(ca. 200 mL) to the residual anisole solution gave a precipitate, which following 3 h at 4 °C was collected, washed with ether, and dried over P_2O_5; 581 mg. This material was dissolved in warm DMF (ca. 10 mL), reprecipitated with water, collected, and dried in vacuo over P_2O_5 to give the desired protected acylheptapeptide (XIIb, Table V). The remaining desGly(NH_2) protected precursors were obtained in essentially the same manner by acidolytic cleavage from the appropriate peptidyl resin. Their structures are as follows: Ib, HBr-Cys(Bzl)-Tyr-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos); IIb, [β-(benzylthio)propionyl]-Tyr-Phe-Gln-Asn-Cys(Bzl)-Pro-D-Arg(Tos); IIIb, [β-(benzylthio)propionyl]-Tyr-Phe-Val-Asn-Cys(Bzl)-Pro-D-Arg(Tos); IVb, [β-(benzylthio)-β,β-pentamethylenepropionyl]-Tyr-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg-(Tos); Vb, [β-(benzylthio)-β,β-pentamethylenepropionyl]-Tyr-Phe-Val-Asn-Cys(Bzl)-Pro-D-Arg(Tos); VIb, [β-(benzylthio)-β,β-dimethylpropionyl]-Tyr-Phe-Val-Asn-Cys(Bzl)-Pro-D-Arg(Tos); VIIb, [β-(benzylthio)-β,β-pentamethylenepropionyl]-Tyr(Me)-Phe-Gln-Asn-Cys(Bzl)-Pro-Arg(Tos); VIIIb, [β-(benzylthio)-β,β-pentamethylenepropionyl]-D-Phe-Ile-Asn-Cys(Bzl)-Pro-Arg(tos); IXb, [β-(benzylthio)-β,β-pentamethylenepropionyl]-D-Phe-Phe-Val-Asn-Cys(Bzl)-Pro-Arg(Tos); Xb, [β-(benzylthio)-β,β-pentamethylenepropionyl]-D-Tyr(Et)-Phe-Val-Asn-Cys(Bzl)-Pro-Arg-(Tos); XIb, [β-(benzylthio)-β,β-pentamethylenepropionyl]-Tyr-(Et)-Phe-Val-Asn-Cys(Bzl)-Pro-Arg(Tos). The physiochemical properties of all 12 desGlyNH_2 protected peptide (Ib–XIIb) are given in Table V.

Desglycinamide[1-(β-mercapto-β,β-pentamethylenepropionic acid),2-*O*-methyltyrosine]arginine-vasopressin [desGly(NH_2)d(CH_2)$_5$Tyr(Me)AVP] (7b, Table VII). The protected acylheptapeptide amide (VIIb, Tables V) 120 mg) was dissolved in dry ammonia (500 mL) redistilled from sodium. The solution was treated at the boiling point and with stirring with sodium from a stick of sodium contained in a small-bore glass tube until a light-blue color persisted in the solution for ca. 30 s. Dry acetic acid (0.4 mL) was added to discharge the color. The ammonia was evaporated, and nitrogen was passed through the flask. After 5 min, the residue was dissolved in degassed aqueous acetic acid (50%, 50 mL) and quickly poured into ice-cold water (ca. 1000 mL). The pH was adjusted to ca. 7.0 with concentrated ammonium hydroxide. Following the neutralization, an excess of a solution of potassium ferricyanide (0.01 M, 15 mL) was added gradually with stirring. The yellow solution was stirred for an additional 20 min and for 10 min with anion-exchange resin (Bio-Rad AG-3, Cl^- form, 30 g damp weight). The suspension was slowly filtered through a bed of resin (30 g damp weight). The bed was washed with water (200 mL), and the combined filtrate and washings were lyophilized. The resulting powder (2.51 g) was desalted on a Sephadex G-15 column (110 × 2.7 cm) eluting with aqueous acetic acid (50%) with a flow rate of 5 mL/h. The eluate was fractioned and monitored for absorbance at 254 nm. The fractions comprising the major peak were checked by TLC (A), pooled, and lyophilized, and the residue (43 mg) was further subjected to gel filtration on a Sephadex G-15 column (100 × 1.5 cm) eluting with aqueous acetic acid (0.2 M) with a flow rate of 4 mL/h. The peptide was eluted in a single peak (absorbance 254 nm). Lyophilization of the pertinent fractions gave the vasopressin analogue (**7b**, Table VII). Its physiochemical properties are given in Table VII. With minor modifications this procedure was utilized to give all the free peptides in Tables VI and VII.

Acknowledgment. This work was supported by part by research grants from the National Institute of General Medical Sciences (No. GM-25280) and the National Institute of Diabetes, Digestive and Kidney Diseases (No. DK-01940). We thank Dr. Roger Roeske, Indiana University School of Medicine, Indianapolis, IN, for the amino acid analyses and Ann Chlebowski for expert assistance in the preparation of the manuscript.

Registry No. **1a**, 47914-57-8; **1b**, 37552-33-3; **2a**, 110551-37-6; **2b**, 84236-22-6; **3a**, 110551-38-7; **3b**, 102136-54-9; **4a**, 90332-78-8; **4b**, 90332-79-9; **5a**, 110551-39-8; **5b**, 110612-13-0; **6a**, 110551-40-1; **6b**, 110551-43-4; **7a**, 110551-41-2; **7b**, 110551-44-5; **8a**, 90332-83-5; **8b**, 105107-73-1; **9a**, 90352-21-9; **9b**, 90332-80-2; **10a**, 90332-82-4; **10b**, 105107-72-0; **11a**, 90332-81-3; **11b**, 110567-67-4; **12a**, 110551-42-3; **12b**, 110551-45-6; Ia, 110551-14-9; Ib, 110551-26-3; IIa, 110551-15-0; IIb, 110567-66-3; IIIa, 110551-16-1; IIIb, 110551-27-4; IVa, 110551-17-2; IVb, 110551-28-5; Va, 110551-18-3; Vb, 110551-29-6; VIa, 110551-19-4; VIb, 110551-30-9; VIIa, 110551-20-7; VIIb, 110551-31-0; VIIIa, 110551-21-8; VIIIb, 110551-32-1; IXa, 110551-22-9; IXb, 110551-33-2; Xa, 110551-23-0; Xb, 110551-34-3; Xia, 110551-24-1; XIb, 110551-35-4; XIIa, 110551-25-2; XIIb, 110551-36-5; BOC-Arg(Tos), 13836-37-8; BOC-D-Arg(Tos), 61315-61-5; BOC-Pro, 15761-39-4; BOC-Cys-(Bzl), 5068-28-0; BOC-Asn NPE, 4587-33-1; BOC-Gln NPE, 15387-45-8; BOC-Val, 13734-41-3; BOC-Ile, 13139-16-7; BOC-Phe, 13734-34-4; BOC-Tyr(Bzl), 2130-96-3; BOC-Tyr(Me), 53267-93-9; BOC-D-Tyr(Et), 76757-92-1; BOC-D-Phe, 18942-49-9; BOC-D-Ile, 55721-65-8; Z-Cys(Bzl), 3257-18-9; β-(benzylthio)propionic acid, 2899-66-3; β-(benzylthio)-β,β-dimethylpropionic acid, 7536-39-2; β-(benzylthio)-β,β-pentamethylenepropionic acid, 55154-80-8.

Synthesis and 5-Hydroxytryptamine Antagonist Activity of 2-[[2-(Dimethylamino)ethyl]thio]-3-phenylquinoline and Its Analogues

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Received May 11, 1987

A series of 2-[(2-aminoethyl)thio]quinolines substituted at the 3-position with alkyl, aryl, or heteroaryl groups has been prepared in the search for novel and selective 5-HT_2 antagonists. The affinity of the compounds for 5-HT_1 receptor sites was measured by their ability to displace [^{3}H]-5-HT from rat brain synaptosomes whereas the affinity for 5-HT_2 receptor sites was measured by their ability to displace [^{3}H]spiperone from synaptosomes prepared from rat brain cortex. The 5-HT_2 antagonist properties of the compounds were measured in vivo by their antagonism of 5-hydroxytryptophan-induced head twitches in the mouse and by their antagonism of hyperthermia induced by fenfluramine (*N*-ethyl-α-methyl-*m*-(trifluoromethyl)phenethylamine hydrochloride) in the rat. The structure–activity relationships in this series are discussed and the properties of 2-[[2-(dimethylamino)ethyl]thio]-3-phenylquinoline hydrochloride (**70**) are highlighted.

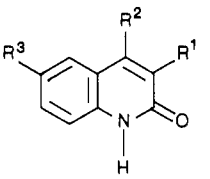
During the past few years there has been a marked increase in research on 5-hydroxytryptamine (5-HT) as summarized in recent reviews.[1,2] Attempts have been made to explain the physiology of 5-HT and the pharmacology of various 5-HT agonists and antagonists by the

(1) Glennon, R. A. *J. Med. Chem.* **1987**, *1*, 1.

(2) Middlemiss, D. N.; Hibert, M.; Fozard, J. R. *Annu. Rep. Med. Chem.* **1986**, *21*, 41.

0022-2623/87/1830-2252$01.50/0

Table I. Substituted 2-(1*H*)-Quinolones



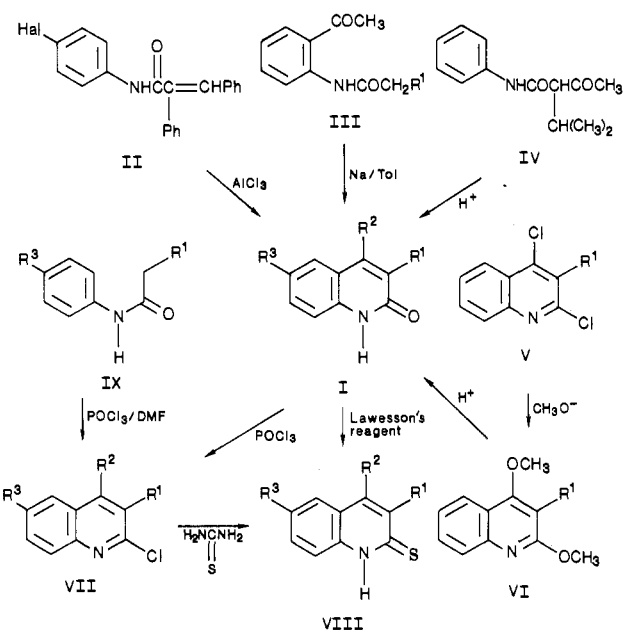
compd	R^1	R^2	R^3	prep[a]	mp, °C	formula[b]
1	C_6H_5	H	Cl	A	207–208[c]	$C_{15}H_{10}ClNO$[d]
2	C_6H_5	H	Br	A	251–252	$C_{15}H_{10}BrNO$[d]
3	C_6H_5	CH_3	H	B	272–274[e]	$C_{16}H_{13}NO$[d]
4	2-MeO-C_6H_4	CH_3	H	B	250–251	$C_{17}H_{15}NO_2$
5	4-F-C_6H_4	CH_3	H	B	289	$C_{16}H_{12}FNO$
6	3-thienyl	CH_3	H	B	238–239	$C_{14}H_{11}NOS$[d]
7	$CH(CH_3)_2$	CH_3	H	C	248–249	$C_{13}H_{15}NO$[d]
8	C_6H_5	OCH_3	H	D	229–232[f]	$C_{16}H_{13}NO_2$[d]
9	4-F-C_6H_4	OCH_3	H	D	240–243	$C_{16}H_{12}FNO_2$[d]
10	2-CH_3-C_6H_4	OCH_3	H	D	215	$C_{17}H_{15}NO_2 \cdot 0.25H_2O$
11	3-thienyl	OCH_3	H	D	205–209	$C_{14}H_{11}NO_2S$[d]

[a] See Experimental Section for details. [b] C, H, N analyses were within 0.4% of theory. [c] Literature[7] mp 207–208 °C. [d] Unanalyzed intermediate gave satisfactory ^1H NMR and mass spectra. [e] Literature[18] mp 273 °C. [f] Literature[19] mp 229–230 °C.

postulation of receptor subtypes.[3,4] Radioligand binding studies by Peroutka and Synder[5] identified two sites subsequently named 5-HT_1 and 5-HT_2. Ketanserin[6] [3-[2-[4-(*p*-fluorobenzoyl)piperidino]ethyl]-2,4(1*H*,3*H*)-quinazolinedione] has been described as a 5-HT_2 antagonist, but it has, in addition, affinity for the α_1-adrenoreceptor and the histaminergic H_1 receptor. We describe now a series of 2-[[2-(alkylamino)ethyl]thio]quinolines substituted at the 3-position with alkyl, aryl, or heteroaryl groups that are 5-HT antagonists with a selectivity for the 5-HT_2 receptor subtype. The preferred compound, 2-[[2-(dimethylamino)ethyl]thio]-3-phenylquinoline (**70**) has been shown to be a potent and selective 5-HT_2 antagonist with a low affinity for the receptors of other neurotransmitter amines as demonstrated by activity in binding assays, isolated tissues, and in vivo models. It has a 10 times greater selectivity for the 5-HT_2 receptor over the adrenergic α_1-receptor compared to ketanserin as shown by action on the rat caudal artery.

Chemistry. The key intermediates in the syntheses of 2-[[2-(alkylamino)ethyl]thio]-3-phenylquinolines are shown in generic form in Scheme I with Roman numerals. Several methods were used, according to the nature of the substituents involved, to prepare the quinolones I. Thus the 6-halo derivatives **1** and **2**, shown in Table I, were prepared by the method of Manimaran and Ramakrishnan[7] (method A) in which phenylcinnamanilides (II) were cyclized with aluminum chloride. 3-Aryl-4-methyl-2(1*H*)-quinolones **3** and **6** were conveniently prepared by the base-catalyzed cyclization of the readily available anilides III (method B). In the case of 3-isopropyl-4-methyl-2(1*H*)-quinolone (**7**), acid cyclization of the anilide IV gave the required intermediate (method C). The 3-substituted 2,4-dichloroquinolines V underwent facile reaction with sodium methoxide to give the 2,4-dimethoxy derivatives VI, which

Scheme I

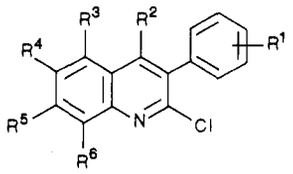


could be selectively demethylated[8] with acid to give the 4-methoxy-2(1*H*)-quinolones (I) (method D). The quinolones prepared by these routes are listed in Table I. They could be converted to 2-chloroquinolines VII (Table II) with phosphorus oxychloride (method E) or into the corresponding thiones (VIII) (Table IV) with Lawesson's reagent (method G).

The most convenient method for the preparation of 2-chloro-3-substituted-quinolines VII optionally substituted in the benzenoid ring with electron-donating substituents is that described by Meth-Cohn et al.[9] Substituted acetanilides (IX) were treated with Vilsmeier's reagent and the 2-chloroquinolines shown in Table III were isolated directly (method F). The 2-chloroquinolines were converted to the desired thioethers either by direct reaction with the appropriate 2-aminoethanethiol (method I) or by intermediate conversion to the thiones (VIII) with thiourea (method H) followed by reaction with the appropriate

(3) Saxena, P. R.; Richardson, B. P.; Mylecharane, E. J.; Middlemiss, D. N.; Humphrey, P. P. A.; Fozard, J. R.; Fenuik, W.; Engel, G.; Bradley, P. B. *Trends Pharmacol. Sci.* **1986**, *7*, 270–272 (center-page diagram).
(4) Bradley, P. B.; Engel, G.; Fenuik, W.; Fozard, J. R.; Humphrey, P. P. A.; Middlemiss, D. N.; Mylecharane, E. J.; Richardson, B. P.; Saxena, B. P. *Neuropharmacology* **1986**, *25*, 563.
(5) Peroutka, S. J.; Snyder, S. H. *Mol. Pharmacol.* **1979**, *16*, 687.
(6) Leysen, J. E.; Awouters, F.; Kennis, L.; Laduron, P. M.; Vandenberk, J.; Janssen, P. A. J. *Life Sci.* **1981**, *28*, 1015.
(7) Manimaran, T.; Ramakrishnan, V. T. *Indian J. Chem., Sect. B* **1979**, *18B*, 324.
(8) Arndt, F.; Loewe, L.; Un, R.; Ayca, E. *Chem. Ber.* **1951**, *84*, 319.
(9) Meth-Cohn, O.; Rhouati, S.; Tarnowski, B.; Robinson, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1537.

Table II. 3-Aryl-2-chloroquinolines



compd	R^1	R^2	R^3	R^4	R^5	R^6	prep[a]	mp, °C	formula[b]
12	H	H	H	Cl	H	H	E	147–149	$C_{15}H_9Cl_2N$
13	H	H	H	Br	H	H	E	146–147	$C_{15}H_9BrClN$
14	H	CH_3	H	H	H	H	E	94–95	$C_{16}H_{12}ClN$
15	2-OCH_3	CH_3	H	H	H	H	E	123	$C_{17}H_{14}ClNO$
16	4-F	CH_3	H	H	H	H	E	126–127	$C_{16}H_{11}FClN$
17	H	H	H	H	H	H	F	54–55[c]	$C_{15}H_{10}ClN$
18	4-F	H	H	H	H	H	F	88–89	$C_{15}H_9ClFN{\cdot}0.25H_2O$
19	4-Cl	H	H	H	H	H	F	90–92	$C_{15}H_9Cl_2N$
20	4-Br	H	H	H	H	H	F	96–98	$C_{15}H_9BrClN$
21	4-OCH_3	H	H	H	H	H	F	87–88	$C_{16}H_{12}ClNO$[d]
22	3-OCH_3	H	H	H	H	H	F	oil	$C_{16}H_{12}ClNO$[e]
23	2-OCH_3	H	H	H	H	H	F	84–85	$C_{16}H_{12}ClNO$
24	4-OC_3H_7	H	H	H	H	H	F	oil	$C_{18}H_{16}ClNO$[e]
25	2,5-$(OCH_3)_2$	H	H	H	H	H	F	102–104	$C_{17}H_{14}ClNO_2$
26	4-CH_3	H	H	H	H	H	F	oil	$C_{16}H_{12}ClN$[e]
27	2-CH_3	H	H	H	H	H	F	97–98	$C_{16}H_{12}ClN$
28	4-CN	H	H	H	H	H	F	112–114	$C_{16}H_9ClN_2$[f]
29	4-CF_3	H	H	H	H	H	F	89–92	$C_{16}H_9ClF_3N$
30	4-SCH_3	H	H	H	H	H	F	105–108	$C_{16}H_{12}ClNS$
31	2-OCH_3	H	H	CH_3	H	H	F	oil	$C_{17}H_{14}ClNO$[e]
32	H	H	H	H	CH_3	H	F	85[g]	$C_{16}H_{12}ClN$
33	H	H	H	OCH_3	H	H	F	oil	$C_{16}H_{12}ClNO$[e]
34	H	H	H	$O(CH_2)_2CH_3$	H	H	F	68–69	$C_{18}H_{16}ClNO$
35	2-F	H	H	H	H	H	F	111–113	$C_{15}H_9ClFN$
36	2-Cl	H	H	H	H	H	F	116–118	$C_{15}H_9Cl_2N$
37	3-F	H	H	H	H	H	F	50–52	$C_{15}H_9ClFN$
38	3-CH_3	H	H	H	H	H	F	77–78	$C_{16}H_{12}ClN$
39	4-OH	H	H	H	H	H	F	167–168	$C_{15}H_{10}ClNO$[h]
40	H	H	H	SCH_3	H	H	F	74–75	$C_{16}H_{12}ClNS$[e]
41	H	H	H	H	$N(CH_3)_2$	H	F	134–135	$C_{17}H_{15}ClN_2$[e]
42	H	H	H	H	SCH_3	H	F	88–90	$C_{16}H_{12}ClNS$
43	H	H	H	H	OCH_3	H	F	126–128	$C_{16}H_{12}ClNO$
44	H	H	H	H	H	OCH_3	F	oil	$C_{16}H_{12}ClNO$[e]

[a] See Experimental Section for details. [b] C, H, N analyses were within 0.4% of theory. [c] Literature[9] mp 53–54 °C. [d] C: calcd, 71.2; found, 71.7. [e] Unanalyzed intermediates gave satisfactory ^1H NMR and/or mass spectra. [f] C: calcd, 72.6; found, 72.1. [g] Literature[9] mp 86–87 °C. [h] N: calcd, 5.5; found, 5.0.

2-chloroethylamine derivative (method J).

An alternative approach was adopted for the synthesis of 2-[[2-(*N*-ethyl-*N*-methylamino)ethyl]thio]-3-phenylquinoline (**71**). This compound was prepared by the reductive ethylation of the methylamino analogue (**69**) as shown in Scheme II (method K).

Biology. The 2-[(2-aminoethyl)thio]-3-substituted-quinolines shown in Tables V–VII were tested as 5-HT antagonists by using two in vitro and two in vivo assays. Receptor binding affinity at the 5-HT_1 site was measured by the method of Peroutka and Snyder[5] using a radioligand-binding assay in which [^{3}H]-5-HT was displaced from rat brain synaptosomes. Affinity for the 5-HT_2 receptor subtype was determined in a similar manner[5] with [^{3}H]spiperone (8-[3-(*p*-fluorobenzoyl)propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one) as the radioligand and rat brain frontal cortex. This tissue is used to avoid interference from the binding of spiperone to dopamine receptors in other brain regions. The results are expressed for both assays as pI_{50} values, the pI_{50} being the negative logarithm of the concentration of test agent required to displace 50% of the specifically bound radioligand.

Central 5-HT_2 antagonist activity was demonstrated in the mouse head-twitch model,[6] which involves the administration of the 5-HT precursor, 5-hydroxytryptophan (5-HTP) to mice. The resultant high levels of 5-HT produced in the brain produce a spontaneous head and ear twitching which is blocked by centrally acting 5-HT antagonists. The results are expressed as ID_{50} values, i.e., the dose of test agent required to reduce by 50% the twitch

Scheme II

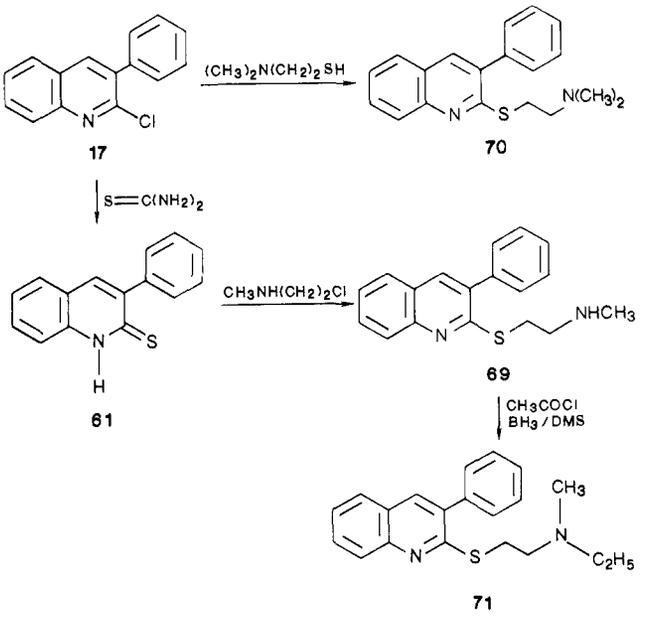
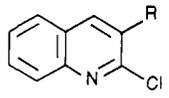


Table III. Alkyl- and Heteroaryl-Substituted 2-Chloroquinolines Prepared by Method F



compd	R	mp, °C	formula[a]
45	CH_3	82–84[b]	$C_{10}H_8ClN$
46	C_2H_5	72–75[c]	$C_{11}H_{10}ClN$
47	$CH(CH_3)_2$	oil	$C_{12}H_{12}ClN$[d]
48	$(CH_2)_2CH_3$	31	$C_{12}H_{12}ClN$
49	$(CH_2)_3CH_3$	55–56	$C_{13}H_{14}ClN$
50	$C(CH_3)_3$	oil	$C_{13}H_{14}ClN$[d]
51	cyclopropyl	oil	$C_{12}H_{10}ClN$[d]
52	cyclopentyl	oil	$C_{14}H_{14}ClN$[d]
53	cyclohexyl	oil	$C_{15}H_{16}ClN$[d]
54	$CH(CH_3)C_2H_5$	oil	$C_{13}H_{14}ClN$[d]
55	CH_2Ph	69–70	$C_{16}H_{12}ClN$
56	$CH(CH_3)Ph$	74–76	$C_{17}H_{14}ClN$[e]
57	2-pyridyl	79–82	$C_{14}H_9ClN_2$[e]
58	2-thienyl		$C_{13}H_8ClNS$[f]
59	3-thienyl	134–135	$C_{13}H_8ClNS$[e]
60	5-(2-Me)thiazolyl	167	$C_{13}H_9ClN_2S$

[a] C, H, N analyses were within 0.4% of theory. [b] Literature[9] mp 86–87 °C. [c] Literature[20] mp 72–73 °C. [d] Unanalyzed intermediate gave satisfactory ^1H NMR spectra. [e] Unanalyzed intermediates gave satisfactory ^1H NMR and mass spectra. [f] Unpurified intermediate.

score resulting from a standard challenge of 5-HTP. In a second in vivo assay the compounds were tested for their ability to antagonize the hyperthermia induced by fenfluramine (*N*-ethyl-α-methyl-*m*-(trifluoromethyl)phenethylamine hydrochloride), an agent that releases 5-HT from endogenous stores. The ID_{50} values quoted in the tables for this test are the doses of test compound required to reduce the hyperthermic response to a standard dose of fenfluramine by 50%.

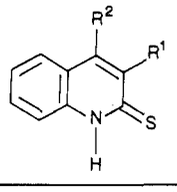
In Table V comparative results are given for ketanserin and methysergide ((+)-*N*-[1-(hydroxymethyl)propyl]-1-methyl-D-lysergamide).

Discussion

Table V shows results for a group of 2-[(2-aminoethyl)thio]-3-phenylquinolines with small alkyl substituents on the amino group. It can be seen that the dimethyl substituent is optimal (compound **70**) with a sharp fall in both receptor binding affinity and 5-HT_2 selectivity for alternative substituents. As a consequence of this observation, the vast majority of analogues with substituents elsewhere in the molecule were made initially with [(dimethylamino)ethyl]thio side chains as shown in Tables VI and VII.

Table VI shows a range of analogues of 2-[[2-(dimethylamino)ethyl]thio]-3-phenylquinoline with substituents in the phenyl ring or on the quinoline ring. Receptor affinity and 5-HT_2 selectivity together with in vivo 5-HT_2 antagonist activity are retained particularly with the 2-fluorophenyl (**75**), 3-methylphenyl (**80**), and 2,5-dimethoxyphenyl (**90**) derivatives, but none of these compounds was superior to the parent compound (**70**). Substitution in the benzenoid ring of the quinoline with alkoxy, alkyl,

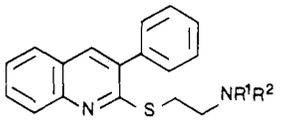
Table IV. Substituted 2(1*H*)-Quinolinethiones



compd	R^1	R^2	prep[a]	mp, °C	formula[b]
61	Ph	H	H	242–244	$C_{15}H_{11}NS$
62	Ph	OCH_3	G	221–224	$C_{16}H_{13}NOS$
63	2-CH_3-C_6H_4	OCH_3	G	208–210	$C_{17}H_{15}NOS$
64	4-F-C_6H_4	OCH_3	G		$C_{16}H_{12}FNOS$[c]
65	3-thienyl	OCH_3	G	217–220	$C_{14}H_{11}NOS_2$[d]
66	3-thienyl	CH_3	G	278–280	$C_{14}H_{11}NS_2$
67	$CH(CH_3)_2$	CH_3	G	232–234	$C_{13}H_{15}NS$

[a] See Experimental Section for details. [b] C, H, N analyses were within 0.4% of theory. [c] Unpurified intermediate. [d] Unanalyzed intermediate gave satisfactory ^1H NMR and mass spectrum.

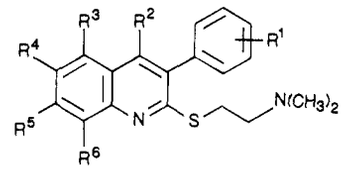
Table V. 2-[(2-Aminoethyl)thio]-3-phenylquinolines: Physical Properties and Pharmacological Activities



compd	R^1	R^2	prep[a]	mp, °C	formula[b]	salt	binding pI_{50} values[c] 5-HT_1	5-HT_2	head shake ID_{50},[d] mg/kg ip	FH ID_{50},[e] mg/kg po
68	H	H	I	232–235	$C_{17}H_{16}N_2S$	HCl	6.1	5.6	50	4.8
69	H	CH_3	J	168–170	$C_{18}H_{18}N_2S$	HCl·0.5H_2O	6.6	6.6	6.2	7.0
70	CH_3	CH_3	I/J	195–198	$C_{19}H_{20}N_2S$	HCl	5.7	7.5	1.6 (1.0–2.5)[f]	1.2 (0.3–4.3)[f]
71	CH_3	C_2H_5	K	179–181	$C_{20}H_{22}N_2S$	oxalate·0.5H_2O	6.1	6.8	50	
72	C_2H_5	C_2H_5	I	144–146	$C_{21}H_{24}N_2S$	HCl	6.2	6.8	25	50
ketanserin							<6.0	8.3	0.5 (0.02–0.9)[f]	0.1 (0.02–0.3)[f]
methylsergide							7.5	8.3	0.52 (0.35–0.77)[f]	0.4 (0.1–1.3)[f]

[a] See Experimental Section for details. [b] All compounds gave C, H, N analyses within 0.4% of the theoretical values. [c] 5-HT_1 binding affinities determined by displacement of [^3H]-5-HT from rat brain synaptosomes. 5-HT_2 binding affinities determined by displacement of [^3H]spiperone from rat brain frontal cortex synaptosomes. Results expressed as pI_{50} values, which are the negative logarithm of the molar concentration causing 50% displacement of the radioligand. [d] 5-Hydroxytryptophan-induced head-shake antagonism. ID_{50} values given in mg/kg ip, $n = 5$. [e] FH is the fenfluramine-induced hyperthermia antagonism. ID_{50} values given in mg/kg po, $n = 8$. [f] 95% confidence limits.

Table VI. Substituted 2-[[2-(Dimethylamino)ethyl]thio]-3-phenylquinolines Prepared by Method I: Physical Properties and Pharmacological Activities



compd.	R^1	R^2–R^6	mp, °C	formula[a]	salt	binding pI_{50} values[b] 5-HT_1	5-HT_2	head-shake ID_{50},[c] mg/kg ip	FH ID_{50},[d] mg/kg po
73	4-F	H	198–201	$C_{19}H_{19}FN_2S$	HCl·0.25H_2O	5.9	7.2	1.7	2.9
74	3-F	H	169–171	$C_{19}H_{19}FN_2S$	HCl	6.0	6.8	2.5	4.6
75	2-F	H	187–189	$C_{19}H_{19}FN_2S$	HCl	6.2	7.3	1.9	7.2
76	4-Cl	H	209–211	$C_{19}H_{19}ClN_2S$	HCl	6.2	6.6	9.1	NA[e]
77	2-Cl	H	210–212	$C_{19}H_{19}ClN_2S$	HCl	5.8	7.2	50	9.9
78	4-Br	H	216–218	$C_{19}H_{19}BrN_2S$	HCl	5.5	6.8	19.1	50
79	4-CH_3	H	165–166	$C_{20}H_{22}N_2S$	HCl	6.2	6.5	1.9	4.2
80	3-CH_3	H	157–159	$C_{20}H_{22}N_2S$	HCl	5.6	7.1	1.7	5.9
81	2-CH_3	H	207–209	$C_{20}H_{22}N_2S$[f]	HCl	5.9	6.7	3.0	50
82	4-OCH_3	H	194–195	$C_{20}H_{22}N_2OS$	HCl·0.5H_2O	6.0	6.9	5.9	28
83	3-OCH_3	H	191–193	$C_{20}H_{22}N_2OS$	HCl	5.8	6.8	25	5.1
84	2-OCH_3	H	214–216	$C_{20}H_{22}N_2OS$	HCl	6.2	6.9	1.2	4.6
85	4-$O(CH_2)_2CH_3$	H	156–162	$C_{22}H_{26}N_2OS$	HCl	6.2	6.3	0.5	5.3
86	4-OH	H	220–222	$C_{19}H_{20}N_2OS$	HCl	6.2	6.9	7.9	50
87	4-CN	H	251–252	$C_{20}H_{19}N_3S$	HCl·0.25H_2O	6.6	6.9	1.2	10.7
88	4-CF_3	H	220–222	$C_{20}H_{19}F_3N_2S$[g]	HCl	6.2	6.3	50	NA
89	4-SCH_3	H	208–211	$C_{20}H_{22}N_2S_2$	HCl·0.75H_2O	6.1	7.2	10	7.8
90	2,5-$(OCH_3)_2$	H	205	$C_{21}H_{24}N_2O_2S$	HCl	5.3	7.1	3.0	4.2
91	H	R^5 = OCH_3	84–85	$C_{20}H_{22}N_2OS$	2HCl	5.7	5.7	50	3.1
92	H	R^4 = OCH_3	176–178	$C_{20}H_{22}N_2OS$	oxalate	6.0	6.6	50	8.3
93	H	R^5 = $O(CH_2)_2CH_3$	174–175	$C_{22}H_{26}N_2OS$	oxalate	5.0	5.1	50	50
94	H	R^5 = CH_3	210–212	$C_{20}H_{22}N_2S$	oxalate	5.6	6.2	50	50
95	H	R^4 = Br	208–210	$C_{19}H_{19}BrN_2S$	oxalate		5.8	50	6.7
96	H	R^4 = Cl	200–202	$C_{19}H_{19}ClN_2S$	oxalate	6.0	5.6	50	50
97	H	R^2 = CH_3	194–196	$C_{20}H_{22}N_2S$	oxalate	6.0	6.7	6.2	50
98	H	R^2 = OCH_3	184–188	$C_{20}H_{22}N_2OS$[h]	oxalate	5.8	7.0	3.5	5.5
99	H	R^4 = SCH_3	187–189	$C_{20}H_{22}N_2S_2$	oxalate	5.2	5.5	50	10.3
100	H	R^6 = CH_3	67–68	$C_{20}H_{22}N_2S$				NA	NA
101	H	R^5 = SCH_3	89–91	$C_{20}H_{22}N_2S_2$		5.8	5.5	NA	50
102	H	R^5 = $N(CH_3)_2$	125–127	$C_{21}H_{25}N_3S$	oxalate	5.0	5.4	NA	50
103	H	R^2 = $CONH_2$	98–99	$C_{20}H_{21}N_3OS$		5.3	5.0	NA	NA
104	2-OCH_3	R^4 = CH_3	164	$C_{21}H_{24}N_2OS$	oxalate	5.0	6.4	50	50
105	4-F	R^2 = OCH_3	213–216	$C_{20}H_{21}FN_2OS$[h]	oxalate	6.0	6.3	50	3.3
106	2-OCH_3	R^2 = CH_3	183–185	$C_{21}H_{24}N_2OS$	oxalate	6.3	6.7	50	50
107	4-F	R^2 = CH_3	217–220	$C_{20}H_{21}FN_2S$	oxalate	5.0	6.6	50	11.1
108	2-CH_3	R^2 = OCH_3	196–198	$C_{21}H_{24}N_2OS$[h]	HCl	5.6	6.7	50	7.2

[a] All compounds gave C, H, N analyses within 0.4% of the theoretical values. [b] 5-HT_1 binding affinities determined by displacement of [^{3}H]-5-HT from rat brain synaptosomes. 5-HT_2 binding affinities determined by displacement of [^{3}H]spiperone from rat brain frontal cortex synaptosomes. Results expressed as pI_{50} values, which are the negative logarithm of the molar concentration causing 50% displacement of the radioligand. [c] 5-Hydroxytryptophan-induced head-shake antagonism. ID_{50} values given in mg/kg ip, n = 5. [d] FH is the fenfluramine-induced hyperthermia antagonism. ID_{50} values given in mg/kg po, n = 8. [e] NA means not active at a dose of 50 mg/kg. [f] N: calcd, 7.8; found, 7.3. [g] C: calcd, 58.2; found, 58.7. [h] Prepared by method J.

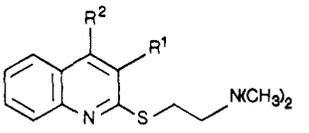
halo, methylthio, or dimethylamino groups gave compounds with reduced potency and loss of selectivity for the 5-HT_2 receptor relative to the 5-HT_1 receptor. However, substitution at the 4-position of the quinoline with a methoxy group gave the quinoline **98**, which retained potency and selectivity.

In Table VII the results are shown for a group of quinolines with alkyl, cycloalkyl, and heteroaryl substituents at the 3-position. The isopropyl analogue (**111**) showed the greatest in vivo potency albeit with less 5-HT_2 receptor selectivity, while among the heteroaryl analogues the thiophene isostere (**124**) was the most potent and selective. The chemistry, biological activity, and conformational properties of compounds with branched (aminoalkyl)thio side chains will be the subject of a further paper.

The compound with the optimum combination of selectivity in the in vitro assays and potency in the in vivo tests, 2-[[2-(dimethylamino)ethyl]thio]-3-phenylquinoline hydrochloride (**70**) (ICI 169,369) was selected for more detailed investigation in ligand-binding assays, vascular smooth muscle preparations, and a range of cardiovascular and central nervous system models to assess its potency and selectivity as a 5-HT_2 antagonist. The results of these experiments have been reported in preliminary form.[10] Thus in binding studies in brain tissue, compound **70** has K_i values at common neurotransmitter receptors as follows: 5-HT_1, 1.58×10^{-6} mol; 5-HT_2, 1.79×10^{-8} mol; α_1, 5.6×10^{-7} mol; α_2, 1.37×10^{-6} mol; β_1, 3.72×10^{-6} mol; β_2, 2.8×10^{-6} mol. In the in vivo models of central 5-HT_2 activity, compound **70** has ID_{50} values (with 95% confidence limits) in the head-twitch test of 1.6 (1.0–2.5) mg/kg) ip and 0.8 (0.5–1.2) mg/kg iv and in the fenfluramine hyperthermia model the ID_{50} values are 1.0 (0.3–5.6) mg/kg sc and 1.2 (0.3–4.3) mg/kg po. Moreover, the compound has an ID_{50}

(10) Blackburn, T. P.; Thornber, C. W.; Pearce, R. J.; Cox, B. *Abstracts of Papers*, Society for Neuroscience, Washington, DC, 1986; Abstracts 119.7 and 119.8, p 423.

Table VII. 3-Alkyl- and 3-Heteroaryl-2-[[2-(dimethylamino)ethyl]thio]quinolines: Physical Properties and Pharmacological Activities



compd	R^1	R^2	prep[a]	mp, °C	formula[b]	salt	binding pI_{50} values 5-HT_1	binding pI_{50} values 5-HT_2	head shake ID_{50},[d] mg/kg ip	FH ID_{50},[e] mg/kg po
109	CH_3	H	I	167–170	$C_{14}H_{18}N_2S$	2HCl	5.8	5.6	NA[f]	NA
110	C_2H_5	H	I	159–161	$C_{15}H_{20}N_2S$	2HCl	5.4	5.0	50	50
111	$CH(CH_3)_2$	H	I	170–173	$C_{16}H_{22}N_2S$	HCl	5.6	6.6	2.6	2.7
112	$CH(CH_3)_2$	CH_3	J	178–180	$C_{17}H_{24}N_2S$	oxalate	5.0	6.1	50	NA
113	$(CH_2)_2CH_3$	H	I	164–166	$C_{16}H_{22}N_2S$	oxalate	6.5	6.8	5.0	NA
114	$(CH_2)_3CH_3$	H	I	150	$C_{17}H_{24}N_2S$	HCl	6.4	6.7	2.3	50
115	$CH(CH_3)CH_2CH_3$	H	I	153–155	$C_{17}H_{24}N_2S$	oxalate	5.7	6.6	1.5	50
116	$C(CH_3)_3$	H	I	158–159	$C_{17}H_{24}N_2S$	oxalate	5.7	6.0	50	NA
117	cyclopropyl	H	I	158	$C_{16}H_{20}N_2S$	oxalate	5.0	6.8	3.4	25
118	cyclopentyl	H	I	176–177	$C_{18}H_{24}N_2S$	oxalate	6.7	5.9	50	NA
119	cyclohexyl	H	I	140–142	$C_{19}H_{26}N_2S$[g]	$HCl{\cdot}1.5H_2O$	6.1	6.3	50	50
120	$C_6H_5CH_2$	H	I	162–164	$C_{20}H_{22}N_2S$	2HCl	5.8	6.6	50	NA
121	$C_6H_5(CH_3)CH$	H	I	166–168	$C_{21}H_{24}N_2S$	oxalate	6.6	6.6	50	NA
122	2-pyridyl	H	I	140–142	$C_{18}H_{19}N_3S$	oxalate	6.4	6.4	3.4	50
123	2-thienyl	H	I	189–194	$C_{17}H_{18}N_2S_2$	oxalate	6.4	6.3	4.9	6.9
124	3-thienyl	H	I	167–169	$C_{17}H_{18}N_2S_2$	oxalate	5.8	7.4	3.4	7.9
125	3-thienyl	CH_3	J	176–178	$C_{18}H_{20}N_2S_2$	oxalate	6.0	7.2	3.1	50
126	3-thienyl	OCH_3	J	178–181	$C_{18}H_{20}N_2OS_2$	oxalate	6.3	6.1	50	NA
127	5-(2-CH_3-thiazolyl)	H	I	167	$C_{17}H_{19}N_3S_2$	oxalate	6.4	6.3	4.9	6.9

[a] See Experimental Section for details. [b] All compounds gave C, H, N analyses within 0.4% of the theoretical values. [c] 5-HT_1 binding affinities determined by displacement of [^{3}H]-5-HT from rat brain synaptosomes. 5-HT_2 binding affinities determined by displacement of [^{3}H]spiperone from rat brain cortex synaptosomes. Results expressed as pI_{50} values, which are the negative logarithm of the molar concentration causing 50% displacement of the radioligand. [d] 5-Hydroxytryptophan-induced head-shake antagonism. ID_{50} values given in mg/kg ip, $n = 5$. [e] FH is the fenfluramine-induced hyperthermia antagonism. ID_{50} values given in mg/kg po, $n = 8$. [f] NA means not active at a dose of 50 mg/kg. [g] N: calcd, 7.4; found, 6.9.

value of 0.18 mg/kg iv against 5-HT-induced pressor responses as shown in the pithed rat model described by Gillespie and Muir.[11] The selectivity of compound **70** for 5-HT_2 against other neurotransmitters has been demonstrated in vivo in a range of tests. Thus compound **70** is inactive[10] as an antagonist of oxotremorine-induced tremor and hypothermia in the mouse[12] at 100 mg/kg po, as an antagonist of histamine-induced bronchospasm[13] in the guinea pig at 2.0 mg/kg iv, as an antagonist of noradrenaline-induced contraction of the cat nictitating membrane[14] at 3.0 mg/kg iv, as an antagonist of isoproterenol-induced tachycardia and vasodilation in the dog[15] at 10 mg/kg po, and as an antagonist of amphetamine-induced stereotypy in the rat[16] at 100 mg/kg po. Of particular significance are the results obtained by comparison of compound **70** with ketanserin as antagonists of 5-HT and methoxamine (an α_1-adrenergic stimulant) on the rat caudal artery.[17] The pA_2 values found for compound **70** were 8.18 and <6.0 and for ketanserin 8.4 and 7.12 for 5-HT and methoxamine, respectively. It can be seen, therefore, that compound **70** is a potent, centrally acting 5-HT_2 antagonist with a high degree of selectivity for 5-HT_2 receptors, which is demonstrated in binding, isolated tissue, and in vivo models. It is now in phase two clinical trials for evaluation in psychiatric and cardiovascular disorders.

Experimental Section

Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Bruker HX90E, JEOL FX90Q, or Varian EM390 spectrometer using deuteriochloroform or DMSO-d_6 as solvents with tetramethylsilane as internal standard and are consistent with the assigned structures. Melting points were determined with a Büchi apparatus in glass capillary tubes and are uncorrected. Where analyses are indicated by the symbols of the elements, the results obtained were within ±0.4% of the theoretical values. Chromatography was carried out with 230–400-mesh ASTM silica gel unless stated otherwise. Mass measurements were made with an AEI MS 902S spectrometer.

1. **Preparation of 2(1*H*)-Quinolones. 6-Chloro-3-phenyl-2(1*H*)-quinolone (1). Method A.** This compound was prepared by the method of Manimaran and Ramakrishnan.[7]

4-Methyl-3-phenyl-2(1*H*)-quinolone (3). Method B. A solution of 2′-acetyl-1-phenylacetanilide (1.9 g, 0.0075 mol) in toluene (50 mL) was treated with sodium metal (1.5 g) and the mixture was heated under reflux in an atmosphere of argon for 1 h. The solution was cooled to room temperature, methanol (20 mL) was added, and the mixture was stirred for 1 h and then evaporated to dryness. The residue was dissolved in the minimum volume of water and acidified with 6 M HCl to give a white precipitate, which was collected and washed with water to give 1.4 g of the quinolone (3) in a yield of 80%: mp 272–274 °C (lit.[18] mp 273 °C).

3-Isopropyl-4-methyl-2(1*H*)-quinolone (7). Method C. A solution of acetoacetanilide (1.77 g, 0.01 mol) in DMF (15 mL) was treated at 20 °C with sodium hydride (0.24 g, 0.01 mol) and the mixture was stirred for 30 min before the addition of 2-bromopropane (1.5 g, 0.012 mol). The solution was heated at 60 °C under argon for 5 days, cooled, and poured into water (100 mL). The solution was acidified with 6 M HCl and the product

(11) Gillespie, J. S.; Muir, T. C. *Br. J. Pharmacol.* **1967**, *30*, 78.
(12) Cho, A. K.; Haslett, W. L.; Jenden, B. J. *J. Pharmacol. Exp. Ther.* **1962**, *138*, 249.
(13) Konzett, H.; Rossler, R. *Arch. Exp. Pathol. Pharmakol.* **1940**, *195*, 71.
(14) Paton, W. D. M.; Perry, W. L. M. *J. Physiol.* **1953**, *119*, 43, Trendelenberg, U. *Br. J. Pharmacol.* **1954**, *9*, 481.
(15) Bilski, A. J.; Halliday, S. E.; Fitzgerald, J. D.; Wale, J. *J. Cardiovas. Pharmacol.* **1983**, *5*, 430.
(16) Costall, C.; Marsden, D.; Naylor, R. J.; Pycock, C. J. *Brain. Res.* **1977**, *123*, 89.
(17) Leysen, J. E.; Niemegeers, C. J. E.; Van Nueten, J. M.; Laduron, P. M. *Mol. Pharmacol.* **1982**, *21*, 301.
(18) Bischler, A.; Howell, F. J. *Chem. Ber.* **1893**, *26*, 1384.

was extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water (100 mL) and dried (Na_2SO_4). The residue obtained after evaporation of the solvent was chromatographed on silica gel, and the products were eluted with ethyl acetate/hexane (1:4) to give, after recrystallization from cyclohexane, 0.9 g of 3-isopropylacetanilide (41%): mp 133–137 °C. Anal. ($C_{13}H_{17}NO_2$) C, H, N. A solution of the above anilide (2.2 g, 0.01 mol) in 75% sulfuric acid (25 mL) was stirred at 95–100 °C for 1 h, cooled, and poured into ice/water (100 mL). The precipitate was collected, washed with a small volume of 2-propanol, and dried to give 0.9 g of the quinolone (7) in 44% yield: ^1H NMR (DMSO-d_6) δ 1.32 (d, 6 H, J = 7.7 Hz), 3.41 (m, 1 H), 7.3 (complex 5 H).

4-Methoxy-3-phenyl-2(1*H*)-quinolone (8). Method D. A solution of 2,4-dichloro-3-phenylquinoline[17] (3 g, 0.011 mol) and sodium methoxide (2.7 g, 0.05 mol) in DMF (35 mL) was heated at 65–70 °C for 2 h. The reaction mixture was then poured into water (500 mL) and the product was extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with water (3 × 100 mL), dried (Na_2SO_4), and evaporated to dryness. The oily product was heated on a steam bath in 2 M HCl (50 mL) for 2 h. When the solution was cooled the product (8) separated in a yield of 2.4 g (87%): mp 229–232 °C (lit.[19] mp 234–235 °C).

2. Preparation of 2-Chloroquinolines. 2,6-Dichloro-3-phenylquinoline (12). Method E. A solution of the quinolone 1 (5.3 g, 0.02 mol) in phosphorus oxychloride (100 mL) was heated under reflux for 2 h, evaporated under reduced pressure to a low volume, and poured into ice/water (1 L). The mixture was stirred at room temperature for 1 h and the product extracted with ethyl acetate (3 × 100 mL). The combined extracts were washed with saturated sodium carbonate solution, dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on silica gel, with ethyl acetate/hexane (1:3) as eluant, to give, after recrystallization from hexane, 4.1 g of 2,6-dichloro-3-phenylquinoline (12) (75%): mp 147–149 °C. Anal. ($C_{15}H_{10}Cl_2N$) C, H, N.

2-Chloro-3-phenylquinoline (17). Method F. This compound was prepared from phenylacetanilide by the method of Meth-Cohn et al.[9]

3. Preparation of 2(1*H*)-Thioquinolones. 3-Isopropyl-4-methyl-2(1*H*)-thioquinolone (67). Method G. 3-Isopropyl-4-methyl-2(1*H*)-quinolone (7) (0.4 g, 0.0022 mol) was heated under reflux in toluene (10 mL) with Lawesson's reagent (0.45 g, 0.0011 mol) for 2 h. The mixture was cooled and the precipitate was collected and recrystallized from toluene to give 0.35 g of the thioquinolone (67) in 75% yield: mp 232–234 °C. Anal. ($C_{13}H_{15}NS$) C, H, N.

3-Phenyl-2(1*H*)-thioquinolone (60). Method H. A mixture of 2-chloro-3-phenylquinoline (17) (3.4 g, 0.014 mol) and thiourea (1.2 g, 0.016 mol) in ethanol (20 mL) was heated under reflux for 1 h. The solution was cooled to room temperature and diluted with diethyl ether (10 mL). The precipitate was collected and heated on a steam bath for 2 h with 1 M NaOH (70 mL). The reaction mixture was then acidified with 2 M HCl and the resulting solid was collected and washed with hot ethanol (50 mL) to give the thioquinolone (60) in a yield of 2.6 g (90%): mp 242–244 °C. Anal. ($C_{15}H_{11}NS$) C, H, N.

4. Preparation of 2-[2-(Aminoethyl)thio]-3-phenylquinolines. 2-[[2-(*N*,*N*-Dimethylamino)ethyl]thio]-3-phenylquinoline Hydrochloride (70). Method I. To a stirred suspension of sodium hydride (15.8 g, 0.66 mol) in dry DMF (500 mL) at 0–5 °C was added over 25 min 2-(dimethylamino)-ethanethiol hydrochloride (58.4 g, 80% w/w, 0.33 mol). The mixture was allowed to warm to room temperature and was stirred for 1 h. A solution of 2-chloro-3-phenylquinoline (17) (72.7 g, 0.3 mol) in dry DMF (100 mL) was added and the mixture was heated at 75 °C for 5 h, allowed to stand at room temperature overnight, and poured into ice/water (4 L).

The product was extracted with ethyl acetate (6 × 500 mL), and the combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give an oily residue, which was chromatographed on Woelm grade III basic alumina (1.2 kg). Elution with hexane/chloroform (9:1) gave after evaporation a yellow solid, which was dissolved in ethanol (800 mL) and treated with concentrated HCl (25.2 mL). The ethanolic solution was evaporated to dryness and the residue dried by azeotropic distillation of toluene. The residue was crystallized from ethanol/ether to afford the product (70) in a yield of 87.5 g (83.7%): mp 195–198 °C, ^1H NMR (DMSO-d_6) δ 2.8 (s, 6 H), 3.3 (m, 2 H), 3.5 (m, 2 H), 7.45 (s, 5 H), 7.8 (m, 5 H). Anal. ($C_{19}H_{20}N_2S$·HCl) C, H, N.

2-[[2-(*N*-Methylamino)ethyl]thio]-3-phenylquinoline (69). Method J. Sodium hydride (0.86 g, 0.04 mol) was added to a stirred mixture of 3-phenyl-2(1*H*)-thioquinolone (61) (4.75 g, 0.02 mol) and DMF (50 mL) at room temperature. The mixture was stirred for 0.5 h and treated with 2-(methylamino)ethyl chloride hydrochloride (2.6 g, 0.02 mol) and stirring was continued for 20 h. The reaction mixture was then poured into water (600 mL) and the product extracted with ethyl acetate (2 × 100 mL). The extracts were dried ($MgSO_4$) and evaporated to dryness, and the residue was dissolved in ether. A saturated solution of HCl in ether was added until precipitation ceased. The precipitate was collected and recrystallized from ethanol/ether to give (69): yield 3.8 g (57.6%); 168–170 °C. Anal. ($C_{18}H_{18}N_2S$·HCl·0.5H_2O) C, H, N.

2-[[2-(*N*-Ethyl-*N*-methylamino)ethyl]thio]-3-phenylquinoline (71). Method K. A solution of the secondary amine 69 (0.8 g, 0.0028 mol) in dichloromethane (10 mL) containing triethylamine (0.56 mL, 0.0056 mol) was treated with acetyl chloride (0.2 mL, 0.0028 mol). The mixture was stirred at room temperature for 1 h and the dichloromethane solution was washed with 2 M NaOH (2 × 10 mL), water (10 mL), 2 M HCl (2 × 10 mL), and water (3 × 10 mL). The dichloromethane solution was dried (Na_2SO_4) and evaporated to dryness. A portion of the residue (0.5 g) was dissolved in dry THF (10 mL) and treated dropwise with borane–dimethyl sulfide complex (0.37 mL). The solution was heated under reflux for 4 h in an atmosphere of argon and evaporated to dryness. The residue was heated on a steam bath for 1.5 h with 2 M HCl (10 mL) and methanol (5 mL). The solution was cooled and basified with 2 M NaOH, and the product was extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with water (3 × 10 mL), dried (Na_2SO_4), and evaporated to dryness. The residue was chromatographed on silica gel by elution with 10% methanol in ethyl acetate to afford a fraction (0.23 g) which was treated in methanol (10 mL) with oxalic acid (0.065 g). The solution was evaporated to dryness and the residue was recrystallized from ethanol/ether to yield the tertiary amine (71) in a yield of 0.24 g (38%): mp 179–181 °C. Anal. ($C_{22}H_{24}N_2O_4S$) C, H, N.

Binding Studies. The method of Peroutka and Snyder[5] was used. The compounds were tested initially at a concentration of 0.3 μg/mL, and those producing more than 30% inhibition of the specific binding were tested at a range of concentrations to determine the pI_{50} value. All determinations at each concentration of drug were performed in triplicate.

Head-Twitch Model. The method of Corne et al.[21] was employed. The test agent at various dose levels was administered intraperitoneally to male mice (average weight 18–20 g) in groups of five, 15 min before an intraperitoneal injection of 300 mg/kg of 5-HTP. The mice were observed 15 min later for head twitches. Nonspecific inhibition of the response because of sedation was eliminated by determining the presence or absence of the pinna reflex to tactile stimulation of the ear. The ID_{50} value is the dose of test agent required to reduce by 50% the head-twitch response.

Fenfluramine-Induced Hyperthermia Model. Compounds were tested according to the method of Blackburn et al.[22] Eight female rats (Alderley Park strain, 180–220 g) for each dose level were housed four per cage at 25–28 °C for 1 h. Rectal temperatures were recorded, and the animals were then dosed orally with the test agent or control vehicle (distilled water). After another hour, rectal temperatures were recorded again. A dose of 15 mg/kg of fenfluramine or control (distilled water) was then injected intraperitoneally, and rectal temperatures were measured 30 min,

(19) Nishimura, H.; Nagai, Y.; Suzuki, T.; Sawayama, T. *Yakugaku Zasshi* **1970**, *90*, 818.

(20) Bayer, A.; Jackson, O. P. *Chem. Ber.* **1880**, *13*, 120.

(21) Corne, S. J.; Pickering, R. W.; Warner, B. T. *Br. J. Pharmacol.* **1963**, *20*, 106.

(22) Blackburn, T. P.; Cox, B.; Heywood, B.; Kemp, J. D. *Br. J. Pharmacol.* **1983**, *79*, 223P, Blackburn, T. P.; Rourke, J. D.; Cox, B. *Pharmacologist* **1985**, *27*, 75P, 456.

1, 2, 3, 4, 5, and 6 h later. The ID_{50} value is the dose of test agent required to reduce hyperthermic response to the standard dose of fenfluramine by 50%.

Registry No. 1, 85274-64-2; 2, 110486-57-2; 3, 19069-84-2; 4, 70751-26-7; 5, 89080-92-2; 6, 89080-93-3; 7, 89081-03-8; 8, 28563-01-1; 9, 110486-58-3; 10, 89090-29-9; 11, 89090-96-0; 12, 85274-46-0; 13, 85274-48-2; 14, 89081-06-1; 15, 110486-59-4; 16, 110486-60-7; 17, 2859-30-5; 18, 85273-99-0; 19, 85274-81-3; 20, 85274-82-4; 21, 85274-80-2; 22, 85274-79-9; 23, 85274-01-7; 24, 85274-83-5; 25, 85274-86-8; 26, 85274-00-6; 27, 85274-88-0; 28, 85274-84-6; 29, 85274-85-7; 30, 85274-87-9; 31, 110486-61-8; 32, 73863-47-5; 33, 85274-57-3; 34, 110486-62-9; 35, 85274-89-1; 36, 85274-90-4; 37, 85274-91-5; 38, 85274-92-6; 39, 85275-18-9; 40, 110486-63-0; 41, 110486-64-1; 42, 110486-65-2; 43, 85274-56-2; 44, 2859-50-9; 45, 57876-69-4; 46, 67525-28-4; 47, 85273-92-3; 48, 85274-50-6; 49, 79249-33-5; 50, 110486-66-3; 51, 85274-12-0; 52, 110486-67-4; 53, 110486-68-5; 54, 85274-51-7; 55, 110486-69-6; 56, 110486-70-9; 57, 85274-52-8; 58, 85274-53-9; 59, 85274-54-0; 60, 110486-71-0; 61, 85274-02-8; 62, 89080-84-2; 63, 89080-83-1; 64, 110486-72-1; 65, 89081-01-6; 66, 89080-98-8; 67, 89081-04-9; 68, 110487-07-5; 68·HCl, 85275-04-3; 69, 85274-03-9; 69·HCl, 85274-04-0; 70, 85273-95-6; 70·HCl, 85273-96-7; 71, 85275-10-1; 71·oxalate, 85275-11-2; 72, 110487-08-6; 72·HCl, 85275-08-7; 73, 110487-09-7; 73·HCl, 85273-97-8; 74, 110487-10-0; 74·HCl, 85274-77-7; 75, 110487-11-1; 75·HCl, 85274-75-5; 76, 110487-12-2; 76·HCl, 85274-67-5; 77, 110487-05-3; 77·HCl, 85274-76-6; 78, 110487-13-3; 78·HCl, 85274-68-6; 79, 110487-14-4; 79·HCl, 85273-98-9; 80, 110487-15-5; 80·HCl, 85274-78-8; 81, 110487-16-6; 81·HCl, 85274-74-4; 82, 110487-17-7; 82·HCl, 85274-66-4; 83, 110487-18-8; 83·HCl, 85274-65-3; 84, 110487-19-9; 84·HCl, 85285-20-7; 85, 110487-20-2; 85·HCl, 85274-69-7; 86, 85275-19-0; 86·HCl, 85275-20-3; 87, 110487-21-3; 87·HCl, 85274-70-0; 88, 110487-22-4; 88·HCl, 85274-71-1; 89, 110487-23-5; 89·HCl, 85274-73-3; 90, 110487-24-6; 90·HCl, 85274-72-2; 91, 110487-25-7; 91·2HCl, 85274-30-2; 92, 85274-31-3; 92·oxalate, 85274-32-4; 93, 85274-33-5; 93·oxalate, 85274-34-6; 94, 85274-35-7; 94·oxalate, 85274-36-8; 95, 85274-41-5; 95·oxalate, 85274-42-6; 96, 85274-39-1; 96·oxalate, 85274-40-4; 97, 89081-24-3; 97·oxalate, 110486-73-2; 98, 89081-07-2; 98·oxalate, 110486-74-3; 99, 110486-75-4; 99·oxalate, 110486-76-5; 100, 110486-77-6; 101, 110486-78-7; 102, 110487-26-8; 102·oxalate, 110486-79-8; 103, 110486-80-1; 104, 85274-18-6; 104·oxalate, 85274-17-5; 105, 110486-82-3; 105·oxalate, 110486-81-2; 106, 89081-28-7; 106·oxalate, 110486-83-4; 107, 89081-34-5; 107·oxalate, 110486-84-5; 108, 110509-41-6; 108·HCl, 110486-85-6; 109, 110487-27-9; 109·2HCl, 110486-86-7; 110, 110487-28-0; 110·2HCl, 110486-87-8; 111, 85273-93-4; 111·HCl, 85273-94-5; 112, 110486-88-9; 112·oxalate, 110486-89-0; 113, 85274-15-3; 113·oxalate, 85274-16-4; 114, 110487-29-1; 114·HCl, 85274-19-7; 115, 85274-20-0; 115·oxalate, 85274-21-1; 116, 110486-90-3; 116·oxalate, 110486-91-4; 117, 85274-13-1; 117·oxalate, 85274-14-2; 118, 110486-92-5; 118·oxalate, 110486-93-6; 119, 110487-30-4; 119·HCl, 110486-94-7; 120, 110487-31-5; 120·2HCl, 110486-95-8; 121, 110486-96-9; 121·oxalate, 110486-97-0; 122, 85274-22-2; 122·oxalate, 85274-23-3; 123, 85274-24-4; 123·oxalate, 85274-25-5; 124, 85274-26-6; 124·oxalate, 85274-27-7; 125, 89081-32-3; 125·oxalate, 110486-98-1; 126, 89081-16-3; 126·oxalate, 110486-99-2; 127, 110487-00-8; 127·oxalate, 110487-01-9; 2-$H_3CCOC_6H_4NHCOCH_2C_6H_5$, 41296-66-6; 2,2'-$H_3CCOC_6H_4NHCOCH_2C_6H_4OCH_3$, 70779-65-6; 2,4'-$H_3CCOC_6H_4NHCOCH_2C_6H_4F$, 89080-86-4; 3-$H_3CCOC_6H_4CH(CH_3)_2$, 7766-63-4; $H_2N(CH_2)_2SH$·HCl, 156-57-0; $(CH_3)_2N(CH_2)_2SH$·HCl, 13242-44-9; $(C_2H_5)_2N(CH_2)_2SH$·HCl, 1942-52-5; $H_3CCOCH_2CONHC_6H_5$, 102-01-2; $H_3CCHBrCH_3$, 75-26-3; $H_3CNH(CH_2)_2Cl$·HCl, 4535-90-4; 2'-acetyl-1-thienylacetanilide, 110487-02-0; 2,4-dichloro-3-phenylquinoline, 108832-15-1; 2,4-dichloro-3-(4-fluorophenyl)quinoline, 110487-03-1; 2,4-dichloro-3-(2-methylphenyl)quinoline, 89090-28-8; 2,4-dichloro-3-(3-thienyl)quinoline, 110487-04-2; 2-chloro-3-phenyl-4-carbamoylquinoline, 110487-06-4; 2-(2-(*N*-methyl-*N*-acetylamino)ethylthio)-3-phenylquinoline, 85275-09-8; thiourea, 62-56-6.

Synthesis and Cardiac Electrophysiological Activity of 2- and 3-[(Substituted phenyl)alkyl]quinuclidines. Structure–Activity Relationships

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The syntheses and cardiac electrophysiological effects of 21 2- and 3-substituted quinuclidines and some quaternary ammonium derivatives are described. The 2-substituted quinuclidines **2–8** were prepared by alkylation of 2-methylene-3-quinuclidinone. The Wittig reaction with 3-quinuclidinone afforded the 3-substituted derivative **9**, which was subsequently converted to **10** and **11**. The electrophysiological profiles of the compounds were determined in canine cardiac Purkinje fibers and ventricular muscle strips. The 3-[(substituted phenyl)alkyl]quinuclidines selectively increased action potential duration (Vaughan Williams class III activity). In the 2-substituted series some of the compounds both increased action potential duration and decreased conduction velocity (class I activity). For some of the 2-substituted quinuclidines, appropriate substitution of the phenyl ring was shown to be a requirement for significant class III electrophysiological activity. Selected compounds were efficacious in a programmed electrical stimulation model in the anesthetized dog.

Although there are a variety of antiarrhythmic agents in use, most of these are class I antiarrhythmic drugs (Vaughan Williams classification).[1] This type of agent slows conduction in cardiac tissue. Since arhythmias can result from a variety of etiologies, treatment of arrhythmias by class I agents is not always effective. Clearly there is a need for alternate therapeutic approaches. One approach that is beginning to receive attention is the use of class III antiarrhythmic agents. This type of agent increases the refractory period of cardiac tissue with minimal effects on conduction. There are few agents in use that exhibit selective class III activity. Amiodarone, sotalol, and bretylium are designated as class III agents but possess other actions as well.[2] Clofilium phosphate (**1**) is a clinically effective, selective class III antiarrhythmic agent;[3] however,

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(1) Vaughan Williams, E. M. In *Symposium on Cardiac Arrhythmias*; Sandoe, E., Flensted-Jansen, E., Olesen, K. H., Eds.; AB Astra, Sodertalje, Sweden, 1970; pp 449–472.
(2) Steinberg, M. I.; Michelson, E. L. In *Mechanism and Treatment of Cardiac Arrhythmias; Relevance of Basic Studies to Clinical Management*; Reiser, H. J., Horowitz, L. N., Eds.; Urban & Schwarzenberg, Baltimore, MD, 1985; pp 263–281.
(3) (a) Steinberg, M. I.; Molloy, B. B. *Life Sci.* **1979**, *25*, 1397. (b) Molloy, B. B.; Steinberg, M. I. U.S. Patent 4 289 787, 1981. (c) Greene, H. L.; Werner, J. A.; Grass, B. W.; Sears, G. K.; Trobaugh, G. B.; Cobb, L. A. *Am. Heart J.* **1983**, *106*, 492. (d) Platia, E.; Reid, P. R. *Clin. Pharmacol. Ther.* **1984**, *35*, 193.

0022-2623/87/1830-2259$01.50/0