Synthesis and Hypotensive Properties of New 4-Aminoquinolines

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A series of 6,7-dimethoxy-4-(substituted amino)quinolines, several 6,7-dimethoxy-4-aminoquinolinium iodides, and some miscellaneous 4-substituted quinolines were synthesized and evaluated for hypotensive activity in dogs. Several of the simple 4-(alkylamino)-6,7-dimethoxyquinolines exhibited good hypotensive activity, equal to that of the parent 4-amino-6,7-dimethoxyquinoline (1).

Several 4-aminoquinolines (**1**, **54–57**, Table I), a variety of 6,7-dimethoxy-4-(substituted amino)quinolines[1] (**2–26**, **27–29**, **30–32**, **33–35**), four 6,7-dimethoxy-4-aminoquinolinium iodides (**50–53**), and a few 4-phenoxy-, 4-thio-, 4-hydrazino-, and 4-chloroquinolines (**36–41**, **42**, **43**, **46**) were synthesized and screened for hypotensive activity in anesthetized dogs in the present work. Previously the hypotensive activity and the mechanism of action of the parent 6,7-dimethoxy-4-aminoquinoline·HCl (**1**) and of 6,7-dimethoxy-4-veratrylideneaminoquinoline (**33**) were reported by Buckley, *et al.*[2]

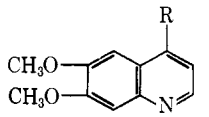
Chemistry.—The 4-aminoquinolines described in this paper were prepared primarily by halogen displacement of the corresponding 4-chloroquinolines with amines in phenol (methods A1, A3, A4). Compd **1** was obtained through the reaction of 6,7-dimethoxy-4-chloroquinoline (**47**)[3] with phenolic NH_3.[4] The 6,7-dimethoxy-4-phenoxyquinoline (**36**, free base) was obtained by refluxing **47** in phenol (method B); **36** (free base) was easily converted to **1** (free base) by heating in excess NH_4OAc (method A2). This latter reaction indicates that **36** is a possible intermediate in the "phenolic reaction" of **47** and NH_3 to give **1**.

The product of the reaction between **47** and *p*-aminophenol was 4-(*p*-hydroxyanilino)quinoline (**26**). The structure of **26** was verified through independent synthesis of the other possible isomer, the *p*-aminophenoxy ether (**38**), through catalytic reduction of **37**.

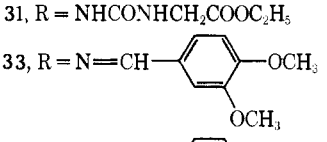
The 4-mercapto- and 4-hydrazino-6,7-dimethoxyquinolines (**39**, **41**) were prepared through displacement reactions of **47**; methylation of **39** with Me_2SO_4 gave 6,7-dimethoxy-4-methylthioquinoline (**40**).

Various derivatives (**22**, **30–32**, **33–35**) of **1** (free base) were prepared. Examples are acetylation with Ac_2O to give **30**; addition of ethyl isocyanatoacetate to give **31**; condensation with veratrylaldehyde to give **33**, followed by catalytic reduction to give **22**.

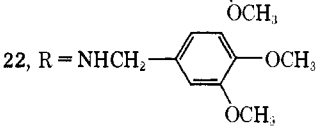
Three 1-alkyl-6,7-dimethoxy-4-aminoquinolinium iodides (**50–52**), Table I) were synthesized through (1) alkylation of the 4-chloroquinoline with alkyl iodides



1, R = NH_2·HCl
36, R = OC_6H_5·HCl
47, R = Cl
26, R = NHC_6H_4-*p*-OH·HCl
37, R = OC_6H_4-*p*-NO_2·HCl
38, R = OC_6H_4-*p*-NH_2·2HCl
39, R = SH
40, R = SCH_3·HCl
41, R = $NHNH_2$·2HCl
30, R = $NHCOCH_3$
31, R = $NHCONHCH_2COOC_2H_5$



33, R = N=CH-



22, R = $NHCH_2$-

·HCl

followed by displacement with amines, or (2) amine displacement of the 4-chloroquinoline followed by alkylation (Scheme I). While the ethylation of 4-chloro-6,7-dimethoxyquinoline (**47**) with EtI was easily achieved, the ethylation of **42** for preparation of the projected intermediate **49** failed to occur. Although the synthesis of 3-carboxyl-1-ethyl-6,7-dimethoxy-4-methylaminoquinolinium iodide (**52**) was carried out through alkylation of the 4-methylamino-3-quinolinecarboxylate (**44**) with EtI and base (NaOH), the nmr spectrum indicates that **52** may be contaminated with the product of ethylation at the 4-CH_3NH grouping.

4-Amino-6,7-dimethoxy-1-methylquinolinium iodide (**50**) was prepared by the reaction of **1** (free base) with MeI. Passage of **50** over a basic ion-exchange resin afforded the corresponding chloride **53**. The physical properties of **53** were compared with those of the isomeric 6,7-dimethoxy-4-methylaminoquinoline hydrochloride (**2**) of known structure; the 2 compounds were different. The nmr spectrum of **2** shows that the (NCH_3) protons are split by the (NH) proton of the (4-CH_3NH) substituent; in the case of **53** the (NCH_3) protons shown only a singlet.

The ring closure of **19** (Scheme II) in PPA gave 2,3-dehydro-8,9-dimethoxybenzo[*h*]-1,6-naphthyridin-4-

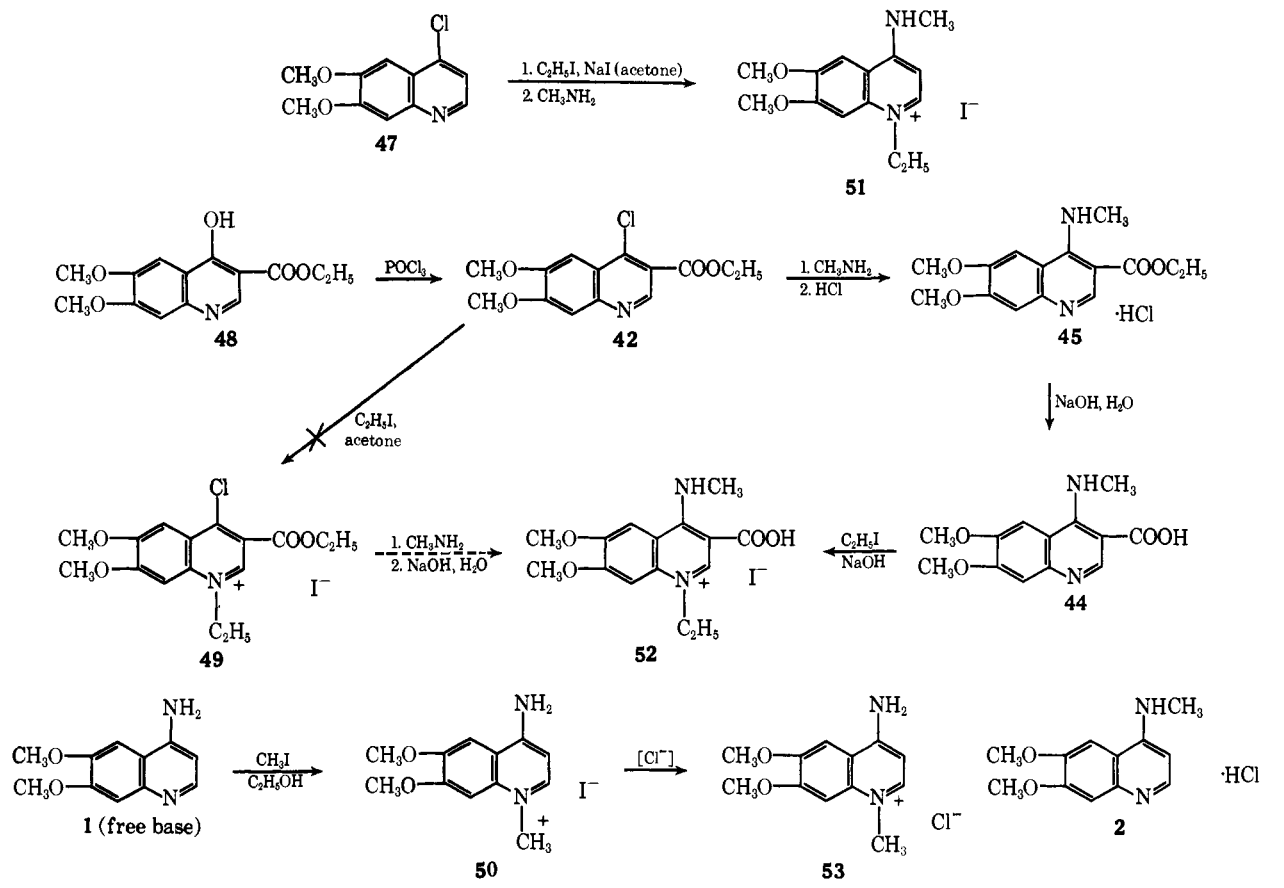
(1) (a) F. F. Ebetino and G. C. Wright, U. S. Patent 3,272,824 (1966); *Chem. Abstr.*, **63**, P589*b* (1965). (b) A. Winterstein, U. S. Patent 3,272,806 (1966); *Chem. Abstr.*, **65**, P18567*a* (1966).

(2) B. S. Jandhyala, G. J. Grega, and J. P. Buckley, *Arch. Int. Pharmacodyn.*, **167**, 217 (1967).

(3) B. Riegel, G. R. Lappin, B. H. Adelson, R. I. Jackson, C. J. Albisetti, Jr., R. M. Dodson, and R. H. Baker, *J. Amer. Chem. Soc.*, **68**, 1264 (1946).

(4) A modification of the procedure for the synthesis of 4-aminoquinaldines, by O. G. Backeberg and J. L. C. Marais, *J. Chem. Soc.*, 381 (1942).

SCHEME I



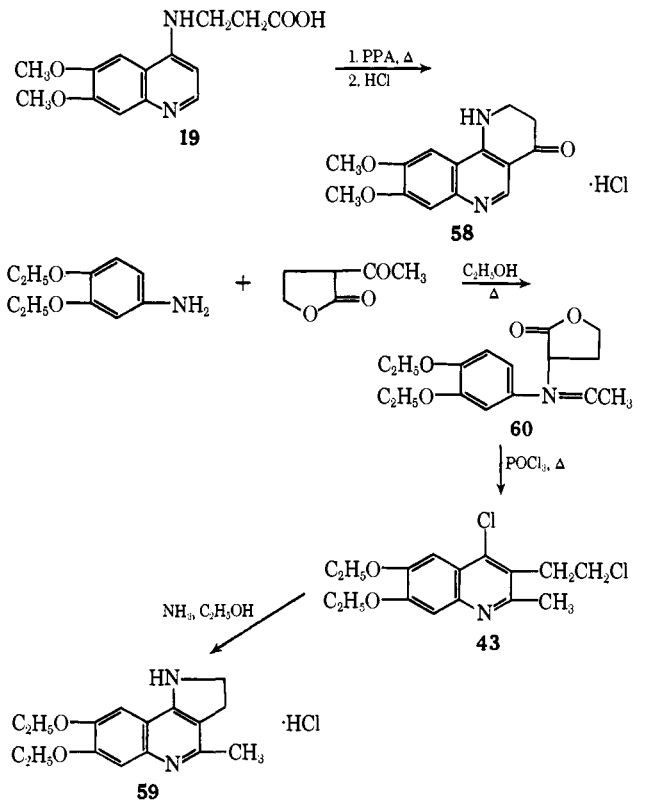
(1*H*)-one (**58**). This is similar to the reaction of 4-aminoquinaldine and ethyl trifluoroacetoacetate in PPA to give the completely aromatic 5-methyl-2-trifluoromethylbenzo[*h*]-1,6-naphthyridin-4-ol.[5]

That ring closure of **19** did not occur on the benzo ring was established by the nmr spectrum, which contained 3 singlets for aromatic protons. The spectrum of a benzo ring closure product would exhibit a pair of aromatic ortho proton doublets, not observed in the spectrum of **58**.

A second tricyclic compound, 7,8-diethoxy-2,3-dihydropyrrolo-1*H*-[3,2-*g*]quinoline·HCl (**59**), was obtained through ring closure of 4-chloro-3-(2-chloroethyl)-2-methyl-6,7-diethoxyquinaldine (**43**) with NH_3 in phenol (Scheme II). Compd **43** was synthesized through the reaction of 3,4-diethoxyaniline and 2-acetylbutyrolactone[6] to give the intermediate 1-(tetrahydro-2-oxo-3-furyl)ethylidene-2,4-diethoxyaniline (**60**), followed by chlorination of **60** with $POCl_3$ to give **43**. The 3,4-diethoxyaniline was obtained by catalytic reduction of 3,4-diethoxynitrobenzene.[7]

Pharmacology.—All compounds were evaluated for hypotensive activity in barbiturate-anesthetized mongrel dogs. Blood pressure was recorded from a cannulated femoral artery. Experimental materials were administered iv in H_2O when the solubility permitted or ip when the solubility was such that iv administration was not feasible. The hypotensive activity was evaluated on the basis of the maximum decrease in blood pressure and the duration of action of the respective

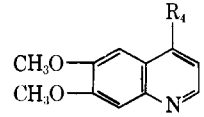
SCHEME II

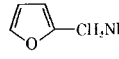
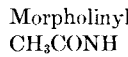


effective doses. Generally the lowest dose is cited which caused the highest rating using the following classifications: minimal activity, + (<40% decrease

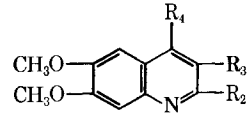
(5) A. S. Dey and M. M. Joullie, *J. Heterocycl. Chem.*, **2**, 120 (1965).
(6) Purchased from Columbia Organic Chemical Co.
(7) D. F. Page and R. O. Clinton, *J. Org. Chem.*, **27**, 224 (1962).

TABLE I

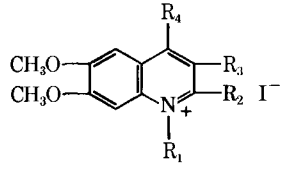


Compd Class	Compd No.	R_4	Method	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Formula	Analyses	Hypotensive activity in dogs: Dose, mg/kg	Route	Rating[c]
I	1	H_2N	A1	33	J	274–276	$C_{11}H_{12}N_2O_2 \cdot HCl \cdot H_2O$	C, H, N, Cl	10	Iv	+++
			A2	61		273–276					
	2	CH_3NH	A1	31	K	265–267	$C_{12}H_{14}N_2O_2 \cdot HCl$	C, H, N	20	Iv	+++
	3	CH_3CH_2NH	A3	60	M	236–237	$C_{13}H_{16}N_2O_2 \cdot HCl$	C, H, N, Cl	15	Iv	+++
	4	$(CH_3)_2CHNH$	A3[d]	16	Q	240–242	$C_{14}H_{18}N_2O_2 \cdot HCl$	C, H, N	15	Iv	++
	5	$CH_3CH_2CH_2NH$	A3	79	Z	244–245	$C_{14}H_{18}N_2O_2 \cdot HCl$	C, H, N, Cl	10	Iv	+++
	6	$CH_3(CH_2)_3NH$	A3	34	M	206–208	$C_{15}H_{20}N_2O_2 \cdot HCl$	C, H, N, Cl	10	Iv	+++
	7	$CH_3(CH_2)_4NH$	A3	40	R	198–200	$C_{16}H_{22}N_2O_2 \cdot HCl \cdot 0.5H_2O$	C, H	5	Iv	+++
	8	$NHCH_2CH_2NH$	A3[e]	47	N	315–319 dec	$C_{24}H_{26}N_4O_4 \cdot 2HCl$	C, H, N	20	Ip	Pressor
	9	HONH	A4	35	S	270–274	$C_{11}H_{12}N_2O_3 \cdot HCl$	C,[r] H, N, Cl	10	Iv	+
	10	$HOCH_2CH_2NH$	A3	51	J	238–239	$C_{13}H_{16}N_2O_3 \cdot HCl \cdot H_2O$	C, H, N, Cl	10	Iv	++
	11	$HO(CH_2)_3NH$	A3	43	L	235–236	$C_{14}H_{18}N_2O_3 \cdot HCl$	C, H, N, Cl	10	Iv	+
	12	$CH_3CHOHCH_2CH_2NH$	A3	52	Q	200–201	$C_{15}H_{20}N_2O_3 \cdot HCl$	C, H, N, Cl	10	Iv	+++
	13	$HOCH_2CHOHCH_2NH$	A3	50	L	232–233	$C_{14}H_{18}N_2O_4 \cdot HCl \cdot H_2O$	C, H, N	10	Iv	+
	14	$CH_3O(CH_2)_3NH$	A3	66	Q	228–229	$C_{15}H_{20}N_2O_3 \cdot HCl$	C, H, N, Cl	10	Iv	++
	15	$CH_3CH_2OCH_2CH_2NH$	A3[e]	44	M	191–193	$C_{15}H_{20}N_2O_3$	C, H, N	20	Ip	+
	16	$H_2NCH_2CH_2NH$	A3	56	L	245–246	$C_{13}H_{17}N_3O_2 \cdot 2HCl \cdot 2H_2O$	C, H, N, Cl	10	Iv	++
	17	$(CH_3)_2NCH_2CH_2NH$	A3[e]	21	M	262–264	$C_{15}H_{21}N_2O_2 \cdot 2HCl \cdot H_2O$	C, H, N, Cl	10	Iv	+
	18	$C_2H_5OOCCH_2NH$	A3	27	M	228–230	$C_{15}H_{18}N_2O_4 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	10	Iv	+
	19	$HOOCCH_2CH_2NH$	A3[e]	57	T	272–274	$C_{14}H_{16}N_2O_4 \cdot 1.5H_2O$	C, H, N	100	Ip	+
	20	$C_2H_5OOCH_2CH_2NH$	*f*	52	Q	237–239	$C_{16}H_{20}N_2O_4 \cdot HCl$	C, H, N, Cl	5	Iv	+++
	21	$C_6H_5CH_2NH$	A3	69	L	250–251	$C_{18}H_{18}N_2O_2 \cdot HCl$	C, H, N	10	Iv	+
	22	$3,4\text{-}(CH_3O)_2C_6H_3CH_2NH$	*g*	75	K	199–201	$C_{20}H_{22}N_2O_4 \cdot HCl$	C, H, N	20	Iv	+++
	23		A3[h]	17	I	252–254	$C_{16}H_{16}N_2O_3 \cdot HCl$	C, H, N, Cl	10	Iv	+++
	24	$C_6H_{11}NH$	A3	26	R[r]	241–242	$C_{17}H_{23}N_2O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N	10	Iv	+
	25	C_6H_5NH	*i*	41	Q	248–251	$C_{17}H_{16}N_2O_2 \cdot HCl$	C, H, N	10	Iv	+
	26	$p\text{-}HOC_6H_4NH$	A3[i]	47	X	255–256 dec	$C_{17}H_{16}N_2O_3 \cdot HCl \cdot H_2O$	C, H, N	10	Iv	+
II	27	$(CH_3)_2N$	A5	54	K	243–245	$C_{13}H_{16}N_2O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N	5	Iv	+
	28		A3	28	L	251–257	$C_{16}H_{21}N_3O_2 \cdot 2HCl \cdot H_2O$	C, H, N, Cl	10	Iv	+
	29	Morpholinyl	A3	74	Q	212–216	$C_{15}H_{18}N_2O_3 \cdot HCl \cdot H_2O$	C, H, N	10	Iv	+
III	30	CH_3CONH	C1	47	U	254–259	$C_{13}H_{14}N_2O_3 \cdot HCl \cdot H_2O$	C, H, N, Cl	10	Iv	+
	31	$C_2H_5OOCCH_2NHCONH$	C2	45	R	223–235 dec	$C_{16}H_{19}N_3O_5$	C, H, N	100	Ip	Pressor
	32	$C_2H_5NHCONCONHC_2H_5$ (with O)	C2	37	R	185–187	$C_{17}H_{22}N_4O_4$	C, H, N	100	Ip	+
IV	33	$3,4\text{-}(CH_3O)_2C_6H_3CH{=}N$	C3	59	Q	165–167	$C_{20}H_{20}N_2O_4$	C, H, N	10	Iv	+++
	34	$p\text{-}(CH_3)_2NC_6H_4CH{=}N$	C3	49	M	199–202	$C_{18}H_{21}N_3O_2$	C, H, N	15	Iv	+
	35	$p\text{-}O_2NC_6H_4CH{=}N$	C3	54	V	218–224	$C_{18}H_{15}N_3O_4$	C, H, N	25	Ip	+
V	36	C_6H_5O	B	40	M	201–204	$C_{17}H_{15}NO_3 \cdot HCl \cdot 1.5H_2O$	C, H, N, Cl	20	Iv	+

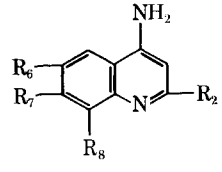
	37	p-$O_2NC_6H_4O$		B	46	Q	215–220	$C_{17}H_{14}N_2O_5 \cdot HCl$	C, H, N, Cl	100	Ip	+
	38	p-$H_2NC_6H_4O$		*k*	43	Y	215–218	$C_{17}H_{16}N_2O_3 \cdot 2HCl \cdot 2H_2O$	C, H, N[s]	50	Iv	+++
	39	HS		*l*	68	P	232–235	$C_{11}H_{11}NO_2S$	C, H, S	10	Iv	+
	40	CH_3S		*l*	41	M[q]	227–229	$C_{12}H_{13}NO_2S \cdot HCl \cdot H_2O$	C, H, N	20	Iv	++
	41	NH_2NH		*l*	21		283–288	$C_{11}H_{13}N_3O_2 \cdot 2HCl$	C, H, Cl	30	Iv	+



Compd Class	Compd No.	R_1	R_2	R_3	R_4	Method	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Formula	Analyses	Dose, mg/kg	Route	Rating[c]
VI	42		H	$COOC_2H_5$	Cl	*l*	46	M	159–160	$C_{14}H_{14}ClNO_4$	C, H, Cl	20	Ip	+
	43	6,7-$(OC_2H_5)_2$	CH_3	$ClCH_2CH_2$	Cl	*l*	48	Q	158–159	$C_{16}H_{19}Cl_2NO_2$	C, H, N, Cl	20	Ip	+
	44		H	COOH	CH_3NH	*m*	54	T	248–250	$C_{13}H_{14}N_2O_4$	C, H, N	50	Ip	+++
	45		H	$COOC_2H_5$	CH_3NH	A1[e,n]	46		215–216	$C_{15}H_{18}N_2O_4 \cdot HCl \cdot 0.5H_2O$	C,[t] H, N, Cl	100	Ip	+
	46	6,7-$(OC_2H_5)_2$	H	H	Cl	*l*	15	R	180–200	$C_{13}H_{14}ClNO_2 \cdot HCl \cdot H_2O$	C, H, Cl	20	Iv	Pressor



Compd Class	Compd No.	R_1	R_2	R_3	R_4	Method	Yield, %	Recrystn[a] Solvent	Mp, °C[b]	Formula	Analyses	Dose, mg/kg	Route	Rating[c]
VII	50	CH_3	H	H	H_2N	*l*	51	L	272–276 dec	$C_{12}H_{15}IN_2O_2$	C, H, I	10	Iv	+
	51	C_2H_5	H	H	CH_3NH	*l*	42	W	240–244	$C_{14}H_{19}IN_2O_2$	C, H, N	100	Ip	+
	52	C_2H_5	H	COOH	CH_3NH	*l*	43	66% EtOH	171–174	$C_{15}H_{19}IN_2O_4 \cdot H_2O$	C, H, N	10	Iv	+
	53	CH_3 (Anion is Cl^-)	H	H	H_2N	*l*		75% MeOH	280–283	$C_{12}H_{15}ClN_2O_2$	C, H, Cl			



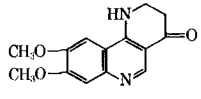
Compd Class	Compd No.	R_2	R_6	R_7	R_8	Method	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Formula	Analyses	Dose, mg/kg	Route	Rating[c]
VIII	54	H	H	H	H	*o*	29	Q	303–311 dec	$C_9H_8N_2 \cdot HCl$		25	Iv	+++
	55	H	H	CH_3O	H	A1[p]	58	L	250	$C_{10}H_{10}N_2O \cdot HCl$	C, H,[u] N, Cl	30	Iv	++
	56	H	C_2H_5O	C_2H_5O	H	A1	54	L	273–275	$C_{13}H_{16}N_2O_2 \cdot HCl$	C, H, N, Cl	10	Iv	++
	57	CH_3	CH_3O	CH_3O	H	A3[d]	63		292–293	$C_{12}H_{14}N_2O_2 \cdot HCl$	C, H, N, Cl	10	Iv	+
IX	58					*l*	41	Q	266–270	$C_{14}H_{14}N_2O_3 \cdot HCl$	C, H, N, Cl	10	Iv	++

TABLE I (*Continued*)

Compd Class	No.	R_2	R_6	R_7	R_8	Method	Yield, %	Recrystn[a] solvent	Mp, °C[b]	Formula	Analysis	Dose, mg/kg	Route	Rating[c]
X	59	C_2H_5O	HN	CH_3		A1[d]	29	H	280–282	$C_{16}H_{20}N_2O_2 \cdot HCl \cdot 0.5H_2O$	C, H, N, Cl	10	Iv	+++
		C_2H_5O		N								2	Iv	++
		Phenoxybenzamine[e]										1	Iv	++
		Mecamylamine[e]												

[a] Recrystn solvents: H, 10% aq HCl; I, *i*-PrOH–10% aq HCl; J, MeOH–H_2O; K, 95% EtOH; L, MeOH; M, *i*-PrOH; N, $HO(CH_2)_2OH$; O, 0.05 *M* HCl; P, 12% EtOH (DMF); Q, EtOH; R, MeCN; S, 25% MeOH (0.05 *M* HCl); T, HOAc; U, 95% EtOH (HCl); V, C_6H_6; W, $MeNO_2$; X, 25% MeOH (0.01 *M* HCl); Y, MeOH (HCl); Z, 95% EtOH (MeOH). [b] Melting points were determined on a Fisher-Johns (hot stage) apparatus, and are uncorrected. [c] + (<40% decrease in blood pressure or a duration of action of <45 min); ++ (>40% decrease in blood pressure with a duration of action >45 min but <270 min; +++ (>40% decrease in blood pressure with a duration of action >270 min. [d] Et_2O ppte crude product required neutralization with strong base (10–40% NaOH) to enable isolation of crystalline product, as free base. [e] Reaction temp at 90–125° was below the usual reaction temp (160–180°). [f] By esterification of **19** with HCl in EtOH. [g] From **33** through H_2 Pd/C reduction at 2–3 atm and 35–40°. [h] The cooled phenolic soln was first dissolved in acetone, then ppte with Et_2O. [i] From **47** and $PhNH_2$ in dil HCl at 85–90° in 3.5 hr; a modified lit. [C. K. Banks, *J. Amer. Chem. Soc.*, **66**, 1127 (1944)] procedure. [j] The reactant *p*-$HOC_6H_4NH_2$ also served as the reaction solvent. [k] From **37** through H_2–Ra Ni reduction at 2–3 atm and 45–50°. [l] See Experimental Section for details. [m] By hydrolysis of **45** in 7% NaOH at 85–90°. [n] Addl HCl was required to form the hydrochloride. [o] Reported in lit. [E. Hasyahi, H. Yamanaka, and K. Shimizer, *Chem. Pharm. Bull.*, **6**, 323 (1958); *Chem. Abstr.*, **53**, 375*i* (1959)]; prepd by catalytic reduction of 4-nitroquinoline 1-oxide (Aldrich Chem. Co.). [p] The 4-chloro-7-methoxyquinoline intermediate was purchased from Maybridge Chem. Co. STD. [q] Solvent used for free base of the compound. [r] C: calcd, 51.46; found, 50.99. [s] N: calcd, 6.95; found, 6.53. [t] C: calcd, 53.65; found 54.24. [u] H: calcd, 5.26; found, 5.81. [v] Standard hypotensive drugs.

in blood pressure or a duration of action of <45 min); moderate activity, ++ (>40% decrease in blood pressure with a duration of action >45 min but <270 min); maximum activity, +++ (>40% decrease in plood pressure with a duration of action >270 min).

Results

This paper has dealt primarily with 6,7-dialkoxy-4-(substituted amino)quinolines (I, II, VIII). The hypotensive activity of these compounds as determined in anesthetized dogs and evaluated by the previously described rating system is delineated in Table I. Although a wide variation of these 4-(substituted amino)-quinolines exhibited various degrees of activity, the essential fact is that the basic 4-(substituted amino)-quinoline molecule generally elicits hypotensive activity in anesthetized dogs. Also lesser degrees of hypotensive activity were observed (a) where the 4 position of the quinoline was substituted by amido (III), methyleneamino (IV), phenoxy, thio, and hydrazino (V), and (b) where the 1 position of the 4-(substituted amino)quinoline was quaternized (VII).

Experimental Section

4-Amino-6,7-dimethoxyquinoline·HCl·H_2O (1) (Method A1[3]**).**—A 5-l. flask fitted with stirrer, thermometer, condenser, and gas-inlet tube was charged with molten PhOH (2000 ml) and **47**[3] (600 g, 2.68 moles). The mixt was heated to 100° with a Glas-Col mantle, then satd with anhyd NH_3 in 10 min. The NH_3 addn was interrupted, while the mixt was heated to reflux (166–176°), and then resumed at a moderate rate at reflux for 3.5 hr. The reaction soln was air-cooled to 50° and poured rapidly into stirred Et_2O (12 l). The product was collected (on paper over cloth) by filtration and rinsed with *i*-PrOH and Et_2O: mp 261°; yield, 613 g (88%). Recrystn of 306 g from boiling 85% aq MeOH (3000 ml) with slow addn of H_2O (200 ml) with charcoal gave white cryst 1.

Method A2.—NH_4OAc (12 g, 0.16 mole) was heated in an open flask at 110–173° in 18 min and cooled in air for 7 min. To the preheated NH_4OAc was added the free base of **36** (2.0 g, 0.0071 mole), and the mixt was heated at 178–180° for 1.1 hr. The cooled reaction mixt was dissolved in *i*-PrOH, then treated with 10% HCl (5 ml) in the cold. The cryst product was collected by filtration and washed with *i*-PrOH and ether.

6,7-Dimethoxy-4-propylaminoquinoline·HCl (5) (Method A3).—To a warm soln of **47** (34 g, 0.15 mole) in PhOH (110 ml) was added $PrNH_2$ (10 g, 0.17 mole) with mechanical stirring. The reaction soln was refluxed for 2 hr, and then added to anhyd Et_2O (1250 ml); the resultant sticky material gradually solidified upon trituration. The solid was collected by filtration and immediately recrystd from a mixt of 95% EtOH (250 ml) and MeOH (140 ml) to give cryst **5**.

4-Hydroxyamino-6,7-dimethoxyquinoline·HCl (9) (Method A4).—To a soln of **47** (60 g, 0.27 mole) in PhOH (640 ml) was added 54% NaH (14.6 g, 0.33 mole) in mineral oil at 55–70°, with mechanical stirring; the reaction was exothermic. After 10 min $H_2NOH \cdot HCl$ (15.0 g, 0.22 mole) was added to the mixt, which was heated on the steam bath for 0.5 hr. A second portion of $H_2NOH \cdot HCl$ (15.0 g) was added, and the reaction mixt was heated at 94–103° for 2.5 hr. The cooled mixt was added to *i*-PrOH and cooled in an ice bath, and the resultant brown solid was collected by filtration and washed with *i*-PrOH (90 ml) and Et_2O; yield, 58 g.

Recrystn of the product (25 g) from a mixt of 25% MeOH (4 l.) and 10% HCl (80 ml) with charcoal gave **9**.

6,7-Dimethoxy-4-dimethylaminoquinoline·HCl·0.5H_2O (27) (Method A5).—A soln of **47** (70 g, 0.31 mole) in DMF (450 ml) was satd with dry Me_2NH at 40–85° over 35 min with mechanical stirring. The satd soln was heated to 140° in 40 min, then the addn of Me_2NH was contd at 145–150° over 6.5 hr. The cooled soln was added to anhyd Et_2O (2300 ml) and filtered. The filtrate was evapd to dryness under reduced pressure. In order

to remove residual DMF the crude residue was treated with *i*-PrOH (150 ml) and evapd to dryness. Treatment of a soln of the residue in *i*-PrOH (500 ml) and 10% HCl (110 ml) gave the hydrochloride **27**.

6,7-Dimethoxy-4-phenoxyquinoline·HCl·1.5H$_2$O (36) (Method B).—A soln of **47** (70 g, 0.31 mole) in PhOH (240 ml) was refluxed for 2.3 hr. The cooled soln was treated with H_2O (500 ml) and C_6H_6 (650 ml), and the mixt was neutralized with 10% NaOH to pH 8–9. The aq layer was further extd with C_6H_6 (800 ml). The combined exts were dried over a mixt of $MgSO_4$ and charcoal, filtered, concd to a vol of 115 ml, and cooled in the refrigerator. The resultant light yellow, cryst free base of **36** was collected by filtration and washed with cold C_6H_6 and Et_2O: mp 115–120°; yield, 35 g (40%).

A soln of the free base of **36** (46 g, 0.16 mole) in C_6H_6 (700 ml) was treated with dry HCl with cooling. The hydrochloride was collected by filtration and recrystn from *i*-PrOH (290 ml) to give **36**.

4-Mercapto-6,7-dimethoxyquinoline (39).—Dry H_2S was bubbled through a soln of Na_2S (54 g, 0.69 mole) in DMF (1300 ml) at 25–30° for 3.5 hr. To the soln was added the free base of **47** (136 g, 0.6 mole) with mechanical stirring. The reaction soln was refluxed at 132–139° for 1.2 hr. The cooled mixt was added gradually to ice and H_2O (6 l.). The resultant yellow, cryst solid was collected by filtration, washed with H_2O (375 ml), and dried in air. Recrystn from 12% EtOH–DMF gave **39**.

6,7-Dimethoxy-4-methylthioquinoline·HCl·H$_2$O (40).—To a soln of **39** (60 g, 0.27 mole) in 5% NaOH (258 ml) was added Me_2SO_4 at 3–10° in 20 min with rapid stirring. The ice-cooled mixt was stirred for 1 hr, then warmed in the air for 2.5 hr. The resultant yellow, cryst solid was collected by filtration, washed with H_2O (200 ml), and dried in air at 65°. Recrystn from *i*-PrOH (700 ml) with charcoal gave the free base of **40**: mp 174–175°; yield, 29.8 g. The free base in 95% EtOH (1500 ml) was treated with dry HCl in the cold. The hydrochloride **40** was collected by filtration and washed with EtOH and Et_2O.

4-Hydrazino-6,7-dimethoxyquinoline·2HCl (41).—A suspension of **47** (5.0 g, 0.022 mole) and $N_2H_4·H_2O$ (20 ml) was refluxed for 75 min. The reaction soln was cooled, and the resultant solid was collected by filtration. Recrystn from 5% HCl gave **41**.

4-Acetamido-6,7-dimethoxyquinoline·HCl·H$_2$O (30) (Method C1).—A soln of the free base of 1 (30 g, 0.15 mole) in $(MeCO)_2O$ (450 ml) was refluxed for 6 hr. The reaction soln was concd under reduced pressure, the residue was heated on the steam with *i*-PrOH (60 ml) and cooled, and the resultant solid was collected by filtration and washed with *i*-PrOH (3 × 10 ml). A mixt of the solid product was treated with dry HCl in *i*-PrOH (200 ml). Recrystn of the resultant hydrochloride (26 g) from a mixture of 95% ethanol (1400 ml) and concd HCl with charcoal gave **30**.

Ethyl 5-(6,7-Dimethoxy-4-quinolyl)hydantoate (31) (Method C2).—A mixt of hydrated free base of 1 (90 g, 0.41 mole on anhyd basis) and C_6H_6 (900 ml) was refluxed with Dean–Stark trap and mechanical stirring for 6 hr, until the H_2O (7.0 ml) was removed. To the mixt was added dropwise, a soln of ethoxycarbonylmethyl isocyanate (63 g, 0.49 mole) in dry C_6H_6 (225 ml) in 2 hr with heating on a steam bath. The reaction mixt was further heated for 1.5 hr, then cooled at 8–15° for 1 hr. The resultant brown solid was collected by filtration and washed with C_6H_6 (100 ml) and Et_2O: yield, 100 g. Recrystn of the product (67 g) from MeCN (3800 ml) with charcoal gave **31**.

Ethyl 4-Chloro-6,7-dimethoxy-3-quinolinecarboxylate (42).—A mixt of **48**[3] (18 g, 0.065 mole) and $POCl_3$ (150 ml) was refluxed for 30 hr. The reaction mixt was worked up in the usual manner.

4-(3,4-Dimethoxybenzylideneamino)-6,7-dimethoxyquinoline (33) (Method C3).[8]—A mixt of hydrated free base of **1** (80 g, 0.34 mole on anhyd basis) and PhMe (1500 ml) was refluxed (a Dean–Stark trap) until the H_2O (10 ml) was removed. Then veratraldehyde (66 g, 0.40 mole) and piperidine (35 ml) were added to the mixt, which was refluxed for 18.5 hr. The hot reaction soln was decanted from an insoluble solid (4 g) and cooled in an ice bath, and the product was collected by filtration and washed with petroleum ether: mp 155–157°; yield, 95 g. Recrystn from EtOH (1700 ml) with charcoal gave **33**.

4-Chloro-6,7-diethoxyquinoline·HCl·H$_2$O (46).—To Dowtherm A (780 ml) at 250° was added portionwise 6,7-diethoxy-4-hydroxyquinoline-3-carboxylic acid[9] (78 g, 0.25 mole), and the mixt was refluxed 1 hr. The cooled mixt was treated with hexane (1000 ml) then decanted from the amorphous residue, which was triturated with petr ether and C_6H_6, resp. Recrystn from H_2O (1200 ml) gave 6,7-diethoxy-4-hydroxyquinoline: mp 95°; yield, 39.5 g. The compd was chlorinated in the usual manner with $POCl_3$ to give **46**.

4-Amino-6,7-dimethoxy-1-methylquinolinium Iodide (50).—To a soln of 1 (50 g, 0.25 mole) in EtOH (1300 ml) was added MeI (60 ml, 0.96 mole) at 21° over 4 min with mechanical stirring. The reaction mixt was refluxed for 1 hr and then cooled in an ice bath. The resultant white, cryst solid was collected by filtration and washed with i-PrOH–ether: yield, 78 g. Recrystn of the product (30 g) from MeOH (35 ml) with charcoal gave **50**.

1-Ethyl-6,7-dimethoxy-4-methylaminoquinolinium Iodide (51).—A mixt of **47** (112 g, 0.50 mole), acetone (1500 ml), NaI (1.0 g, 0.0067 mole), and EtI (80 ml, 1.0 mole) was refluxed for 5 days. The resultant cryst iodide (101 g) was collected by filtration of the cooled reaction mixt. Dry $MeNH_2$ was passed through a mixt of the iodide (75, g 0.20 mole) and $MeNO_2$ (1350 ml) at 24–41° for 9 hr with mechanical stirring; the reaction was exothermic. The reaction mixt was stirred for 15 hr at 24–26°, and then cooled in an ice bath. The yellow cryst product was collected by filtration and recrystn from $MeNO_2$ (600 ml) with charcoal.

3-Carboxy-1-ethyl-6,7-dimethoxy-4-methylaminoquinolinium Iodide·H$_2$O (52).—To a soln of NaOH (17 g, 0.42 mole) in 66% EtOH (900 ml) was added **44** (50 g, 0.19 mole) at 30° with mechanical stirring. Next, EtI (100 ml, 1.25 mole) was added at 25–27° in 2 min. The reaction mixt was refluxed 17 hr, then cooled in an ice bath. The resultant tan solid was collected by filtration and recrystd from 66% EtOH (600 ml) with charcoal.

4-Amino-6,7-dimethoxy-1-methylquinolinium Chloride (53).—A soln of **50** (3.0 g) in a mixt of MeOH (200 ml) and H_2O (150 ml) was passed slowly through a 44 × 150 mm column, of Dowex 1-X8 (ionic Cl^- form) resin. A center cut of the effluent (150 ml) was evapd to dryness under reduced pressure; the resultant white crystals (mp 277–279° dec) were recrystd from 75% MeOH (H_2O), mp 280–283° dec, mmp 252–255° dec with **2** (mp 254–257° dec). The ir absorption of **53** and **2** differed greatly. Nmr spectrum (δ) showed: (DMSO) 3.98, singlet (CH_3); 4.04, 4.08, singlets ($2CH_3O$); 6.73, 6.85 and 8.30, 8.41, pair doublets (2 heterom); 7.31, 8.06, singlets (2 arom); 8.8, broad absorption (NH_2, exchanged with D_2O).

6,7-Dimethoxy-4-methylaminoquinoline·HCl (2) was prepd by method A1. Nmr spectrum (δ) showed: (DMSO) 3.05, 3.13, doublet (CH_3, a singlet at 3.1 with D_2O exchange); 3.96, 3.98, singlets ($2CH_2O$); 6.55, 6.67, and 8.27, 8.38, pair doublets (2 heterom); 7.50, 8.05, singlets (2 arom); 9.4, broad absorption (NH, exchanged with D_2O).

2,3-Dihydro-8,9-dimethoxybenzo[*h*]-1,6-naphthyridin-4(1*H*)-one·HCl (58).—To warm PPA (800 g) was added **19** (80 g, 0.29 mole) with mechanical stirring; the resultant soln was heated at 85–90° for 2 hr. The cooled soln was added to H_2O (3500 ml) at 20–30° with stirring. The crude product was collected by filtration and washed with *i*-PrOH (125 ml) and Et_2O. Recrystn from 10% HCl (7 l.) with charcoal gave **58**. Nmr spectrum (δ) showed: (DMSO) 3.70 singlet ($2CH_3O$); 6.96, singlet (1 heterom); 7.54, 8.30 singlets (2 arom); the CH_2CH_2 protons were unresolved.

4-Chloro-3-(2-chloroethyl)-6,7-diethoxyquinaldine (43).—A mixt of 3,4-diethoxynitrobenzene[9] (30 g, 0.14 mole), 5% Pd/C (3 g), and EtOH (200 ml) was hydrogenated in a Parr apparatus. The catalyst was removed by filtration. The process was repeated, and the combined 3,4-diethoxyaniline soln were treated with 2-acetylbutyrolactone[8] (36 g, 0.28 mole) and refluxed for 2 hr. The reaction soln was concd to 0.5 vol and cooled, and the resultant anil **60** was collected by filtration: mp 113–116°; yield, 60 g (74%).

To a soln of $POCl_3$ (112 ml) in PhMe (100 ml) at 40–50° was added portionwise **60** (94 g, 0.32 mole) in PhMe (700 ml). The reaction mixt was heated at 85–90° for 1 hr then refluxed for 3 hr. Excess solvents were removed under reduced pressure, addnl PhMe (250 ml) was added and again removed, and the residue was dissolved in PhMe and treated with ice H_2O (2000 ml). The mixt was made fully basic with NH_4OH and filtered. The solvent

(8) A minor modification of the procedure of V. G. Ramsey, W. E. Baldwin, and R. S. Tipson, *J. Amer. Chem. Soc.*, **69**, 67 (1947).

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was removed from the org layer under reduced pressure, and the residue was recrystd from *i*-PrOH to give **43**.

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Quaternary Pilocarpine Derivatives Acting as Acetylcholine Antagonists

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Several quaternary *d*-pilocarpine derivatives have been prepared in order to investigate the influence of structural changes on the biological activity of this alkaloid. The effect of the substituents in the reagent, as well as of the temp and the solvent (its dielectric constant), on the rate of the quaternization has been studied, and the products have been analyzed by various spectroscopic means. The anticholinergic activities of the compounds are reported, and a relation has been sought in connection with the structural changes.

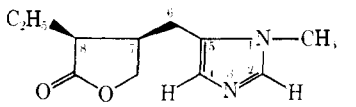
Pilocarpine (I) is the main alkaloid obtained from the leaves of the South American shrubs *Pilocarpus jaborandi* and *Pilocarpus microphyllus* Stapf. The structures of pilocarpine and its isomer, isopilocarpine, were determined by Jowett[1] and both were synthesized by several routes.[2] The absolute configuration of pilocarpine has been established as being 7*R*,8*S*.[3] *d*-Pilocarpine, one of the oldest parasympathomimetic drugs,[4] may act as an anticholinergic in certain systems.[5]

The purpose of this study was: (a) to develop methods for the addition of various groups to the alkaloid by quaternization at N-3 and determine the various conditions influencing the reaction and the stability of the products; (b) study some aspects of the relative reactivity of the alkaloid with various halo organic reagents; (c) test the pharmacological activity of the new compds as a function of structural change. It has been reported that quaternization of atropine and scopolamine with different substituted phenacyl bromides induces changes in their pharmacological activities.[6]

Results and Discussion

The free base of *d*-pilocarpine (I) was treated with different halo organic compds producing a series of quaternary deriv with the general structure II (Table I).

The effect of the substituents in the halo organic reagents, the temp, and the solvent influence the optimal time of the reaction. The data collected in Table I show a marked decrease in the rate of quaternization in Me_2CO medium passing from Et to *n*-Pr (**1-3**), but in contrast to previous observations,[7,8] with *n*-BuBr practically no reaction took place. In a solvent with higher polarity (2-methoxyethanol) only 6 days were required for completion of the reaction. It was observed that *n*-PrI was about twice as reactive as the bromide, whereas with *i*-PrBr no quaternization would take place. It is therefore difficult to distinguish between electronic and steric effects in these reactions.



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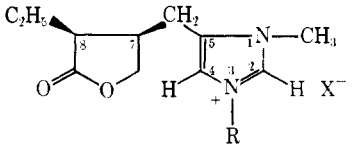

II

In the case of benzyl halides the reactivity is relatively greater, and is influenced by the character and the position of the substituent. Electron-releasing groups in the para position (**7**, **10**, **13**) enhance the displacement of the halogen, the reaction becoming more sluggish with a Me group. With ortho substituents of the same character (**9**, **11**) steric hindrance makes the reaction slower by far. An electron-attracting group, such as NO_2, at the para position induces a decrease of the rate of the reaction, bromide **15** being more reactive than chloride **16**. In contrast, when NO_2 is at the meta position (**14**) the reaction is faster. When Ph is further away from the side-chain halogen atom (**5**), no conjugation between the ring and the side-chain halogen is possible, and the reaction becomes sluggish; it could be accelerated, however, by using a solvent with high dielectric constant (ε) such as 2-methoxyethanol ($\varepsilon \sim 40$). The comparatively high reactivity with the phenacyl bromides (**19-23**) may be explained by the activating effect of the carbonyl group.[9]

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