	725
30	1610	1680	3400	760

References :

1. Jan Moszew and Julian Mirek ; Rozcziniki Chim., 34, 1621-7, 1960. C.A., 55, 22317, 1961.

2. Randolph J. Major and Kari. W. Ohly ; J.Med.Pharm. Chem.4, 317-26, 1961. C.A., 56, 450, 1962.

3. G.E. Morgun, A.S. Volga and L.L. Ivanov ; C.A., 59, 5131, 1963.

4. J.R. Geigy A.G. ; Brit. 789578. C.A., 63, 11521, 1965.

5. I. Nabih and M. Nasar ; Can.J.Chem., 44(15), 1863-5, 1966. C.A., 65, 13650, 1966.

6. Earnest Hodel (J.R. Geigy A.G.) ; Swiss. 408007., C.A., 67, 21845, 1967.

7. Taniguchi Makoto and Satomura Yukio ; Aggr.BiolChem., 36(12), 2169-75, 1972. C.A., 78, 14291 b, 1973.

8. Frank D. Popp ; J.Chem.Soc., 5271-2, 1960.

9. Henry C. Kpppec, Robert H. Springer ; G. Doyle Dares and Jr. and C.C. Cheng ; J.Pharm.Sci., 52(1), 81-3, 1963. C.A., 62, 11808, 1965.

CHAPTER-II

SECTION -III

Synthesis of Nitrogen Mustards from 4-(2-) hydrazino quinoline derivatives :

The present work deals with the synthesis of some new compounds which contain nitrogen mustards on 4-(2-) hydrazino quinoline derivatives as carrier moiety. From early days, 4- or 2-hydrazino quinoline derivatives as well as 2- or 4- hydrazino pyridine and pyrimidine derivative were well known for their physiological activities as well as some of their cyclic derivatives as photographic sensitizers. It will be of interest to review the literature of 4- or 2- hydrazino derivative of quinoline for their hypotensive activity, antifungal, antibacterial, anti inflamatory and analgestical activity.

In early days, Fargher and Furness[1] synthesised-2-pyridyl-2-quinolyl hydrazine (1) by the interaction of 2-chloro quinoline and 2-pyridyl hydrazine. John and Andraschko[2] synthesised 6-methoxy-4-hydrazino quinoline (2), which was condensed with p-acetyl-toluene to get hydrazone derivative(3).

Buchman[3] had prepared 4-hydrazino quinoline-N-oxide(4) from quinoline. Similarly 4-hydrazino-6-methyl quinoline-N-oxide was synthesised by same authors[4]. Ebetino and Wright[5] obtained 4-~~hydrazino~~ chloro-6,7-dimethoxy quinoline which was condensed

with hydrazine hydrate, gave 4-hydrazino-6,7-dimethoxy quinoline (5). In their studies on synthesis of fluorine containing heterocyclic compounds, Dey and Jollie[6] synthesised 2-trifluoromethyl-4-hydrazino quinoline (6).

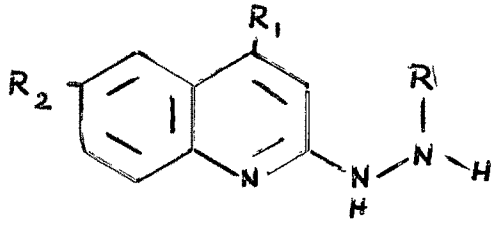
Some hydrazones from 4-hydrazino quinoline (7) were synthesised by Actor and Cesare[7] by condensation of 4-hydrazino quinoline derivatives with 2-pyridine carboxaldehyde and showed that these compounds are active against tapworm infections and possess antibacterial and antifungle activity.

Richard[8] prepared 2-hydrazino quinoline derivatives by heating chloroquinoline with secondary amine or hydrazine hydrate in a sealed tube at 150° for 5-6 hrs. and reported their inflamatory activities. Berkoff and Craig[9] established the structural activity correlationship in a new class of antimycoplasmal agents by synthesising quinolyl hydrazones,(8) the results indicate that the ring substituents R_1 and R_3 were more effective on the activity than the heterocyclic residue R.

Koppec and Springer[10] synthesised some interesting hydrazone (9) from p-(N,N-bis(2-chloroethyl)amino)benzaldehyde and hydrazino pyridine derivatives. Morvin and Majsinger[11] prepared hydrazino quinoline derivatives (10) to use as potential cytostatics.

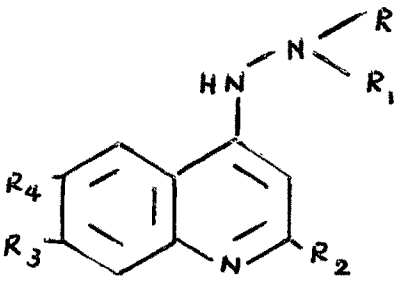
Sarinil and Berkoff[12] prepared more than hundred compounds of 4-quinoline hydrazone and tested them in vivo on mice against the tapworm, Hymenollepisnana. They showed

two compounds, 2,6-dimethyl-4-(2-(6-methyl-pyridinyl) [redacted])hydrazino) quinoline (12), produced 100 % inhibition of Hymenollepisnana on mice at 200 mg./Kg. orally.



(1) R = 2-pyridyl , $R_1 = R_2 = H$

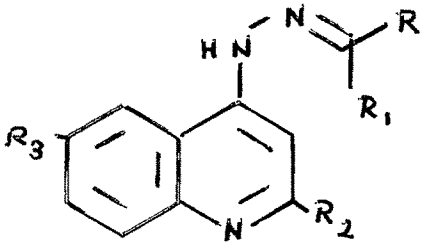
(10) $R = CH_3$, $R_1 = COOH$, $R_2 = NO_2$



(2) $R = R_1 = R_2 = R_3 = H$, $R_4 = OCH_3$

(5) $R = R_1 = R_2 = H$, $R_3 = R_4 = OCH_3$

(6) $R = R_1 = R_3 = R_4 = H$, $R_2 = CF_3$

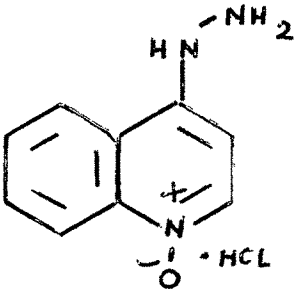


(3) $R_2 = H$, R = p-toluidide , $R_1 = CH_3$, $R_3 = OCH_3$

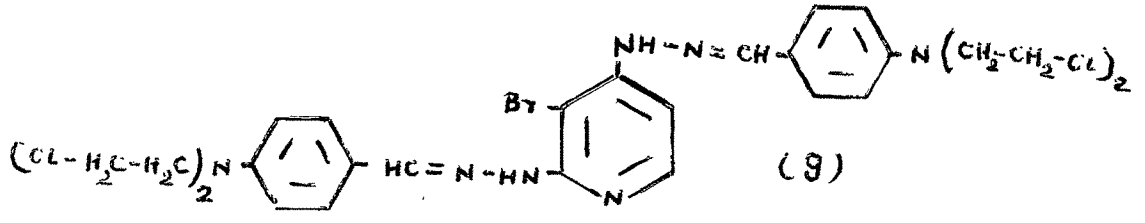
(7) $R_1 = R_2 = R_3 = H$, R = 2-pyridyl

(11) $R_1 = H$, $R_2 = R_3 = CH_3$, R = 2-(6-methyl)pyridyl

(12) $R_1 = H$, $R_2 = R_3 = CH_3$, R = 3-pyridyl

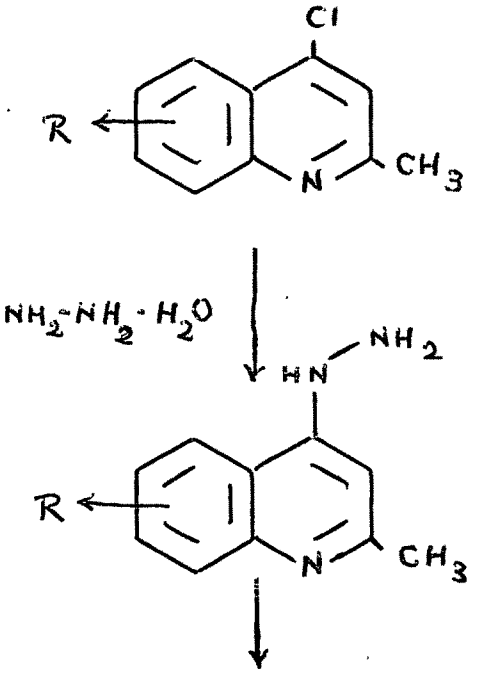


(4)



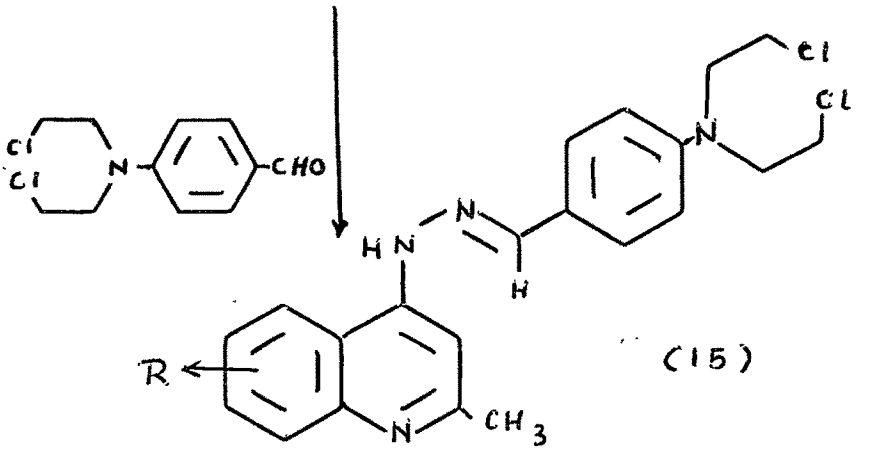
(9)

In the present work 2-quinolyl and 4-quinolyl hydrazino derivative is used as carrier moiety to synthesise some new nitrogen mustards which can be used as potential anticancer agents. The required 2-quinolyl hydrazino and 4-quinolyl hydrazino derivatives were obtained by condensing 2-chloro quinoline derivatives and 4-chloro quinoline derivatives with hydrazine hydrate. The 2-quinolyl and 4-quinolyl hydrazino derivatives were further condensed with p-(N,N-bis-(2-chloroethyl)amino) benzaldehyde in minimum quantity of ethanol gave 4-(-(p-(N,N-bis-(2-chloroethyl)amino)benzylidene)hydrazino) 4-methyl quinoline derivative and 4-(-(p-(N,N-bis-(2-chloroethyl)amino)benzylidene)hydrazino-2-methyl quinoline derivative respectively. The structure of these compounds were assigned on the basis of analytical results and supported by IR spectra.

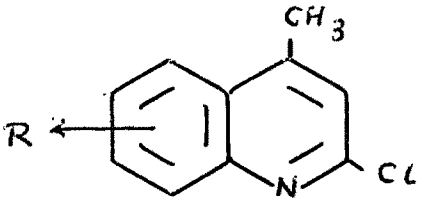


(13)

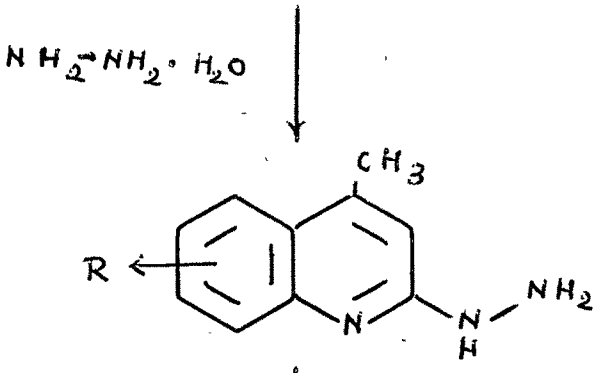
(14)



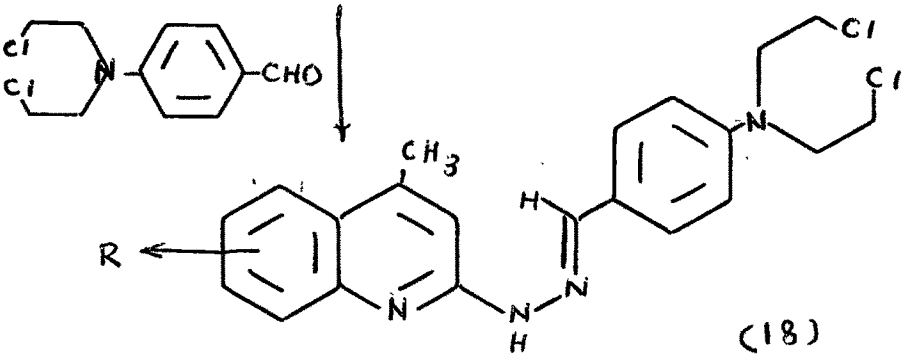
(15)



(16)



(17)



(18)

EXPERIMENTAL

Genral method for the synthesis of 2-(-(p-(N,N-bis-(2-chloroethyl)amino)benzylidene)hydrazino-4-methyl quinoline derivatives :

2-Hydrazino-4-methyl quinoline derivative :

A mixture of 2-chloro-4-methyl quinoline derivative (0.01 M) and hydrazine hydrate (80 % 10 ml) refluxed on sand bath for 5-6 hrs. On cooling the hydrazino quinoline derivative separated, filtered and crystallised from aqueous ethanol. Yield about 1.0-2.0 gm.

2-(-(p-(N,N-bis(2-chloroethyl)amino)benzylidine)hydrazino) -4-methyl quinoline derivatives :

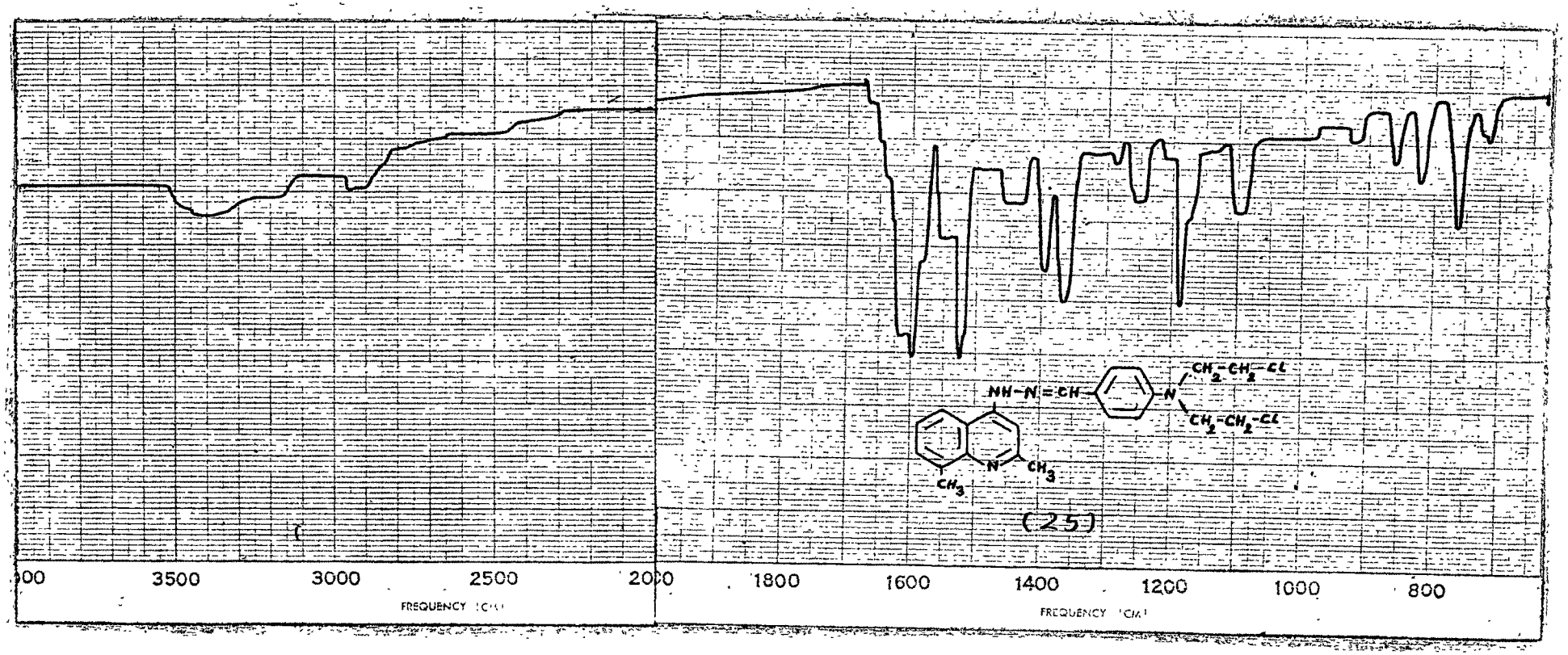
2-Hydrazino-4-methyl quinoline derivative (0.01 M) and p-(N,N-bis(2-chloroethyl)amino)benzaldehyde (0.01 M) were dissolved in ethanol (25 ml) and refluxed for 1 hr. The reaction mixture was cooled and separated product filtered out, crystallised from ethanol. Yield about 1.0 gm. The m.ps. and analytical results are reported in Table 1 and spectral results are in Table 2.

Similar series of reaction were carried out on 2-methyl-4-chloro quinoline derivatives to prepare 4-(-(p-(N,N-bis-(2-chloroethyl)amino)benzylidene)hydrazino)-2-methyl quinoline derivatives. The m.ps. and analytical results are reported in Table 3. The spectral results in Table 2.

Table 1

2-(-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)hydrazino)-4-methyl quinoline derivative

Comp. No.	R	R_1	m.p. °C	Found %				Molecular formula	Required %			
				C	H	N	Cl		C	H	N	Cl
19	6-MeO	CH_3	179	61.25	6.05	13.29	16.52	$C_{22}H_{24}N_4OCl_2$	61.24	5.57	13.00	16.48
20	6-Me	CH_3	168	63.06	5.55	12.90	17.00	$C_{22}H_{24}N_4Cl_2$	63.62	5.78	13.50	17.11
21	8-Me	CH_3	173	63.87	5.77	13.70	17.53	$C_{22}H_{24}N_4Cl_2$	63.62	5.78	13.50	17.11
22	6-EtO	CH_3	193	62.12	5.63	12.45	16.03	$C_{23}H_{26}N_4OCl_2$	62.00	5.84	12.58	15.95
26	H	CH_3	120	62.75	5.50	14.03	17.65	$C_{21}H_{22}N_4Cl_2$	62.85	5.49	13.97	17.71


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

(25)

3500
3000
2500
2000
1800
1600
1400
1200
1000
800
FREQUENCY (CM⁻¹)
CH3
NH-N=CH
N
CH2-CH2-Cl
CH2-CH2-Cl
(26)

Table 2

Comp.No.	IR bands (cm^{-1})		
	C=N	-NH-	C-Cl
25	1620	3400	760
26	1620	3150	760

Table 3

4-(-(p-(N,N-bis(2-chloroethyl)amino)benzylidene)hydrazino)-2-methyl quinoline derivative

Comp. No.	R	R_2	m.p.	Found %				Molecular formula	Required %			
				C	H	N	Cl		C	H	N	Cl
23	H	CH_3	157	63.35	5.43	14.05	18.00	$C_{21}H_{22}N_4Cl_2$	62.85	5.49	13.97	17.71
24	6-Me	CH_3	168	63.82	6.00	13.51	17.25	$C_{22}H_{24}N_4Cl_2$	63.62	5.78	13.50	17.11
25	8-Me	CH_3	125	63.43	5.45	12.96	17.23	$C_{22}N_{24}N_4Cl_2$	63.62	5.78	13.50	17.11

Screening Data Summary

The Quinoline - nitrogen mustards have been evaluated against Carcino Sarcoma Walker 256 and Lymphocytic, Leukemia P-388. The results are summerised as follow.

Sr No.	Compound.	Tumour system	Dose mg/kg	T/C %	Survivors
1.	4-(p-(p-(N,N-bis(2-chloroethyl)amino) benzylidene)carbhydrazide phenyl amino) -2-methyl-6-methoxy quinoline.	Walker 256	40	96	3/3
			20	96	3/3
			10	83	4/4
2.	4-(o-(p-(N,N-bis(2-chloroethyl)amino) benzylidene)carbhydrazide phenyl amino) -2-methyl-7-chloro quinoline.	"	20	128	3/3
			10	54	3/3
3.	4-(p-(p-(N,N-bis(2-chloroethyl)amino) benzylidene)carbhydrazide phenyl amino) -2-methyl-7-chloro quinoline.	"	50	82	4/4
4.	4-(p-(p-N,N-bis(2-chloroethyl)amino) benzylidine)carbhydrazide phenyl amino) -2-methyl-6-chloro quinoline.	"	50	110	4/4
5.	2-(o-(p-(N,N-bis(2-chloroethyl)amino) benzylidine)carbhydrazide phenyl amino) -4-methyl-6-chloro quinoline.	P-388	200	95	6/6
			100	90	6/6
			50	95	6/6

.....2/..

Sr No.	Compound.	Tumour system	Dose mg/kg	T/C %	Survivors
6.	2-(p-(p-(N,N-bis(2-chloroethyl)amino) benzylidine)carbhydrazide phenyl amino) -4-methyl-6-chloro quinoline.	P-388	200 100 50	87 91 90	6/6 6/6 6/6
7.	2-methyl-4-(-(p-(N,N-bis(2-chloroethyl) amino)benzylidine) hydrazizino carbonyl methoxy)-7-chloro quinoline.	"	200 100 50	87 90 95	6/6 6/6 6/6
8.	2-(-(-p-(N,N-bis(2-chloroethyl)amino) benzylidine) hydrazino)-4-methyl-6- chloro quinoline.	"	200 100 50	100 100 97	6/6 6/6 6/6

In walker-256 tomour system a T/C percent value equal to or less than 42 and in P-388 system T/C percent value near or more than 125 is effective, provided the compound is not toxic. The screening tests showed that above all compounds are not effective.

*****
*

References :

1. Robert G. Fargher and Reginald Furness ; J.Chem.Soc., 107, 688-99, 1915.

2. Hannes John and Emil Andraschko ; J.Prakt.Chem. 128, 218-22, 1930. C.A., 25, 954, 1931.

3. Gerhard Buchmann ; Chem.Tech. (Berlin) 9, 388-92, 1957. C.A., 53, 2230 b, 1959.

4. Elmar Profft, Gerhard Buchmann and Norbert Wackrow ; Wiss. Z., Tech.Hochsch. Chem.Leuna-Merseburg, 2, 98-9, 1959. C.A., 55, 1616, 1961.

5. Gevaert Photo-Production, N.V. Belg ; 630906 ; C.A., 61, 8450, 1964.

6. Adrienne Steinacker Dey and Madeleine M. Joullie ; J.Heterocyclic Chem. 2(2), 113-119, 1965. C.A., 63, 4250 h, 1965.

7. Philip P. Actor and Pallerano Cesare E.G., S. African 6906755. C.A., 73, 120517 c, 1970.

8. Carney Richard W.J., U.S. 3542785. C.A., 74, 125470, 1971.

9. Berkoff Charles E., Craig Paul N., Gardon Basil P., and Pallerano Cesare ; Arzneim-Forsch. 23,(6), 830-9, 1973. C.A., 79, 78568, 1973.

10. Sommer L., Maung. Gyee W.P. and Ryan D.E. ; Ser. Fac.Sci., Nature Univ. Purkynianal Brun. 2(6), 115-28, 1972. C.A., 79, 121493, 1973.

11. Henry C. Koppec, Robert H. Springer, G. Doyle Dares Jr. and C.C. Cheng ; J.Pharm Sci., 52(1), 81-3, 1963. C.A., 62, 11808, 1965.

12. Berenyi Edit, Pallos Laszlo, Patocz Lujza, Benkopal, Gorog Peter, Budâi Zoltan, Kiszelly Eniko ; Ger.Offen. 2322486. C.A., 80, 27304 r, 1974.

13. Katyla Mohn, Kundra S.K., Goel D.P. and Singh R.P., J.Indian Chem.Soc., 51(5), 576-7, 1974.

14. Movrin M. and Majsinger D., Eur.J.Med.Chem., Chem.Ther. 9(6), 615-17, 1974. C.A., 82, 170634 v, 1975.

15. Pellerano C., Sarini L., Berkoff C.E., Thomas J. and Actor P. ; C.A., 84, 53784, 1976.

Which Journal ?