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Antimalarials. 9. α-(2-Piperidyl)-4-quinolinemethanols Carrying 2-Aroxy and 2-(*p*-Chloroanilino) Groups†,[1]

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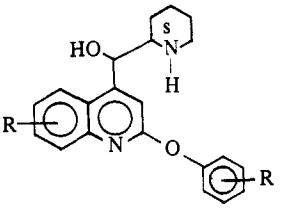
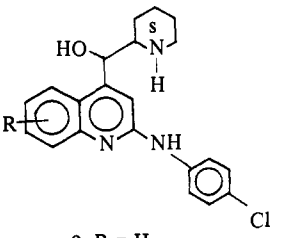
Twelve α-(2-piperidyl)-4-quinolinemethanols were synthesized from 2-chlorocinchoninic acids by additions of 2-PyLi, displacements of 2-Cl of the resulting 4-quinolyl 2-pyridyl ketones by aroxy or *p*-chloroanilino, and hydrogenations of the keto and pyridyl groups. Activities against *Plasmodium berghei* in mice were comparable with those of 2-aryl analogs. The 6,8-dichloro-2-(*p*-chlorophenoxy) compound was curative at 20 mg/kg but was phototoxic. 2-Chloro-α-diethylaminomethyl-4-quinolinemethanol, synthesized by a conventional route, was "inactive" against *P. berghei* but active against *Plasmodium gallinaceum* in birds

Syntheses of 12 α-(2-piperidyl)-4-quinolinemethanols (**1-12**) (and incidentally the 2-chlorodiethylamino alcohols **13** and **14**) were undertaken with the following expectations: that the 2-aroxy and 2-(*p*-chloroanilino) would prevent oxidative biotransformations to less active carbostyryls;[4] that these groups would lead to high activities against *Plasmodium berghei* in mice with firm binding of the molecules to the host tissues;[5] and that phototoxicity, formerly thought to be associated with conjugation of aryl and the 2-quinoline nuclei[6-8] in highly curative drugs such as **15**,[9] might be reduced by intervention between the aromatic nuclei of the heteroelement O or N which would destroy the direct conjugation although replacing it by forked conjugation.[10]

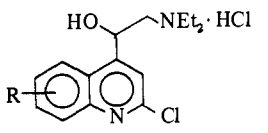
Chemistry. The α-(2-piperidyl)methanols **1-12** were synthesized from appropriate isatins through 2-hydroxy- and 2-chlorocinchoninic acids **16-20** (and ester **21**).[11-14] Rather than displacing the 2-Cl at this stage,[11] the reactions outlined in Scheme I were used, namely, additions of 2-PyLi,[15-19] then aroxy and anilino displacements of the active 2-Cl[20] of the 2-pyridyl ketones **22-26** (more difficult when an 8 substituent was present), and simultaneous Pt-H_2-AcOH[17] hydrogenations of the keto and pyridyl groups of **27-38**. Reduction of the *p*-methylthiophenoxy analog **40**, however, was incomplete and stopped at the α-(2-pyridyl)methanol stage **43**, presumably because of catalyst poisoning by sulfur of the substrate. The products **1-12** were isolated only in one of two possible racemic forms. Difficulties in and deviations from usual procedures are given in the Experimental Section.



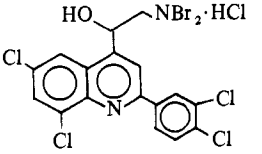
1, R = H; R' = 4-Me
2, R = 6-Me; R' = 4-Me
3, R = 6-Cl; R' = 4-Me
4, R = H; R' = 4-Cl
5, R = 6-Cl; R' = 4-Cl
6, R = 6,8-Me_2; R' = 4-Cl
7, R = 6,8-Cl_2; R' = 4-Cl
8, R = 6,8-Cl_2; R' = 3,4-Cl



9, R = H
10, R = 6-Me
11, R = 6-Cl
12, R = 6,8-Me_2



13, R = H
14, R = 6,8-Cl_2



15

In preliminary experiments toward making α-diethylaminomethyl-4-quinolinemethanols carrying 2-hetero substituents which might then be displaced,[20] **13** and **14** were synthesized by the standard sequence, Scheme II.[9,21]

Biology. Results of tests against *P. berghei* in mice by the method of Rane[22] are given in Table I. In activities, the α-(2-piperidyl)-2-aroxy- and 2-(*p*-chloroanilino)-4-quino-

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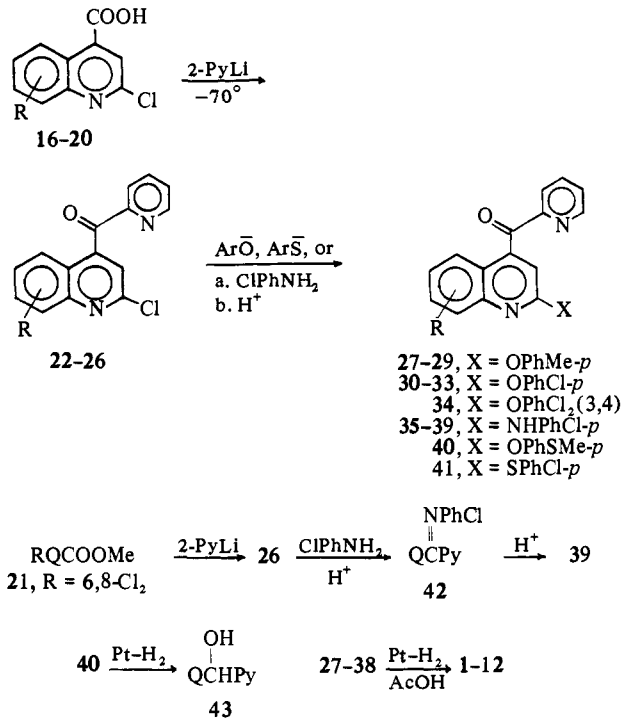
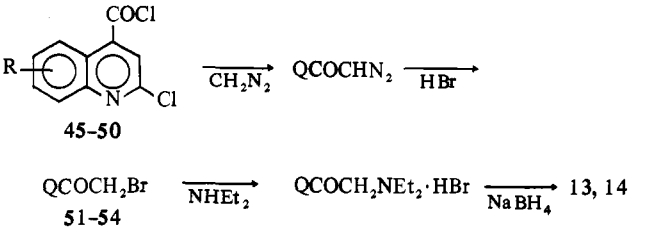
Scheme I[a]



[a] Q = 4-quinolyl; R, see Table II.

linemethanols **1-12** proved to be similar to 2-aryl analogs typified by **15**.[9] That chloro is a more effective auxopharmacophore than methyl is shown by marked and consistent activity differences between analogs, and *p*-chlorophenoxy appears to be slightly more effective than *p*-chloroanilino. The most active compound was the 6,8-dichloro-2-(*p*-chlorophenoxy) (**7**); it was "active" at 10 mg/kg, curative at 20 mg/kg, and somewhat more active than the α-dibutylaminomethyl-6,8-dichloro-2-(3,4-dichlorophenyl)

Scheme II



analog **15**. The combination of three aromatic chlorines plus the 2-aroxy oxygen in **7** has produced almost the same level of antimalarial activity as the combination of four aromatic chlorines in the α-dibutylaminomethyl 2-aryl analog **15**.

Representatives of the more active of the compounds **1-12** proved to have high to moderate phototoxicities[23] comparable with those of 2-aryl and 2-aroyl analogs.[7,8,10] It appears that intervention of the hetero elements, oxygen or nitrogen, between the 2-aryl and the quinoline nuclei (like the carbonyl group in 2-aroyl analogs[10]) has little or only moderate effect on both antimalarial activity and phototoxicity.

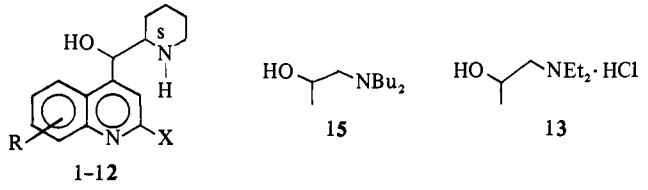
Experimental Section

Satisfactory spectra were obtained where required for structural determination. Instruments used were: for melting point, Thomas-Hoover apparatus; ir, Perkin-Elmer 337; nmr, Hitachi Perkin-Elmer R-20; and mass spectrum, Hitachi Perkin-Elmer RMU 6E. Microanalyses by Galbraith Lab., Inc., were correct within +0.4% (see Table II for data).

2-Hydroxycinchoninic acid (75%) and derivatives, 6-Me (76%) and 7-Cl (30%), were prepared from the isatins through *N*-acetylisatin.[11,12] The derivatives, 6-Cl (51%), 6,8-Me_2 (55%), 6.8-Cl_2 (89%), and 7-Cl (65%), were made from the isatin and malonic acid (AcOH, reflux 15-17 hr).[14]

2-Chlorocinchoninic acids[12] **16-20** were obtained (*ca.* 80%) by treatment of the 2-hydroxy acids[13] with $POCl_3$ (reflux, 3 hr), hydrolysis by H_2O (3 hr; but for 17 and **20**, by solution in dioxane containing excess 2 *N* NaOH), solution in $NaHCO_3$, and reprecipitation by acid.

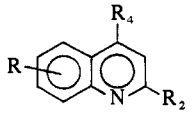
Table I. Bioassay Data[a,b]



Compd	Rel no.	X	R	Antimalarial activities,[a] MST[c] (days), C (cures)[d,e] Dose, mg/kg 20	40	80	160	320	640	Phototoxicity,[b] MED,[f] Ip (oral), dose, mg/kg
1	932	OPhMe-*p*	H	0.4	0.4	0.6	0.8	0.8	1.0	
2	933	OPhMe-*p*	6-Me	0.4	0.4	0.6	0.6	2.6	7.8	
3	934	OPhMe-*p*	6-Cl	0.2	0.6	3.0	3.4	5.2	Toxic	
4	940	OPhCl-*p*	H	0.3	0.5	2.9	7.1	9.1	2C	
5	965	OPhCl-*p*	6-Cl	1.3	5.3	13.7	1C	4C	4C	75 (50)
6	945	OPhCl-*p*	6,8-Me_2	0.5	5.5	12.5	13.9	2C	2C	
7	970	OPhCl-*p*	6,8-Cl_2	2C	3C	5C	5C	5C	5C	(50)
8	973	$OPhCl_2$(3,4)	6,8-Cl_2	13.9	3C	5C	5C	5C	5C	25 (25)
9	930	NHPhCl-*p*	H	0.6	0.6	1.0	7.8	10.0	1C	
10	931	NHPhCl-*p*	6-Me	0.6	0.6	0.8	1.8	11.2	4C	15
11	938	NHPhCl-*p*	6-Cl	0.3	0.5	1.7	6.1	2C	2C	
12	939	NHPhCl-*p*	6,8-Me_2	0.3	0.3	1.7	3.7	6.9	2C	25
15[g]	556	$PhCl_2$(3,4)	6,8-Cl_2	3C[e]	6C	8C	10C	10C	10C[e]	25
13[h]	935	Cl	H		0.4	1.0	1.2	3.2		

[a] Against *P. berghei* in mice (see ref 22). [b] See ref 23. [c] Mean survival times in days; a compound is considered "active" when MST is doubled or more. [d] C = number of cures (mice surviving to 60 days) out of test groups of five mice. [e] For **15** test groups were ten mice. [f] MED = minimum effective dose in milligrams per kilogram. [g] **15** = WR 30090 (SN 15068), the 2-aryl-4-CHOHCH$_2$·HCl analog; it is included for comparison. [h] This is the α-CH$_2$NEt$_2$·HCl analog; it was active at 160 mg/kg against *P. gallinaceum* in birds.

Table II. Quinoline Compounds[a]



Compd	R	R_2	R_4	Crystn solvent[b-l]	Mp, °C	% yield	Formula	Analyses[m-p]
1	H	OPhMe-*p*	CHOHPip	EtOH	199-200	61	$C_{22}H_{24}N_2O_2$	C, H, N
2	6-Me	OPhMe-*p*	CHOHPip	EtOH	167-169	38	$C_{23}H_{26}N_2O_2$	C, H, N
3	6-Cl	OPhMe-*p*	CHOHPip	EtOH	180-181	46	$C_{22}H_{23}ClN_2O_2$	C, H, N
4	H	OPhCl-*p*	CHOHPip	EtOH	173-174	42	$C_{21}H_{21}ClN_2O_2$	C, H, N
5	6-Cl	OPhCl-*p*	CHOHPip	EtOH	183.5-185	40	$C_{21}H_{20}Cl_2N_2O_2$	C, H, N
6	6,8-Me_2	OPhCl-*p*	CHOHPip	EtOH	171-172	52	$C_{23}H_{25}ClN_2O_2$	C, H, N
7	6,8-Cl_2	OPhCl-*p*	CHOHPip	*h*	208-209 dec	42	$C_{21}H_{19}Cl_3N_2O_2$	C, H, N
8	6,8-Cl_2	OPhCl$_2$(3,4)	CHOHPip	Me_2CO[i]	196-198 dec	51	$C_{21}H_{18}Cl_4N_2O_2$	C, H, N, Cl
9	H	NHPhCl-*p*	CHOHPip	EtOH-H_2O[j]	183-185		$C_{21}H_{22}ClN_3O$	C, H, N
9·H_2O				EtOH-H_2O	131-133	87	$C_{21}H_{22}ClN_3O \cdot H_2O$	C, H, N
10	6-Me	NHPhCl-*p*	CHOHPip	EtOH-H_2O[j]	117-119	89	$C_{22}H_{24}ClN_3O$	C, H, N
11	6-Cl	NHPhCl-*p*	CHOHPip	*j*	185-187		$C_{21}H_{21}Cl_2N_3O$	C, H
11·H_2O					115-117		$C_{21}H_{21}Cl_2N_3O \cdot H_2O$	C, H, N
12	6,8-Me_2	NHPhCl-*p*	CHOHPip	EtOH-H_2O[j]	228-229	63	$C_{23}H_{26}ClN_3O$	C, H
13	H	Cl	CHOHCH$_2$NEt$_2$·HCl	EtOH-Et_2O	204-205	15	$C_{15}H_{19}ClN_2O \cdot HCl$	C, H, N
14	6,8-Cl_2	Cl	CHOHCH$_2$NEt$_2$·HCl	*k*	96-99	40	$C_{15}H_{17}Cl_3N_2O \cdot HCl$	C, H[n]
16	6-Me	Cl	COOH	*b*	195 dec		$C_{11}H_8ClNO_2$	C, H
17	6-Cl	Cl	COOH	*b*	187 dec		$C_{10}H_5Cl_2NO_2$	C, H
18	7-Cl	Cl	COOH	*b*	206 dec		$C_{10}H_5Cl_2NO_2$	C, H
19	6,8-Me_2	Cl	COOH	*b*	205 dec		$C_{12}H_{10}ClNO_2$	C, H
20	6,8-Cl_2	Cl	COOH	*b*	250-253 dec		$C_{10}H_4Cl_3NO_2$	C, H
21	6,8-Cl_2	Cl	COOMe	MeOH	167-169		$C_{11}H_6Cl_3NO_2$	C, H
22	H	Cl	COPy	EtOH	149-150	69	$C_{15}H_9ClN_2O$	C, H, N
23	6-Me	Cl	COPy	EtOH	154.5-155.5	68	$C_{16}H_{11}ClN_2O$	C, H
24	6-Cl	Cl	COPy	*d*	203-204.5	54	$C_{15}H_8Cl_2N_2O$	C, H
25	6,8-Me_2	Cl	COPy	EtOH	168-169	74	$C_{17}H_{13}ClN_2O$	C, H
26	6,8-Cl_2	Cl	COPy	EtOH	212-214	68	$C_{15}H_7Cl_3N_2O$	C, H
27	H	OPhMe-*p*	COPy	EtOH	136-137.5	71	$C_{22}H_{16}N_2O_2$	C, H
28	6-Me	OPhMe-*p*	COPy	EtOH	111-112.5	82	$C_{23}H_{18}N_2O_2$	C, H
29	6-Cl	OPhMe-*p*	COPy	EtOH	87-89	35	$C_{22}H_{15}ClN_2O_2$	C, H
30	H	OPhCl-*p*	COPy	EtOH	151-153	40	$C_{21}H_{13}ClN_2O_2$	C, H
31	6-Cl	OPhCl-*p*	COPy	Me_2CO-$CHCl_3$	163.5-165	71	$C_{21}H_{12}Cl_2N_2O_2$	C, H, N, Cl
32	6,8-Me_2	OPhCl-*p*	COPy	EtOH	134-135	73	$C_{23}H_{17}ClN_2O_2$	C, H, N
33	6,8-Cl_2	OPhCl-*p*	COPy	Me_2CO	207-208	80	$C_{21}H_{11}Cl_3N_2O_2$	C, H, N
34	6,8-Cl_2	OPhCl$_2$(3,4)	COPy	EtOH[e,f]	222-223 dec	52	$C_{21}H_{10}Cl_4N_2O_2$	C, H, N, Cl
35	H	NHPhCl-*p*	COPy	EtOH	182-184	83	$C_{21}H_{14}ClN_3O$	C, H
36	6-Me	NHPhCl-*p*	COPy	EtOH	180-182	56	$C_{22}H_{16}ClN_3O$	C, H
37	6-Cl	NHPhCl-*p*	COPy	EtOH	212-213	45	$C_{21}H_{13}Cl_2N_3O$	C, H
38	6,8-Me_2	NHPhCl-*p*	COPy	EtOH	208-209.5	79	$C_{23}H_{16}ClN_3O$	C, H
39	6,8-Cl_2	NHPhCl-*p*	COPy	EtOH[g]	236-237 dec	78	$C_{21}H_{12}Cl_3N_3O$	C, H, N
40	H	OPhSMe-*p*	COPy	Me_2CO	174.5-176	61	$C_{22}H_{16}N_2O_2S$	C, H, N
41	H	SPhCl-*p*	COPy		149.5-151		$C_{21}H_{13}ClN_2OS$	C, H[o]
42	6,8-Cl_2	NHPhCl-*p*	C(Py)=NPhCl-*p*	$CHCl_3$-hexane	165-170[l]		$C_{27}H_{16}Cl_4N_4$	C, H, N
43	H	OPhSMe-*p*	CHOHPy		140-142	71	$C_{22}H_{18}N_2O_2S$	C, H, N
44	6,8-Cl_2	PhCl-*p*	C(Pip)=NOH		264-265.5	58	$C_{21}H_{21}Cl_2N_3O$	C, H, N
45	H	Cl	COCl	C_6H_6[c]	95		$C_{10}H_5Cl_2NO_2$	*q*
46	6-Me	Cl	COCl	C_6H_6[c]	125-126.5		$C_{11}H_7Cl_3NO$	C, H
47	6-Cl	Cl	COCl	C_6H_6[c]	128-129.5		$C_{10}H_4Cl_3NO$	C, H
48	7-Cl	Cl	COCl	C_6H_6[c]	106-107.5		$C_{10}H_4Cl_3NO$	C, H
49	6,8-Me_2	Cl	COCl	C_6H_6[c]	94.5-96	49	$C_{12}H_9Cl_2NO$	C, H
50	6,8-Cl_2	Cl	COCl	C_6H_6[c]	109-110	71	$C_{10}H_3Cl_4NO$	C, H
51	H	Cl	COCH$_2$Br	EtOH	101-102	86	$C_{11}H_7BrClNO$	C, H
52	6-Me	Cl	COCH$_2$Br	EtOH	97-98	80	$C_{12}H_9BrClNO$	C, H
53	6,8-Me_2	Cl	COCH$_2$Br	EtOH	71-72.5	73	$C_{13}H_{11}BrClNO$	C, H
54	6,8-Cl_2	Cl	COCH$_2$Br	EtOH	98-98	77	$C_{11}H_6BrCl_3NO$	C, H[p]
55	H	Cl	CN	EtOH	153-154	78	$C_{10}H_5ClN_2$	C, H
56	6-Me	Cl	CN	EtOH	121-122	55	$C_{11}H_7ClN_2$	C, H
57	6-Cl	Cl	CN	EtOH	178-179.5	63	$C_{10}H_4Cl_2N_2$	C, H
58	7-Cl	Cl	CN	EtOH	145-147	47	$C_{10}H_4Cl_2N_2$	C, H
59	6,8-Me_2	Cl	CN	EtOH	153-154	64	$C_{12}H_7ClN_2$	C, H
60	6,8-Cl_2	Cl	CN	EtOH	174-175	78	$C_{10}H_3Cl_3N_2$	C, H
61[r]	H	OH	COMe	EtOH	199-200	60	$C_{11}H_9NO_2$	C, H
62	H	F	CN	EtOH	141-141.5[c]	67	$C_{10}H_5FN_2$[c]	C, H, N
63	6-Me	F	CN	EtOH	121-122[c]	63	$C_{11}H_7FN_2$[c]	C, H, F
64	6-Cl	F	CN	EtOH	182-183.5[c]	49	$C_{10}H_4ClFN_2$[c]	C, H, F
65	6,8-Me_2	F	CN	EtOH	125-126[c]	43	$C_{12}H_9FN_2$[c]	C, H, N
66	6,8-Cl_2	F	CN	EtOH	155-156[c]	54	$C_{10}H_3Cl_2FN_2$[c]	C, H, F

[a]Py = 2-pyridyl; Pip = 2-piperidyl; Ph = phenyl. [b]Partial purification by solution in $NaHCO_3$ and precipitation by HCl, oven dried. [c]Vacuum sublimed. [d]Chromatography; Al_2O_3, C_6H_6-$CHCl_3$. [e]Chromatography; Florisil, $CHCl_3$. [f]Chromatography; Florisil, $CHCl_3$-hexane. [g]EtOH-$CHCl_3$. [h]Me_2CO-CH_2Cl_2 or CH_2Cl_2 (entrapment of C_6H_6 or Me_2CO shown by nmr); dried at 100° (0.05 mm) (48 hr) or crystallized from CH_2Cl_2. [i]Crystallization from Me_2CO rapidly gave polymorph A; crystallization slowly gave polymorph B with the same melting point and nmr ($CDCl_3$) but differing in the ir (KBr) fingerprint region; the ir (KBr) of A after solution in $CHCl_3$ and evaporation over KBr was identical with that of B (KBr). [j]Vacuum dried (100°). [k]Sample not recrystallized. [l]Solidified at 175°; remelted at 261.5-263°. [m]Analyses were within ±0.4% of theory except as follows. [n]C: calcd, 46.90; found, 47.40. [o]H: calcd, 3.48; found, 3.85. [p]C: calcd, 37.39; found, 38.15 (sample not recrystallized). [q]See ref 13. [r]See ref 12.

Methyl 2,6,8-Trichlorocinchoninate (21).[14] A solution of 10.8 g of 2-hydroxy-6,8-dichlorocinchoninic acid in 30 ml of $SOCl_2$, 9 ml of DMF, and 25 ml of C_6H_6 was refluxed (15 hr) and evaporated. Treatment of the residue with 5 l. of refluxing MeOH (10 min) gave **21** [ir (KBr) 1745 cm^{-1} (C=O); nmr ($CDCl_3$) δ 4.10 (s, **3**, OCH_3), 7.92 (d, 1, J = 3 Hz, 7-H), 8.05 (s, 1, 3-H), 8.78 (d, 1, J = 3 Hz, 5-H)].

2-Chloro-4-quinolyl 2-Pyridyl Ketones (22–25). To 51.5 g of 22% *n*-BuLi (in hexane, 0.177 mol), in 75 ml of Et_2O (distilled from dry-Na) (−60°, under N_2, stirring), was added 28.2 g (0.179 mol) of 2-BrPy (30 min) and then 11.6 g of **17** (0.048 mol) in 450 ml of THF (distilled from $LiAlH_4$) with stirring (4.5 hr). Warming to −35°, addition of 100 ml of H_2O, H_2O quenching, standing, filtering, washing, drying (110°), and chromatography (Al_2O_3, elution with C_6H_6 and $CHCl_3$) gave **24** [ir (KBr) 1680 cm^{-1} (C=O)]. The use of Et_2O, Et_2O–THF, or THF–glyme as reaction solvent generally gave poorer yields (4% of **26**).

2,6,8-Trichloro-4-quinolyl 2-Pyridyl Ketone (26). Portionwise addition of ester **21** to 2-PyLi in Et_2O (−78°) (charcoal treatment: $CHCl_3$, Celite) gave **26** [ir (KBr) 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 340 (18), 338 (54), 336 (55), 311 (36), 309 (100), 307 (100), 275 (74), 273 (100), 234 (9), 232 (32), 230 (32), 78 (78)]. A similar run in 1:1 Et_2O–THF (−60°) and chromatography (Al_2O_3, C_6H_6–CHCl) gave 4% of **26**.

2-(*p*-Methylphenoxy)-, 2-(*p*-Methylthio)phenoxy-, and 2-(*p*-Chlorophenylthio)-4-quinolyl 2-Pyridyl Ketones (27, 40, 41). A solution of 2.6 g (9.2 mmol) of **22** and 3 g of $NaOC_6H_4Me$-*p* (23 mmol) in 35 ml of dioxane (distilled from CaH_2) was refluxed (15 hr); **27** was then precipitated by H_2O quenching. **40** and **41** were made like **27** (dioxane, reflux, *ca.* 22 hr). Under similar conditions **25** was recovered (90%), and in diglyme (reflux, 6 hr) the product was an intractable oil.

2-(*p*-Chlorophenoxy)-6-chloro and 6,8-Dimethyl-4-quinolyl 2-Pyridyl Ketones (31 and 32). Under the above conditions using NaOPhCl-*p* (reflux, 48 hr) **24** was recovered (80%). Use of DMSO or $DMSO_2$ as solvent (160 and 125°) gave intractable products. A solution of 1.36 g (4.5 mmol) of **25** and 4.5 g (30 mmol) of NaOPhCl-*p* in 32 g of molten *p*-chlorophenol was stirred at 95° (13 hr) and quenched in H_2O. The product, **32**, was charcoaled (Et_2O) [ir (KBr) 1685 (C=O), 1232 cm^{-1} (COC)]. Reaction of **24** under the above conditions was incomplete in 10 hr (tlc) but in 22 hr gave **31**.

2-(*p*-Chloro- and 3,4-dichlorophenoxy)-6,8-dichloro-4-quinolyl 2-Pyridyl Ketones (33 and 34). To C_6H_6-washed NaH (0.069 mol, from 3 g of a 55% dispersion in mineral oil) in 200 ml of DMF (molecular sieve 4A, 48 hr) was added dropwise a solution of 22 g (0.17 mol) of *p*-chlorophenol (in 100 ml of DMF) and then 4 g (1.32 mmol) of **26**. Heating (95°, 11 hr), H_2O quenching, and crystallization from Me_2CO (charcoal) gave **33** [ir (KBr) 1680 (C=O), 1235, 1215 cm^{-1} (COC); mass spectrum (70 eV) *m/e* (rel intensity) 432 (15.6), 430 (43.8), 428 (43.8), 326 (26.5), 324 (79), 222 (79), 78 (100)]. Compound **34** was made similarly from 3,4-dichlorophenol.

2-(*p*-Chloroanilino)-4-quinolyl 2-Pyridyl Ketones (35–38). A 50-ml solution of 3.5 g (0.0118 mol) of **25** and 6 g of *p*-chloroaniline in absolute EtOH was refluxed (48 hr; **23** and **24** required only 6 hr). After adding 50 ml of H_2O and 25 ml of concentrated HCl, and again refluxing (1 hr), **38** was precipitated by H_2O–NaOH quenching [ir (KBr) 1720 cm^{-1} (C=O)]. Without HCl the anil was obtained, mp 198–200° (not analyzed) [ir (KBr) 1630 cm^{-1} (C≡N)]. The 2,6-Cl_2 ketone **26** under these conditons failed to react with 2,4-dimethylaniline (24 hr).

2-(*p*-Chloroanilino)-6,8-dichloro-4-quinolyl 2-Pyridyl Ketone (39) and Its Anil (42). A solution of 5.9 g (17.6 mmol) of **26** and 5.1 g of *p*-chloroaniline·HCl in 100 ml of *p*-chloroaniline was stirred at 95° (under N_2, 8 hr). H_2O quenching gave **42**. Solution in 1.8 l. of 1.5 *M* HCl in 60% EtOH and refluxing (2 hr) gave **39**. In a separate experiment, anil **42** was washed with dilute NaOH [ir (KBr) 1685 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 431 (36), 429 (98), 427 (100), 325 (20), 323 (59), 321 (59), 290 (8), 288 (27), 286 (34), 78 (61)]. It is evident that displacement of 2-Cl by an aniline is impeded by an 8-quinoline substituent and by *o*-Me in the aniline and that the reaction is autocatalyzed by HCl liberated.[24]

2-Aroxy- and 2-(*p*-Chloroanilino)-α-(2-piperidyl)-4-quinolinemethanols (1–12). Hydrogenations of the 2-pyridyl ketones **27–39** were by Pt–H_2 (0.2 g of 84% PtO_2 per 3 g of substrate at 43 psi in 250 ml of AcOH), followed by filtration (Celite), and NaOH–H_2O quenching (directly or after vacuum evaporation of AcOH and solution in Me_2CO).

α-(2-Pyridyl)-2-[*p*-(methylthio)phenoxy]-4-quinolinemethanol (48) was made from **40** by Pt–H_2–AcOH (as above) [ir (KBr) 3100 cm^{-1} (broad, OH); nmr ($CDCl_3$) δ 2.50 (s, 3, SCH_3), 4.40 (s, 1, OH), 6.42 (s, 1, *CH*OH)].

Attempted Synthesis of α-(2-Piperidyl)-6,8-dichloro-2-(*p*-chlorophenyl)-4-quinolinemethylamine (QCH(NH_2)Pip; for Comparison with 7 and 15). 6,8-Dichloro-2-(*p*-chlorophenyl)-4-quinolyl 2-Pyridyl Ketoxime, QC(2-Pip)=NOH (44). Reaction of 2-PyLi–Et_2O with the cinchoninic methyl ester (−78°, under N_2) and treatment of the resulting ketone (83%) with NH_2OH·HCl–pyridine in absolute EtOH (reflux 6 hr) gave **44** [ir (KBr) 3225 cm^{-1} (OH), no C=O band]. Pt–H_2–AcOH reduction[25] gave an unpromising mixture (six compounds, tlc).

2-Chlorocinchoninyl Chlorides (45–50). For **45** and **48**, see ref 13. For the others, a melt of 69 g (0.278 mol) of (*e.g.*) **20** and 112 g (0.535 mol) of PCl_5 was refluxed (5 hr), cooled, washed (Et_2O), and charcoaled (hot C_6H_6).

2-Chloro-4-quinolyl Bromomethyl Ketones (51–54). Addition of **49** (11.3 g, 0.05 mol) to 6 g (0.14 mol) of CH_2N_2 in 400 ml of alcohol-free Et_2O (4 hr), addition of 40 ml of 48% HBr (1 hr), extractions (Et_2O), drying ($CaSO_4$), and evaporation gave **53**.

2-Chloro-α-diethylaminomethyl-4-quinolinemethanols (13, 14). To a solution of 2.84 g (0.01 mol) of (*e.g.*) **51** in 51 ml of Et_2O was added 2.82 g of Et_2NH (3 hr, 20°). After filtration and vacuum evaporation, a solution of the oil in 50 ml of MeOH was treated with 0.35 g of $NaBH_4$[21] and 4 ml of H_2O (stirring 3 hr). After quenching (1.5 l. of H_2O; standing 5 hr), vacuum evaporation of Et_2O extracts, solution of the residue in Et_2O, and drying ($CaSO_4$), **13**·HCl was precipitated by dry HCl–Et_2O.

2-Chloro-4-cyanoquinolines (55–60).[26,27] The 2-chlorocinchoninic acids (where attempts at direct KF exchange had failed) were converted to acid chlorides **45–50** and thence by C_6H_6–NH_3–H_2O (stirring) to crude amides (air-dried) which were then treated (16 hr) with refluxing $POCl_3$–PCl_5 (rather than $SOCl_2$).

2-Hydroxy-4-acetylquinoline (61). Reaction of 2-chloro-4-cyanoquinoline (**55**) with MeLi (−60°, Et_2O, 3 hr) was incomplete. After recovery of **55** (38%) and hydrolysis of the EtOH filtrate, an equal volume of 18% HCl was added (reflux, 2 hr), giving **61**.

2-Fluoro-4-cyanoquinolines[28] (62–66). With KF in DMSO (anhydrous, under N_2, 180°), **55–60** underwent selective displacement of 2-Cl by F. Attempted hydrolysis of CN of **62** (75%, H_2SO_4, 100°, 4 hr) gave 2-hydroxycinchoninic acid, whereas under these conditions 2-chloronitrile **55** was converted into 2-chlorocinchoninic acid (**16**).

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Emetic Activity of Reduced Lysergamides

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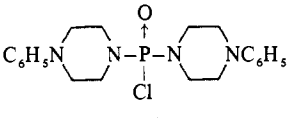
A new efficient method for the direct amidation of *d*-lysergic acid was used to prepare a variety of lysergamides. A pharmacological evaluation of these compounds, their di- and tetrahydro derivatives, and derivatives bearing substituents in the indole portion of the molecule showed that, in general, only 9,10-dihydrolysergamides of primary amines possess activity comparable to the potent emetic activity of the components of dihydroergotoxine.

As part of a study of compounds possessing high CNS activity and a high therapeutic index, we were attracted by derivatives of lysergic acid,[1] in particular, by the reported emetic activity of dihydroergotoxine.[2,†] We have investigated the emetic properties of a wide variety of lysergamides (**1**), their di- (**2** and **3**) and tetrahydro (**7** and **8**) derivatives, and derivatives bearing substituents in the indole portion of the molecule in an effort to relate emetic activity to the structure of the lysergamide. The present study showed that, in general, only 9,10-dihydrolysergamides of primary amines possess activity comparable to the potent emetic activity of the components of dihydroergotoxine.

Chemistry. *d*-Lysergic acid amides have been previously synthesized by way of the azide,[3] the acid chloride,[4] and the mixed anhydrides with trifluoroacetic acid[5] or sulfuric acid.[6] We wish to report a more convenient new method which effects the direct conversion of *d*-lysergic acid to the amide using the appropriate amine and $POCl_3$ in a 4–8-min reaction period. The desired normal amide (8β), free from the iso epimer (8α), was obtained in good yield (reported yields are not optimum) by isolation of the corresponding maleate salt from the crude reaction mixture. All steps were carried out with considerable experimental ease. Table I lists the amides that were prepared by the new method employing either one of two modifications A and B (see Experimental Section). Modification B appears to be more general and effective for the preparation of amides from bulkier amines. For example, the *tert*-butylamide **1b** was not obtained when method A was employed but was isolated in 41% yield when method B was used.

The scope of the reaction was further explored by attempting the amidation of 9,10-dihydrolysergic acid. Using method B this acid was cleanly converted in 70% yield to the *N*-cyclohexylamide **2c**. However, conversion to the *N*-ethyl- and *N,N*-di-*n*-butylamides was unsuccessful.

Attempts to prepare 1-*d*-lysergoyl-4-phenylpiperazine (**1**, $R_1,R_2 = (CH_2CH_2)_2NC_6H_5$) were unsuccessful. The expected amide was isolated in very low yield which was insufficient for complete identification. However, bis(4-phenyl-1-piperazinyl)phosphinic chloride (**4**) was obtained in 32% yield. Compound **4** was identical with the product obtained from the reaction of 2 equiv of 1-phenylpiperazine with 1 equiv of $POCl_3$ in the presence of Et_3N. This was the only instance where compounds of type **4** were isolated from the reaction mixture in our synthesis of numerous lysergamides.



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The 9,10-dihydrolysergamides **2** (Table II) were obtained by the catalytic reduction of the corresponding lysergamides **1** following the method previously described.[7] Catalytic reduction of the normal amide has been shown by Stoll and Hofmann[7,8] to yield only one isomer; hydrogen adds from the backside resulting in a C/D trans fusion.[9,10]

It was not possible to prepare **2i** by the catalytic reduction of *N*-(2-propynyl)lysergamide because of the presence of the acetylenic function. Instead, **2i** was obtained in poor yield from *d*-9,10-dihydrolysergoyl chloride hydrochloride and 2-propynylamine in the presence of pyridine.

The 2,3-dihydrolysergamides **3** (Table III) were obtained by a general procedure previously described by Stadler and coworkers[11,12] involving reduction of the corresponding lysergamide maleate with Zn dust and HCl. This reduction

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†A mixture of equal parts of the 9,10-dihydro derivatives of ergocristine, ergocornine, and ergocryptine methanesulfonates.