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β-Adrenergic Blocking Agents with Acute Antihypertensive Activity

J. J. Baldwin,* E. L. Engelhardt, R. Hirschmann, G. F. Lundell, G. S. Ponticello,

Merck, Sharp and Dohme Research Laboratories, West Point, Pennsylvania 19486

C. T. Ludden, C. S. Sweet, A. Scriabine,

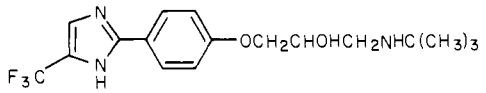
Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486

N. N. Share, and R. Hall

Merck Frosst Research Laboratories, Pointe Clair/Dorval, Quebec, Canada H9R 4P8. *Received December 6, 1978*

Modification of the pharmacological profile of the vasodilating/β-adrenergic blocking agent 2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-4-(trifluoromethyl)imidazole (1) has been investigated. Introduction of selected substitutents onto the imidazole ring, in place of the trifluoromethyl group, has yielded highly cardioselective β-adrenergic blocking agents such as **7**, **17**, and **18**. The placement of alkyl or chloro groups onto the aryl ring of 1, as illustrated by **33**, has produced a class of compounds characterized as antihypertensive β-adrenergic blocking agents. In these examples, the acute antihypertensive activity does not appear to be due to either vasodilating or β_2-agonist properties.

We have previously reported that compounds exemplified by **1** were found to lower mean arterial blood



1

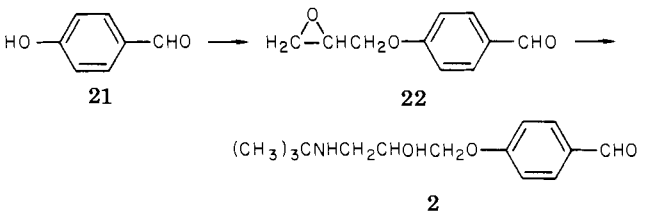
pressure in spontaneously hypertensive (SH) rats and to exhibit vasodilating and β-adrenergic blocking properties in the dog.[1] However, the reduction in peripheral vascular resistance induced by **1** was attenuated by timolol, a β-adrenoceptor antagonist. The assumption was made that the vasodilation was due, in large part, to β_2-agonist activity.

In an extention of this work, we have attempted to reduce this β-agonist component while retaining those structural features which induced the acute antihypertensive and β-adrenergic blocking effects. The approach was based on the premise that the affinity for the β-adrenergic receptor was determined by the aminohydroxypropoxy side chain, while activation of the receptor was induced by an interaction of the bound drug with an aromatic/phenolic binding site on the receptor.

The partial agonist activity of **1** was ascribed to the interaction of the acidic imidazole proton with this postulated binding site. In support of this concept, in has recently been reported that the incorporation of phenolic groups into phenoxypropanolamines was associated with the introduction of agonist properties.[2] Substitution of the imidazole ring with moieties less electronegative or more bulky than the trifluoromethyl group was therefore examined with the aim of reducing the capability of the imidazole proton to act as a phenolic equivalent. Attempts were also made to reduce this postulated interaction by substitution of the aryl ring with chloro and alkyl groups ortho to the trifluoromethylimidazolyl substituent.

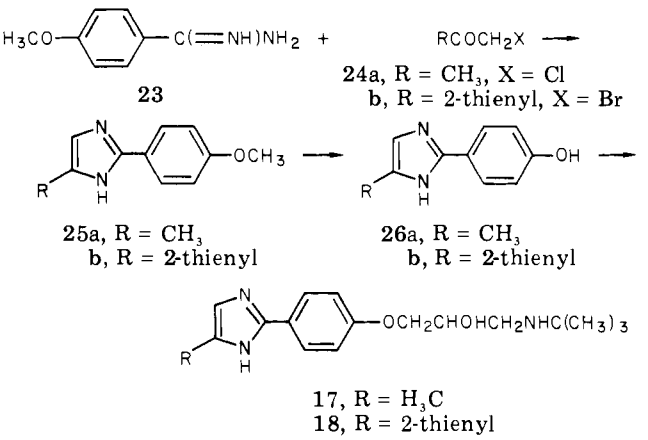
Chemistry. The various 4-substituted 2-[4-[(*tert*-butylamino)-2-hydroxypropoxy]phenyl]imidazoles prepared during this study are listed in Table I. Examples **3**–**15**

Scheme I



21 **22** **2**

Scheme II



23 **24a**, R = CH_3, X = Cl; **b**, R = 2-thienyl, X = Br

25a, R = CH_3; **b**, R = 2-thienyl **26a**, R = CH_3; **b**, R = 2-thienyl

17, R = H_3C
18, R = 2-thienyl

were synthesized via the Radziszewski reaction involving the condensation of the racemic aldehyde **2** with a substituted glyoxal in methanolic aqueous ammonia. The 4-methylimidazole derivative **16** was obtained using the Weidenhagen modification in which **2** was allowed to react with α-acetoxyacetone, aqueous ammonia, and cupric acetate.

The intermediate aldehyde **2** was prepared as outlined in Scheme I. Treatment of *p*-hydroxybenzaldehyde with epichlorohydrin in aqueous base gave **22** in 64% yield after distillation. The potential for a competing Cannizzaro reaction under these conditions did not prove to be a

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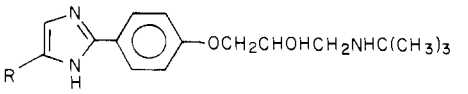
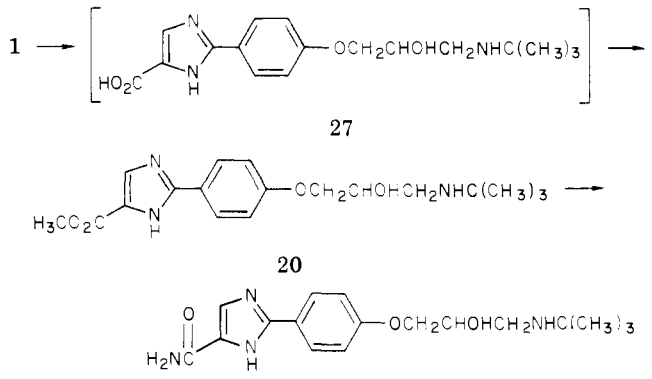
Table I



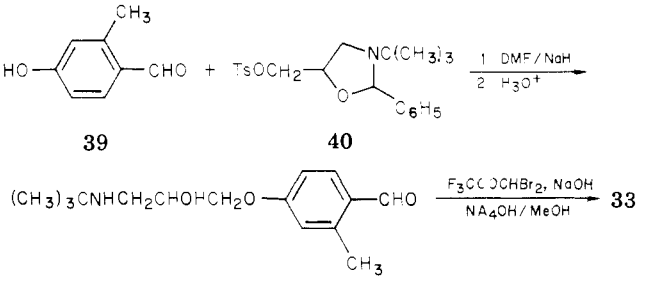
no.	R	optical config	meth of prep	crystn solv	mp, °C	yield,[a] %	formula
3	H	*R,S*	A	H_3CCN	162-164	32	$C_{16}H_{23}N_3O_2$
4	H	*S*	A	H_3CCN	158-162	19	$C_{16}H_{23}N_3O_2$
5	C_6H_5	*R,S*	A	H_3CCN	176-178	14	$C_{22}H_{27}N_3O_2$
6	4-$H_3COC_6H_4$	*R,S*	A	H_3CCN	179-181	13	$C_{23}H_{29}N_3O_2$[b]
7	4-$H_3COC_6H_4$	*S*	A	EtOH	192-194	6	$C_{23}H_{29}N_3O_3 \cdot 2C_4H_4O_4 \cdot H_2O$[c]
8	4-ClC_6H_4	*R,S*	A	H_3CCN	186-188	8	$C_{22}H_{26}ClN_3O_2$
9	4-FC_6H_4	*R,S*	A	H_3CCN	168-170	3	$C_{22}H_{26}FN_3O_2$
10	3,4-$Cl_2C_6H_3$	*R,S*	A	H_3CCN	189-190	6	$C_{22}H_{25}Cl_2N_3O_2$
11	C_6F_5	*R,S*	A	H_3CCN	168-170	3	$C_{22}H_{22}F_5N_3O_2$
12	2-furyl	*R,S*	A	H_2CCl_2-H_3CCN	172-173	5	$C_{20}H_{25}N_3O_3 \cdot H_2O$
13	2-thienyl	*R,S*	A	H_2CCl_2-H_3CCN	178-180	5	$C_{20}H_{25}N_3O_2S$
14	2-pyridyl	*R,S*	A	H_3CCN	138-142	2	$C_{21}H_{26}N_4O_2 \cdot H_2O$
15	3-pyridyl	*R,S*	A	H_3CCN	170-171	7	$C_{21}H_{26}N_4O_2 \cdot H_2O$
16	H_3C	*R,S*	B	MeOH-H_3CCN	202-203	20	$C_{17}H_{25}N_3O_2$[d]
17	H_3C	*S*	C	EtOH	173-175	30	$C_{17}H_{25}N_3O_2 \cdot 2C_4H_4O_4$[c]
18	2-thienyl	*S*	C	EtOH	142-144	34	$C_{20}H_{25}N_3O_2S \cdot 2C_4H_4O_4 \cdot 0.5H_2O$[c]
19	CO_2CH_3	*R,S*	D	H_3CCN	168-172	45	$C_{18}H_{25}N_3O_4$
20	$CONH_2$	*R,S*	D	H_3CCN	190-193	49	$C_{17}H_{24}N_4O_3$

[a] Calculated yield is based on the last synthetic step. [b] Anal. Calcd: C, 69.85; H, 7.40; N, 10.61. Found: C, 69.43; H, 7.44; N, 10.60. [c] Maleate salt. [d] Anal. Calcd: C, 67.35; H, 8.30; N, 13.82. Found: C, 67.41; H, 8.91; N, 13.86.

Scheme III



Scheme IV



serious problem. The epoxide **22** has also been prepared by Weissemel using Levatit MN[3] in place of the aqueous sodium hydroxide. Conversion of **22** to **2** was accomplished through reaction with excess *tert*-butylamine followed by hydrolysis of the intermediate imine.[1] The *S* enantiomer of **2**, required for the preparation of **4** and **7**, was obtained through the reaction of (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine[4] and **21** as previously described.[1]

An alternate synthesis, outlined in Scheme II, was used for the preparation of the *S* enantiomers of the 4-thienyl and 4-methyl derivatives **17** and **18**. In this approach, imidazole formation was achieved prior to the introduction of the aminohydroxypropoxy group. Condensation of *p*-methoxybenzamidine with the α-halo ketones **24a,b** gave the imidazoles **25a,b**. Ether cleavage with 48% aqueous hydrobromic acid yielded the phenols **26a,b**. The side chain was then introduced through reaction with the tosylate of (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)-oxazolidine[1] followed by mild acid hydrolysis.

Derivatives having carbomethoxy and carbamoyl groups in the 4 position of the imidazole ring were prepared as outlined in Scheme III.

Basic hydrolysis of the 4-(trifluoromethyl) group in 2-arylimidazoles has been shown to yield the corresponding 4-carboxylic acid.[5] Thus, derivatives having carbomethoxy and carbamoyl groups were prepared from I by treatment with aqueous base, followed by conversion of the resulting acid **27**, by classical methods, to the ester **19** and amide **20**.

The aryl-substituted derivatives of I, **28–38**, are listed in Table II. The synthetic approach involved first the preparation of the various alkyl- and chloro-substituted *p*-hydroxybenzaldehydes via either the Reimer–Tiemann or Gattermann reactions. In the case of **31**, the intermediate 3-chloro-4-hydroxybenzaldehyde was prepared by chlorination of *p*-hydroxybenzaldehyde according to the procedure of Ginsberg.[6]

Alkylation of the phenolic hydroxyl group with epichlorohydrin in aqueous base followed by treatment of the resulting epoxide with *tert*-butylamine gave the substituted 4-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzaldehydes. These intermediate racemic benzaldehyde derivatives were then converted to the trifluoromethylimidazoles on reaction with trifluoromethylglyoxal and ammonia. The optically pure *S* enantiomer **33** of racemic **32** was prepared as indicated in Scheme IV using the oxazolidine derived from mannitol through 3-(*tert*-butylamino)-1,2-propanediol.[4]

Reaction of 2-methyl-4-hydroxybenzaldehyde (**39**) with the tosylate of (*S*)-2-phenyl-3-*tert*-butyl-5-(hydroxymethyl)oxazolidine (**40**) gave (*S*)-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]-2-methylbenzaldehyde (**41**) after acid

hydrolysis. Optical purity was determined at this stage by NMR spectroscopy using the chiral shift reagent tris[3-(heptafluorobutyryl α-camphorate]europium. In the spectrum of the racemate, two peaks separated by 7 Hz were observed for the aldehyde proton; in the optically pure *S* isomer, only one was seen. By this method, optical purity of the intermediate was determined to be 99 ± 1%. Imidazole formation was accomplished through reaction of **41** with trifluoromethylglyoxal and ammonia.

Discussion

Compounds were evaluated for oral antihypertensive activity in the SH rat and for their ability to antagonize β-adrenergic receptors and increase iliac blood flow in dogs. These preliminary pharmacological data are summarized in Table III. The compounds were initially studied in SH rats using the method of Watson and Ludden.[7] In this model, peripheral vasodilators like hydralazine, but not β-adrenergic antagonists like propranolol and timolol, acutely reduce arterial pressure.

In anesthetized dogs, a nonspecific vasodilator like hydrazaline will increase iliac blood flow in dogs pretreated with a β-adrenoreceptor blocking agent. In saline-treated dogs, iliac blood flow did not significantly increase or decrease over 30 min (79 ± 8 mL/min before, 68 ± 8 mL/min at 30 min). In four dogs pretreated with propranolol, 100 μg/kg, iv, hydralazine increased iliac blood flow 68 ± 5 (SE) mL/min from a pretreatment value of 119 ± 15 (SE) mL/min. Hydralazine alone increased iliac blood flow 78 ± 9 (SE) mL/min at 30 min from a pretreatment value of 88 ± 12 (SE) mL/min.

Thus, it can be inferred that compounds which exhibit oral antihypertensive activity in SH rats and increase iliac blood flow in timolol-pretreated dogs are antihypertensive by virtue of a property other than β-adrenergic blockade or β_2-agonist activity.

The introduction of hydrogen and methyl into the 4 position of the imidazole ring in place of the electronegative trifluoromethyl group, as in examples **3**, **4**, **16**, and **17**, resulted in a decreased antihypertensive activity as compared with **1**. In the dog, **16** and **17** induced changes in blood flow similar to that found with **1**. After timolol pretreatment, blood flow changes were decreased but remained elevated above both control valves and that seen with **1**, indicating that the component of vasodilation dependent on β_2-adrenergic agonism had been decreased.

With the introduction of aryl and heteroaryl groups into the imidazole 4 position, peripheral blood flow was modestly increased both before and after timolol. The dichlorophenyl derivative **10** was an exception, with the induced increase in blood flow being significantly attenuated after timolol pretreatment. This compound with its apparent β-agonist component lowered blood pressure 36 mmHg in the SH rat at 1.25 mg/kg po.

The most interesting feature of this subclass was the tendency toward cardioselectivity of the observed β-adrenergic blockade, as determined by the inhibition of the isoproterenol-induced hypotension and tachycardia (protocol I). Several compounds were therefore selected for a more precise examination of their cardioselectivity by determining the blockade of isoproterenol-induced bronchodilation in dogs in whom bronchial tone was induced by histamine (protocol II). The 4-unsubstituted derivative **3** exhibited high β_1 selectivity, no inhibition of β_2 adrenoceptors being observed up to a dose of 1000 μg/kg iv. The 4-methyl and 4-thienyl derivatives **17** and **18** were found to have ED_{50} β_2/ED_{50} β_1 ratios of 18 and 31, respectively. In comparison, practolol, a cardioselective β-adrenoceptor antagonist, was found to have a β_2/β_1 ratio of only 9. Interestingly, the dichlorophenyl derivative **10**, which appeared to possess a β-agonist component, as judged by an increase in blood flow which was blocked by timolol, was nonselective in its β-adrenergic blockade.

The aryl-substituted derivatives **28–38**, in general, induced only a modest increase in peripheral blood flow in the dogs, indicating the absence of both significant β_2-sympathomimetic activity and a nonspecific vasodilating component, the possible exceptions to this being the monomethyl derivative **33** and the planar naphthalene derivative **38**. In spite of the general lack of a vasodilating component, several examples, especially **28** and **32–34**, exhibited antihypertensive activity in the SH rat at 1.25 mg/kg po and were thus on the order of hydralazine in potency.

The introduction of one substituent onto the aryl group of **1**, as in **28**, **31–33**, and **36**, reduced β-adrenergic blocking activity by a factor of 2; the presence of a second group, as in **30**, **33**, **34**, **37**, and **38**, had a further negative effect on potency, increasing the ED_{50} for the β_1 receptor into the range of 100 μg/kg iv. In all cases, cardioselectivity was reduced as compared to **1**.

In summary, the β_2-antagonist activity present in **1** could be reduced or abolished by variation of the imidazole **4** substituent and by substitution of the aryl ring. The timolol-insensitive vasodilation tended to be increased when the trifluoromethyl group was varied, while substitution of the aryl ring ortho to the imidazole moiety reduced primarily the timolol-sensitive vasodilating component.

Several compounds, especially **7**, **17**, and **18**, were highly cardioselective β-adrenoceptor antagonists having a β_2/β_1 ratio greater than that found for practolol. In their pharmacologic profile, these examples exhibited little or no β-sympathomimetic activity, as indicated by blood-flow studies in the dog. In addition, compounds, exemplified by **33**, were found which reduced arterial pressure acutely in the SH rat; although the exact mechanism of action has not been fully explored, it does not appear to be entirely dependent on peripheral vasodilating activity.

Experimental Section

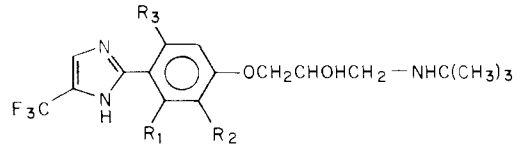
Spectral data were obtained with the following instruments: IR, Perkin-Elmer Models 137 and 257 infrared spectrophotometers; NMR, Varian A-60 and T-60 using tetramethylsilane as internal standard; mass spectra, AEI MS-902; optical rotation measurements, Perkin-Elmer 141 polarimeter. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses are within 0.4% of theoretical values when indicated by symbols of the elements. Silica gel 60 (E. Merck, Darmstadt) and aluminum oxide 90 (of activity grade II, E. Merck, Darmstadt) were used for column chromatography. Solutions were dried over Na_2SO_4 and concentrated using a Buchi rotary evaporator under water aspirator pressure (20 mm).

***p*-(2,3-Epoxypropoxy)benzaldehyde (22).** To a solution of epichlorohydrin (330 g, 3.56 mol) heated at 50 °C was added dropwise over 1 h a solution of **21** (150 g, 1.23 mol) in 2.5 N NaOH (750 mL). After 3 h at 50 °C, the aqueous layer was extracted with $CHCl_3$ (2 × 200 mL), dried, filtered, and concentrated to dryness. The residue was distilled at 155 °C at 0.5 mm to give **22** (140 g, 64%).

Pentafluorophenylglyoxal. A mixture of SeO_2 (10.8 g), dioxane (55 mL), and pentafluoroacetophenone (17.7 g, 0.084 mol) was heated at reflux with stirring. After 4 h, the solution was cooled, filtered through super cel, and concentrated to dryness. The residue was distilled at 60–64 °C at 25 mm to yield 9.5 g (51%) of pentafluorophenylglyoxal: MS *m/e* 195 (M − 29), 167, (M − 57), 117 (M − 107).

3,4-Dichlorophenylglyoxal Monohydrate. A mixture of SeO_2 (8.8 g, 0.079 mol), absolute EtOH (30 mL), and 3,4-dichloroacetophenone (14.9 g, 0.079 mol) was heated at reflux. After

Table II



no.	R_1	R_2	R_3	optical config	crystn solv	mp, °C	yield,[b] %	formula
28	Cl	H	H	*R,S*	H_3CCN	167-171	32	$C_{17}H_{21}ClF_3N_3O_2$
29	Cl	H	Cl	*R,S*	H_3CCN	125-129	4	$C_{17}H_{20}Cl_2F_3N_3O_2$[a]
30	Cl	Cl	H	*R,S*	H_3CCN	181-182	30	$C_{17}H_{20}Cl_2F_3N_3O_2$
31	H	Cl	H	*R,S*	H_3CCN	174-177	16	$C_{17}H_{21}ClF_3N_3O_2$
32	H_3C	H	H	*R,S*	H_3CCN	162-164	28	$C_{18}H_{24}F_3N_3O_2$
33	H_3C	H	H	*S*	H_3CCN	141-143	16	$C_{18}H_{24}F_3N_3O_2$
34	H_3C	H	H_3C	*R,S*	H_3CCN	159-162	9	$C_{19}H_{26}F_3N_3O_2 \cdot 0.5H_2O$
35	H_3C	H_3C	H	*R,S*	H_3CCN	187-190	10	$C_{19}H_{26}F_3N_3O_2$
36	H	H_3C	H	*R,S*	H_3CCN	183-185	15	$C_{18}H_{24}F_3N_3O_2$
37	$(CH_2)_4$		H	*R,S*	H_3CCN	203-205	23	$C_{21}H_{28}F_3N_3O_2$
38	CH=CHCH=CH		H	*R,S*	H_3CCN	207-210	17	$C_{21}H_{24}F_3N_3O_2$

[a] Anal. Calcd: C, 46.00; H, 4.72; N, 9.85. Found: C, 46.45; H, 4.59; N, 9.76. [b] Calculated yield is based on the last synthetic step.

Table III. Comparative Cardiovascular Effects of Compounds on Arterial Pressure of Spontaneously Hypertensive Rats and on Iliac Blood Flow and β-Adrenergic Blockade in Anesthetized Dogs

				activity in anesthetized dogs								
										blockade of IP-induced HT, TC, and BC[a]		
		antihypertensive act. in SH rats		increase in iliac BF, mL/min ± SE						hypotension, tachycardia and bronchoconstriction estimat ED_{50}, μg/kg, iv		
							timolol dose, μg/kg iv					
compd	dose, mg/kg po	no. of SHR	max fall in MAP,[a] mmHg ± SE	no. of dogs	dose, μg ia	before timolol	500	1600	2000	no. of dogs	MAP	HR	pulmonary press.
1	0.312	4	21 ± 7	5	8	52 ± 5			10 ± 7				
	1.25	5	36 ± 8	5	16	58 ± 8			17 ± 7				
	5	5	49 ± 8	5	32	63 ± 6			15 ± 4				
				3	1600	79 ± 8			15 ± 4	4	42	7.6	71
3	20	6	18 ± 3	4	1600	36 ± 18	31 ± 20			4	>1000	98	>1000
4	1.25	4	19 ± 1										
	20	2	41	1	1600	30			0	4	>1000	67	
5	1.25	4	20 ± 6										
	5	4	30 ± 7	3	1600	46			42	2	83	35	95
	20	2	54										
6	0.312	4	12 ± 4										
	1.25	4	21 ± 3	9	1600	25 ± 6			20 ± 5	4	>1000	40	
	5	4	29 ± 2										
7	1.25	4	10 ± 2										
	5	4	28 ± 2	8	1600	26 ± 5			16 ± 2	3	525	27	480
	20	4	39 ± 3										
8	1.25	2	32							2	137	56.2	82.7
	5	2	35										
	20	2	32										
9	20	2	13	4	1600	42 ± 22			32 ± 13	2	139	19	

10	1.25	2	36										
	5	1	35	4	1600	56 ± 13			15 ± 9	2	117	123	97
	20	2	49										
11	1.25	2	21										
	5	2	19	2	1600	56			48	2	300	82	
	20	2	40										
12	20	2	35	3	1600	80 ± 15			40 ± 13	1	300	15	
13	0.312	2	12										
	1.25	1	36										
	5	2	35	3	1600	28 ± 7			10 ± 5	2	635	16	
	20	1	58										
14	1.25	2	6										
	5	2	27										
	20	2	40										
15	5	2	28	6	1600	64 ± 10			40 ± 10	3	>1000	54	
	20	1	13										
16	5	2	6	3	1600	101 ± 34	75		62	2	>1000	106	
	20	2	27										
17	1.25	3	24 ± 6										
	5	4	19 ± 5	4	1600	59 ± 3			32 ± 4	2	1000	30	277
	20	4	41 ± 5										
18	0.312	5	9 ± 3										
	1.25	5	20 ± 5	6	1600	23 ± 5			15 ± 2	3	234	14	433
	5	6	33 ± 5										
19	5	2	17	3	1600	80 ± 37			29 ± 3	1	>1000	40	
	20	2	36										
20	20	2	14							2	>1000	262	>1000
28	1.25	3	28 ± 5	3	250	−2 ± 9				2	552	27	54
	5	3	36 ± 3	3	1600	2 ± 6							
29	1.25	2	16										
	5	1	30										
30	5	4	16 ± 6										
	20	2	49										
31	5	2	5	4	250	5 ± 19				2	17	16	15
	20	2	6	3	1600	17 ± 4							
32	1.25	4	32 ± 4	4	250	11 ± 4				2	361	22.7	29.8
	5	4	43 ± 3	4	1600	27 ± 10							
	20	2	44										
33	1.25	8	36 ± 7	6	1600	36 ± 6		39 ± 9		2	92.7	15.7	36.4
	5	2	51										
34	1.25	2	31	1	1600	5		10		2	>1000	91	163
	5	3	20 ± 6										
	20	2	30										
35	1.25	4	27 ± 2	3	1600	23 ± 8		19 ± 8		2	582	71	55
	5	4	24 ± 3										
	20	2	30										
36	1.25	3	23 ± 4	4	250	6 ± 4				2	22	11	
	5	4	36 ± 9	4	1600	52 ± 36		20					
37	20	2	22	3	1600	−15 ± 13		−10 ± 7		2	167	228	100
38	5	4	21 ± 1	3	1600	35 ± 5		40 ± 15		2	>1000	186	
	20	4	40 ± 11										
hydralazine	0.5	4	15 ± 5	3	400	78 ± 12							
	1	6	30 ± 5	3	1600	66 ± 14							
	2	4	40 ± 3	3	3200	53 ± 9							
practolol										8	1000	115 (92–141)	1084 (629–2664)

[a] Abbreviations used are: MAP, mean arterial pressure; IP, isoproternol; HT, hypotension; TC, tachycardia; BC, bronchoconstriction; BF, blood flow.

18 h, the solution was cooled, filtered through super cel, and concentrated to dryness. The residue was crystallized from hot dilute acid, cooled, and filtered to yield 12.7 g (73%) of 3,4-dichlorophenylglyoxal monohydrate: MS *m/e* 173 (M − 29), 145 (M − 57); ^{1}H NMR (Me_2SO-d_6) δ 4.6 (2 H, br s, exch), 5.63 (1 H, br s), 8.5 (3 H, m).

3-Pyridineglyoxylaldehyde Dimethylacetal. As described for the synthesis of 2-pyridineglyoxylaldehyde dimethylacetal by Schank,[12] *n*-BuLi (1.93 M in hexane, 129 mL, 0.25 mol), Et_2O (450 mL), 3-bromopyridine (33.0 g, 0.2 mol), and 1-piperidineglyoxylaldehyde dimethylacetal (33.6 g, 0.179 mol) were reacted to yield 13.8 g (43%) of 3-pyridineglyoxylaldehyde dimethylacetal: bp 95–100 °C (0.4 mm); ^{1}H NMR ($CDCl_3$) δ 3.5 (6 H, s), 5.1 (1 H, s), 7.4 (1 H, dd), 8.4 (1 H, tt), 8.75 (1 H, dd), 9.28 (1 H, d).

(3-Pyridyl)glyoxylaldehyde. To H_2SO_4 (15 g, 0.15 mol) at 0–4 °C was added dropwise 3-pyridineglyoxylaldehyde dimethylacetal (5.4 g, 0.03 mol). After stirring for 3 days at 25 °C, ice–H_2O (100 g) was added and the solution was carefully neutralized with $NaHCO_3$ (26 g, 0.13 mol). This solution containing the glyoxal was used without further purification.

General Procedure for the Preparation of 4-Monosubstituted 2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]-phenyl]imidazoles. Method A. The preparation of **3** is presented as an example of the synthetic method. The following substituted glyoxals were synthesized by literature procedures, all others were obtained from commercial sources: *p*-methoxyphenyl,[8] 4-chlorophenyl,[9] 2-thienyl,[10] 2-furyl,[10] 4-fluorophenyl,[11] and 2-pyridyl.[12]

A solution of **2** (10 g, 0.04 mol), 40% glyoxal (31 g, 0.22 mol), $NaOAc{\cdot}3H_2O$ (26 g, 0.19 mol), concentrated NH_4OH (100 mL), and MeOH (250 mL) was allowed to stir at 25 °C. After the solution was left standing overnight, the MeOH was removed under reduced pressure. The aqueous layer was treated with saturated Na_2CO_3 (100 mL) and extracted with $CHCl_3$ (3 × 200 mL). The organic layers were dried, filtered, and concentrated. The residue was chromatographed on silica gel and eluted with 30% MeOH–$CHCl_3$. The material was crystallized from H_3CCN to give **3** (3.7 g).

Method B. 4-Methyl-2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]imidazole (16). A solution of α-acetoxyacetone (1.5 g, 0.013 mol), concentrated NH_4OH (25 mL), $Cu(OAc)_2$ (5.0 g, 0.025 mol), **2** (3.2 g, 0.013 mol), and MeOH (25 mL) was heated at reflux. After 15 h, the solution was cooled to 25 °C and the MeOH was removed under reduced pressure. Water (200 mL) was added and H_2S was bubbled into the solution for 1 h. After filtration through super cel, the aqueous solution was treated with saturated Na_2CO_3 (100 mL) and extracted with $CHCl_3$ (3 × 100 mL). The organic layer was dried, filtered, and concentrated to dryness. The residue was chromatographed on alumina and eluted with 5% MeOH–$CHCl_3$. The material was crystallized from MeOH–H_3CCN to give **16** (0.79 g).

Method C. The preparation of (*S*)-2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-4-(2-thienyl)imidazole (**18**) is presented as an example. Compound **17** was obtained by essentially the same procedure.

2-(*p*-Methoxyphenyl)-4-(2-thienyl)imidazole (25b). A solution of 10% NaOH (400 mL) was added to **23**·HCl (67.5 g, 0.36 mol) and the suspension extracted with 10% MeOH–$CHCl_3$ (5 × 400 mL). The organic layers were dried, filtered, and concentrated to dryness. The solid residue of **23** was dissolved in $CHCl_3$ (750 mL) and added dropwise over 1.5 h at 25 °C to a solution of **24b** (26.6 g, 0.12 mol) in $CHCl_3$ (150 mL). After stirring overnight at 25 °C, the mixture was filtered to recover **23**·HBr (37 g). The filtrate was concentrated to dryness and the residue chromatographed on alumina. Elution with C_6H_{14}–$CHCl_3$ (1:1) gave **25b** (26.8 g, 80%): mp 139–141 °C; ^{1}H NMR ($CDCl_3$) δ 3.7 (3 H, s), 6.7–7.8 (8 H, m), 10.5 (1 H, br s); MS (M^+) 256.

2-(*p*-Hydroxyphenyl)-4-(2-thienyl)imidazole (26b). A solution of **25b** (20 g, 0.078 mol), AcOH (100 mL), and 48% HBr (400 mL) was heated at reflux with stirring. After 5 h, the mixture was concentrated to dryness. The residue was treated carefully with saturated $NaHCO_3$ (100 mL) and stirred overnight at 25 °C. The solid was filtered, washed with Et_2O, and dried to give **26b** (14.9 g, 79%): mp 286–288 °C; ^{1}H NMR (Me_2SO-d_6) δ 6.7–7.9 (8 H, m), 9.9 (1 H, br s, exch), 10.8 (1 H, br s, exch); MS (M^+) 242.

(*S*)-4-(2-Thienyl)-2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]imidazole (18). A solution of **40**[1] (0.15 mol) in DMF (150 mL) was added under N_2 with stirring to a solution of the sodium salt of **26b**, prepared from **26b** (36.3 g, 0.15 mol) and 50% NaH (7.2 g, 0.15 mol), in DMF (300 mL). The mixture was then heated at reflux for 15 h. After cooling to 25 °C, the solution was concentrated to dryness. The residue was treated with saturated Na_2CO_3 (400 mL) and extracted with EtOAc (4 × 500 mL). The organic layer was dried, filtered, and concentrated to dryness. The residue was dissolved in 1.2 N HCl (1.5 L) and heated on a steam bath for 1.5 h. After cooling to 0–10 °C, the solution was extracted with Et_2O (2 × 500 mL). The aqueous layer was neutralized with 20% NaOH and extracted with $CHCl_3$ (4 × 500 mL). The organic layer was dried, filtered, and concentrated to dryness. The residue was chromatographed on silica gel and eluted with 20% MeOH–$CHCl_3$. The material was isolated as the maleate salt and recrystallized from EtOH to give **18** (28 g).

Method D. 2-[4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl]-4-imidazolecarboxylic Acid (27). A suspension of **1** (15 g, 0.042 mol) in 1 N NaOH (250 mL) was heated on a steam bath for 1 h and then stirred for 15 min. The solution was decanted and acidified with concentrated HCl. The solution was concentrated on a steam bath under a stream of N_2 and dried overnight at 60 °C and 250 mm to yield **27** (30 g) as a glass, which was used in the next step without purification.

Methyl 2-[4-[3-*tert*-Butylamino)-2-hydroxypropoxy]-phenyl]-4-imidazolecarboxylate (19). A solution of **27** (30 g) in MeOH (750 mL) was heated at reflux. Heating was discontinued as HCl gas was bubbled through the solution for two 1-h periods separated by 1 h at reflux. After stirring at 25 °C for 16 h, the reaction mixture was filtered. The filtrate was concentrated to a solid, which was dissolved in H_2O (150 mL) and made basic (pH 8) with saturated Na_2CO_3 solution. The solution was extracted with EtOAc, and the extracts were dried, filtered, and concentrated to a solid which recrystallized from H_3CCN to yield **19** (6.5 g).

2-[4-[3-(*tert*-Butylamino)-2-hydroxypropoxy]phenyl]-4-imidazolecarboxamide (20). A solution of **19** (10 g, 0.029 mol) in MeOH (100 mL) was reacted with gaseous NH_3 (44 g) for 24 h at 100 °C in a sealed tube. The reaction mixture was concentrated to dryness and the residue chromatographed on silica gel using 9:1 $CHCl_3$ (saturated with NH_3)–MeOH as eluant. Recrystallization from H_3CCN yielded **20** (4.7 g, mp 190–193 °C). A second crystalline form of **20** was observed (mp 149–153 °C). IR spectra of the two forms were not identical in the solid state but were indistinguishable in pyridine solution. The higher melting form was convertible to the lower melting one on recrystallization from acetonitrile.

2,6-Dichloro-4-hydroxybenzaldehyde. $CHCl_3$ (45.3 g, 0.38 mol) was added dropwise to a suspension of $Ca(OH)_2$ (61 g), Na_2CO_3 (69.7 g), and 3,5-dichlorophenol (31 g, 0.19 mol) in H_2O (400 mL) at 70 °C. After the addition was complete, the mixture was heated at reflux for 3 h, acidified with concentrated HCl, and steam distilled. The residual suspension was filtered and the resulting solid dissolved in boiling $C_6H_5CH_3$. After filtration, the $C_6H_5CH_3$ solution was concentrated to a solid, which was sublimed at 160 °C at 0.3 mm and recrystallized from $C_6H_5CH_3$ to yield 1.5 g (3.3%) of 2,6-dichloro-4-hydroxybenzaldehyde, mp 223.5–224.5 °C. Anal. ($C_7H_4Cl_2O_2$) C, H.

General Procedure for the Preparation of Aryl-Substituted 2-[4-[3-(*tert*-butylamino)-2-hydroxypropoxy]-phenyl]imidazoles. The preparation of **28** is presented as an example. The required *p*-hydroxybenzaldehyde derivatives, except for 2,6-dichloro-4-hydroxybenzaldehyde, have been reported in the literature: 4-hydroxynaphaldehyde,[13] 2-methyl-,[14] 3-methyl-,[15] 2,3-dimethyl-,[16] 2,6-dimethyl-,[17] 2-chloro-,[18] 3-chloro-,[19] and 2,3-dichloro-4-hydroxybenzaldehyde,[20] and 8-formyl-5-hydroxy-1,2,3,4-tetrahydronaphthalene.[21] All compounds synthesized by the Gattermann reaction were prepared according to the general method of Adams and Levine.[13]

2-Chloro-4-(2,3-epoxypropoxy)benzaldehyde. To a solution of 2-chloro-4-hydroxybenzaldehyde (12.5 g, 0.08 mol) in 1.5 N NaOH (70 mL) at 50 °C was added dropwise epichlorohydrin (22.0 g, 0.24 mol). After the addition was complete, the reaction mixture was heated at 50 °C for 3 h, cooled, and extracted with $CHCl_3$.

The $CHCl_3$ solution was dried, filtered, and concentrated to an oil, which was distilled at 145–153 °C at 0.1 mm to yield 2-chloro-4-(2,3-epoxypropoxy)benzaldehyde (9.2 g, 53.7%).

2-Chloro-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzaldehyde. A mixture of 2-chloro-4-(2,3-epoxypropoxy)-benzaldehyde (9.0 g, 0.04 mol) and excess *tert*-butylamine (25 mL) was refluxed for 17 h. The excess *tert*-butylamine was removed and the residue dissolved in 6 N hydrochloric acid (125 mL). After refluxing for 5 h, the solution was made basic with saturated Na_2CO_3 solution while nitrogen was bubbled through the solution; heating on a steam bath and N_2 ebullition were continued for 0.5 h. The mixture was then cooled and extracted with $CHCl_3$. The $CHCl_3$ extract was dried, filtered, and concentrated. The resulting oil was crystallized from C_6H_6–C_6H_{14} (9 g, 83%), mp 103–105 °C.

2-[2-Chloro-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]-phenyl]-4-(trifluoromethyl)imidazole (28). A solution of $NaOAc·3H_2O$ (6.0 g, 0.049 mol) and trifluorodibromoacetone (6.0 g, 0.022 mol) in water (40 mol) was heated on a steam bath for 0.5 h. The cooled solution was added to 2-chloro-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzaldehyde (5.5 g, 0.02 mol) in MeOH (300 mL) and concentrated NH_4OH (30 mL). After standing at 25 °C for 5 h, the MeOH was removed under reduced pressure. The residue was dissolved in $CHCl_3$ and made basic with saturated Na_2CO_3 solution, separated, dried, filtered and concentrated to 0.25 volume. After cooling, the solid was filtered and recrystallized from H_3CCN to yield **28** (2.4 g).

(*S*)-2-Methyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzaldehyde. A solution of **40**[1] (0.1 mol) in DMF (100 mL) was added to a refluxing solution of the sodium salt of 2-methyl-4-hydroxybenzaldehyde. The sodium salt was prepared in MeOH (100 mL) from Na (2.3 g, 0.1 mol) and 2-methyl-4-hydroxybenzaldehyde (13.6 g, 0.1 mol). The DMF solution was heated at reflux for 10 h, cooled, poured into H_2O, and extracted with $CHCl_3$. The extract was washed with 5% NaOH, H_2O, and brine. After drying, the $CHCl_3$ was removed, yielding an oil which was hydrolyzed on refluxing in 1 N HCl for 1 h. After cooling, the acidic solution was extracted with Et_2O and then made basic with 20% NaOH. The basic solution was extracted with $CHCl_3$. The extract was dried, filtered, and concentrated to an oil. The oil was crystallized from C_6H_{14}, yielding 6.3 g (37%) of (*S*)-2-methyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzaldehyde, mp 70–72 °C; $[\alpha]^{25}_D$ (MeOH) 6.07.

(*S*)-2-[2-Methyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]phenyl]-4-(trifluoromethyl)imidazole (33). A solution of $NaOAc·3H_2O$ (23.6 g, 0.18 mol) and dibromotrifluoroacetone (23.6 g, 0.09 mol) in H_2O (80 mL) was heated on a steam bath for 40 min and, after cooling, added to a solution of (*S*)-2-methyl-4-[3-(*tert*-butylamino)-2-hydroxypropoxy]benzaldehyde (10.6 g, 0.04 mol) in MeOH (400 mL) and concentrated NH_4OH (60 mL). The resulting solution was allowed to stand at 25 °C overnight. The MeOH was removed under reduced pressure. The residue was dissolved in $CHCl_3$, washed with saturated aqueous Na_2CO_3, dried, filtered, and concentrated to dryness. The resulting residue was chromatographed using silica gel and eluted with 99:1 $CHCl_3$ (saturated with NH_3)–MeOH. After recrystallization from H_3CCN, 4.3 g of **33** was obtained.

Pharmacology. Antihypertensive activity was estimated in the SH rats as described by Watson and Ludden.[7] Compounds were administered orally and/or intraperitoneally.

The peripheral vasodilating activity was estimated in adult mongrel dogs of either sex (8–13 kg body weight). The dogs were anesthetized with vinbarbital, 50 mg/kg iv. The trachea was cannulated and the vagi were cut. Systemic arterial pressure was recorded from the right carotid artery. The right iliac artery was exposed through a midline incision and a Micron blood flow transducer (3.0 mm) was secured around the artery. The left femoral artery was cannulated with PE 90 tubing, and the tip of the catheter was advanced until it was positioned at the iliac bifurcation. Drug injections were made intraarterially through the catheter, and the changes in blood flow were recorded. In each experiment, isoproterenol, 0.4 μg ia, was injected before and after timolol to assess the extent of β-adrenergic blockade. In all experiments, timolol whether administered at 500 or 2000 μg/kg iv completely blocked the vasodilator response to isoproterenol, 0.4 μg ia.

To determine β-adrenergic blocking activity, two protocols were used. In protocol I, mongrel dogs of either sex weighing between 8 and 13 kg were anesthetized with vinbarbital, 50 mg/kg iv; the vagi were cut and blood pressure was recorded through a femoral artery catheter. Drug injections were made through the femoral venous catheter. The trachea was cannulated but artificial respiration was used only if required.

Heart rate was recorded electronically from the blood pressure pulse. Isoproterenol was injected at 0.5 μg/kg iv, and the resultant hypotension and tachycardia were computed. Test compounds were administered cumulatively until nearly complete inhibition of isoproterenol effects was achieved.

In protocol II, the cardioselectivity of compounds was determined. Dogs of either sex in the weight range 5–10 kg were anesthetized with vinbarbital, 60 mg/kg iv, and then supplemented with vinbarbital 20 mg/kg im and succinylcholine chloride, 2 mg/kg im. All dogs were bilaterally vagotomized and artificially ventilated at a rate of 22 breaths per minute, with volume adjusted to provide an intrapulmonary pressure of 16 cms of water. Arterial pressure was monitored from a cannulated femoral artery, heart rate from bilateral needle chest electrodes through a Beckman cardiotachometer, and intrapulmonary pressure from a pressure transducer inserted into the respiratory system. All parameters were recorded on a Beckman dynograph, and injections were made into a cannulated femoral vein.

In nondrug-treated (control) preparations, bronchoconstriction was induced with histamine (diphosphate, USP), 20 μg/kg iv administered at 15-min intervals, and recorded as millimeters of pen excursion over baseline. When these responses had stabilized, 0.4 μg/kg iv of isoproterenol was administered 30 s prior to each histamine challenge. The fall in blood pressure and increase in heart rate from base levels were recorded in mmHg and beats per minute, respectively, and inhibition of histamine-induced bronchoconstriction was calculated as a percentage of control responses.

For evaluation of the test substances, dogs were prepared as described above. When histamine and isoproterenol responses had stabilized, the test compound was injected iv 3 min prior to each standard dose of isoproterenol. Cumulative doses were administered at 15-min intervals until graded inhibition of the isoproterenol responses was achieved for all parameters, where possible, within a reasonable drug dose range. For each parameter, percent inhibition (isoproterenol controls = 100) was plotted against drug dose, and the ED_{50} for each β-adrenergic blocker was computed.

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Synthesis of Some 4-Substituted 8-Amino-6-methoxyquinolines as Potential Antimalarials

F. Ivy Carroll,* Bertold Berrang, C. P. Linn, and Charles E. Twine, Jr.

Chemistry and Life Sciences Division, Research Triangle Institute, Research Triangle Park, North Carolina 27709.
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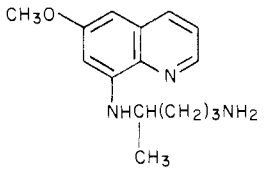
The 4-vinyl, 4-ethyl, and three 4-[β-(arylthio)ethyl] derivatives of primaquine and other 8-aminoquinoline antimalarial agents were prepared for antimalarial evaluation. 8-[(4′-Amino-1′-methylbutyl)amino]-4-ethyl-6-methoxyquinoline (4-ethylprimaquine), which showed activity approximately equal to that of primaquine against *Plasmodia cynomolgi* in Rhesus monkey, was the most active of the compounds tested. 4-Ethylprimaquine was also less toxic than primaquine, as measured in the Rane mouse screen.

In an earlier report,[1] we pointed out the value of 8-aminoquinolines, such as primaquine (**1**), for the radically



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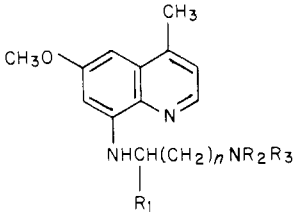
curative treatment (complete eradication of the parasites) of *Plasmodium vivax* malaria and described the synthesis and antimalarial activity of several reduced 8-aminoquinoline analogues.

The major drawback to the use of primaquine (**1**) is its relative toxicity and rapid excretion. A survey of the earlier literature[2-4] reveals that the type of toxicity induced by the 8-aminoquinolines depends largely upon the structure of the 8-amino side chain. However, nuclear substituents appear to have a greater influence upon relative toxicity. For example, several 8-[[(dialkylamino)alkyl]amino]-6-methoxy-4-methylquinolines (**2**) were reported to possess



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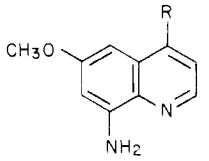
high antimalarial activity combined with reduced toxicity relative to the unsubstituted analogues.[5,6] Based on the above, we initiated a program which involved the synthesis of 4-vinyl, 4-ethyl and 4-[β-(arylthio)ethyl]-8-aminoquinoline analogues.

Chemistry. In order to achieve the synthesis of the desired target compounds, it was first necessary to devise synthetic schemes for the preparation of 8-amino-6-methoxy-4-vinylquinoline (**3a**), 8-amino-4-[(arylthio)-ethyl]-6-methoxyquinoline (**3b–d**), and 8-amino-4-ethyl-6-methoxyquinoline (**3e**). Scheme I outlines the reaction scheme used to prepare the compounds **3a–d**. Subjection of 6-methoxy-4-methyl-8-nitroquinoline (**4**)[5] to the Mannich reaction gave 4-[β-(dimethylamino)ethyl]-6-



3a, R = $CH{=}CH_2$
b, R = $CH_2CH_2SC_6H_4$-*p*-F
c, R = $CH_2CH_2SC_6H_4$-*p*-OCH_3
d, R = $CH_2CH_2SC_6H_4$-*p*-Cl
e, R = CH_2CH_3

methoxy-8-nitroquinoline hydrochloride (**5**). Neutralization of **5** followed by treatment with methyl iodide gave 6-methoxy-8-nitro-4-[β-(trimethylamino)ethyl]quinoline iodide (**6**). Treatment of **6** with aqueous sodium hydroxide gave 6-methoxy-8-nitro-4-vinylquinoline (**7**). Condensation of **6** with *p*-fluorothiophenol and *p*-methoxythiophenol in DMF containing potassium carbonate gave the 4-[(arylthio)ethyl]-6-methoxy-8-nitroquinolines **8**, X = F and OCH_3, respectively. Reduction of **7** and **8** (X = OCH_3) with stannous chloride and hydrochloric acid yielded **3a** and **3c**, respectively. Catalytic reduction of **8** (X = F) using Raney nickel catalyst gives **3b**. The addition of *p*-chlorothiophenol to **3a** gives the addition product **3d**.

Two synthetic procedures for the preparation of 8-amino-4-ethyl-6-methoxyquinoline (**3e**) were developed and are shown in Scheme II. In one case (method A), 4-methoxy-2-nitroaniline (**9**) was converted to 4-ethyl-6-methoxy-8-nitroquinoline (**10**) by a modified Skraup reaction. Reduction of **10** with stannous chloride and hydrochloric acid or catalytically gave the desired amine **3e**. The amine **3e** was also prepared by catalytic reduction of 6-methoxy-8-nitro-4-vinylquinoline (**7**; method B, Scheme II). Scheme III outlines the procedures used to attach the side chain to the 8-aminoquinolines **3a–e**. The results obtained are listed in Table I. The alkylation of **3** with 4-bromo- or 4-iodo-1-phthalimidopentane in the presence of triethylamine,[7,8] followed by removal of the phthaloyl-protecting group with hydrazine, gave the 8-[(4′-amino-1′-methylbutyl)amino]quinolines **11**. If 4-bromo-1-phthalimidobutane or 6-chloro-1-phthalimidohexane was used in place of the 4-bromo-1-phthalimidopentane for the alkylation of **3a**, the 8-[(4′-aminobutyl)amino]quinoline (**12**) and 8-[(6-aminohexyl)amino]quinoline (**13**) were obtained, respectively, after treatment with hydrazine. The condensation of **11e** with acetone, followed by re-

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