Synthesis and Antiarrhythmic and Parasympatholytic Properties of Substituted Phenols. 1. Heteroarylamine Derivatives

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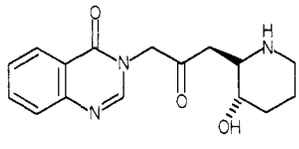
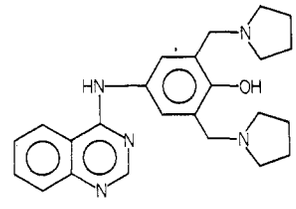
Twenty-four structural derivatives of the antiarrhythmic drug changrolin were synthesized and tested for antiarrhythmic and parasympatholytic activities. It was found that while the bis(pyrrolidinylmethyl)phenol pattern of changrolin appeared to be optimal in this series, a wide latitude existed for the heteroaryl substituent for maintaining good antiarrhythmic activity. Further, the antiarrhythmic and parasympatholytic activities tended to exhibit parallel changes.

More than two centuries ago the antiarrhythmic properties of the antimalarial drug quinine were observed, and nearly 70 years ago it was recognized that quinidine, the optical isomer of quinine, was more effective than quinine in the treatment of rhythm disorders. Though the search for an ideal antiarrhythmic drug has intensified in the last 20 years, quinidine remains the drug of choice for the chronic treatment of supraventricular and ventricular arrhythmias. In spite of its popularity, quinidine, like all antiarrhythmic drugs, has several harmful side effects, most notably cardiotoxicity.

The relationship between antimalarial action and antiarrhythmic activity has not been confined to quinine and quinidine.[1] Recently, a research group in the People's Republic of China, while examining the antimalarial properties of derivatives of febrifugine, noted that one compound in clinical trials, changrolin, was effective as an antiarrhythmic agent.[2]



febrifugine



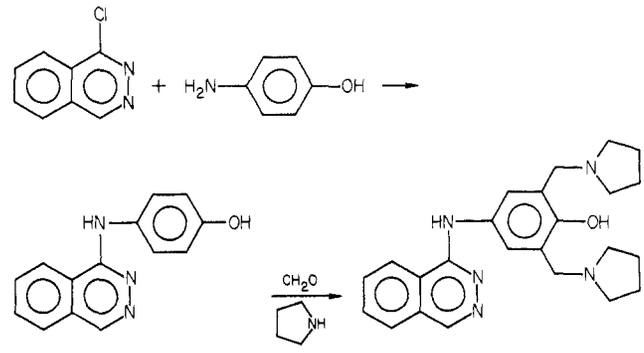
changrolin (1)

Our interest in changrolin as an antiarrhythmic drug was inspired by the dissimilarity of the changrolin structure to currently marketed antiarrhythmics. While the compound has antiarrhythmic utility, changrolin also has unwanted side effects, including the ability to cause skin discoloration in some cases[2b] and, in animal models, parasympatholytic activity[2c] a detrimental property associated with antiarrhythmic drugs, such as disopyramide.

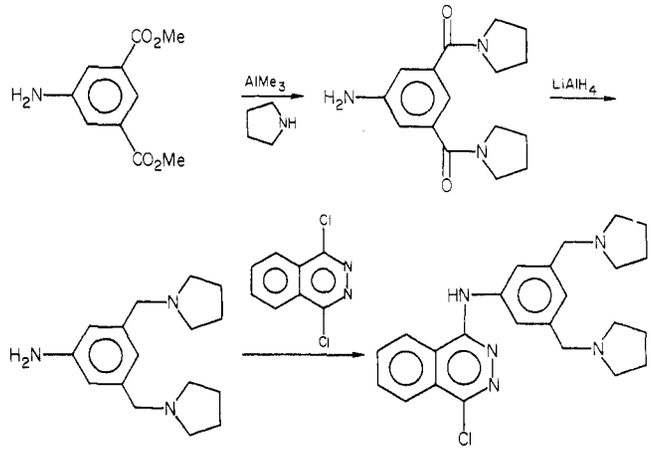
The changrolin molecule can be conceptually divided into the following three regions: (1) the heteroaromatic region consisting of the quinazoline moiety, (2) the aromatic region with the bis(pyrrolidinylmethyl)phenol, and (3) the linkage between the first two regions. We initiated a program of systematically modifying each region in order to determine what features of the molecule were necessary for the antiarrhythmic activity and what features were associated with the parasympatholytic properties.

Chemistry. The compounds tested are shown in Table I. A typical synthesis is exemplified with 1-chlorophthalazine (Scheme I), where the chlorine of the heterocycle is displaced by *p*-aminophenol. Aminomethylation with formaldehyde and pyrrolidine (or dimethylamine for **13**) afforded the final products. Compounds with one pyrrolidinylmethyl moiety (**10** and **22**) were byproducts

Scheme I



Scheme II



from the bisaminomethylation reactions. Compound **6** was prepared by using *m*-aminophenol in place of *p*-aminophenol, compound **5** utilized *o*-aminophenol, and compound **23** utilized *p*-hydroxybenzylamine. Compound **25** was synthesized (Scheme II) by forming the amide of dimethyl 5-aminoisophthalate by the procedure of Weinreb.[3] Reduction to the methylamine with lithium aluminum hydride and reaction with 1,4-dichlorophthalazine afforded the product.

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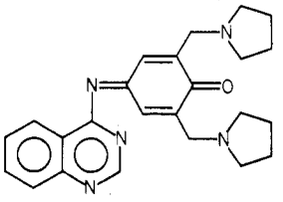
(1) Marshall, R. J.; Ojewole, R. J. *Toxicol. Appl. Pharmacol.* **1978**, *46*, 759. Wenzel, D. G.; Kleoppel, J. W. *Pharmacol. Res. Commun.* **1980**, *12*, 863. Nelson, P. H.; Strosberg, A. M.; Untch, K. G. *J. Med. Chem.* **1980**, *23*, 180.
(2) (a) Liangquan, L.; Zhixiang, Q.; Zhimin, W.; Yanlin, Z.; Guangsheng, D.; Guojun, H.; Xueyi, Y. *Sci. Sin. (Engl. Ed.)* **1979**, *22*, 1220. (b) Coordinations Changkelin Research Group, *Zhongua Yixue Tazhi* **1978**, *58* 84. (c) Chen, W.; Dong, Y.; Ding, G. *Yao Hsueh Hsueh Pao* **1979**, *14*, 710; *Chem. Abstr.* **1979**, *93*, 795*h*.
(3) Basha, A.; Lipton, M; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171.

0022-2623/83/1826-0808$01.50/0

Pharmacology. Antiarrhythmic activity was determined with adult mongrel dogs in a model described by Harris.[4] Parasympatholytic activity was assessed in the isolated guinea pig ileum.

Results and Discussion

The purpose of this study was to assess the effects on the antiarrhythmic and parasympatholytic activities of compounds that were the product of a systematic modification of the three regions of changrolin, as described earlier. In addition, we planned to prepare compounds that lacked the propensity for skin discoloration that is associated with changrolin. We speculated that the skin discoloration was due to the oxidation of the aminophenol moiety to a quinone-like structure (**2**). This process could result in the formation of chromolipids,[5] or the color could arise solely from **2** through extended resonance from the heterocycle through the aminoquinone, affording a strong chromophore.



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The antiarrhythmic activity of the compounds (Table I) was found to be lowest in those products that differed from changrolin at the phenolic region. Thus, **2**, **3**, and **5**, which lacked pyrrolidinylmethyl groups, were inactive, as was **6**, where each substituent was shifted by one carbon relative to the amine. Aminomethyl analogues were less active than the corresponding bis(aminomethyl) analogues (**10** and **22** vs **9** and **21**). The pyrrolidine group was superior to dimethylamino (**4** vs. **13**). The necessity of an aromatic group bonded to the aniline moiety was demonstrated by the inactivity of unsubstituted (**8**) and acetyl-substituted (**7**) derivatives. The linkage between the aromatic groups could also tolerate modification, as evidenced by the activity of the methylamino derivative **23**.

Antiarrhythmic activity generally was maintained in analogues that differed from changrolin at the heteroaromatic region of the molecule. Thus, phthalazine (**4**), 2-substituted quinoline (**21**), 1-substituted isoquinoline (**12**), 4-substituted pyridine (**24**), and 3-substituted pyridazine (**14**) could replace the quinazoline of changrolin, while a 2-pyrimidine (**15**) had low antiarrhythmic activity. The activity of 4-aminoquinolines was variable (**17** and **18** were active, while **19** and **20** had low activity). In the case of the dinitrogen heterocycles quinazoline and phthalazine, addition of an electron-donating group, methoxy, virtually eliminated antiarrhythmic activity (**11** and **16**), while the electron-withdrawing group chlorine resulted in retention of activity (**9**). For the quinoline derivatives (**17–20**), this pattern did not hold up. The addition of a fused benzene ring to a pyridazine (**14**), which is a quinazoline (**9**), resulted in a nearly 80% increase in activity, while the same process with a pyridine (**24**), leading to a quinoline (**20**), resulted in a near elimination of activity.

Ambiguous results were also evident in the parasympatholytic activities of the compounds. All of the compounds tested had parasympatholytic activity, though compounds that had low or no antiarrhythmic activity tended to have low parasympatholytic activity, while compounds having high antiarrhythmic activity tended to have high parasympatholytic activity, the one exception being **24**. The compounds having the best spectrum of activity (low parasympatholytic activity and high antiarrhythmic potency) were changrolin, **4**, **17**, and **24**. Active compounds that lack the ability for extended conjugation are **23** and **25**. Thus, while the bis(pyrrolidinylmethyl)-phenol pattern of changrolin appears to be optimal in this series, a wide latitude exists for the heteroaryl substituent for maintaining good antiarrhythmic activity.

Experimental Section

Pharmacological Evaluation. Coronary Ligation Arrhythmia. Ventricular arrhythmias were induced in adult mongrel dogs (10–15 kg) of either sex by two-stage ligation of the left anterior descending coronary artery.[4] On the following day a high percentage (90–100%) of ectopic beats existed. The test drug was infused intravenously at a rate of 0.3 (mg/kg)/min (base) until normal sinus rhythm or toxicity occurred. Normal sinus rhythm was defined as 90–100% normal complexes over a 5-min period.

Isolated Guinea Pig Ileum. Fasted, male Hartley guinea pigs (300–400 g) were killed by a blow to the head. A 1-cm segment of ileum was removed and placed in a bath containing physiological saline solution (in mmol/L: NaCl, 120; $NaHCO_3$, 25; KCl, 4.7; $MgSO_4$, 0.57; KH_2PO_4, 1.2; $CaCl_2$ 1.96; dextrose, 11.1) at 37 °C and gassed with 95% O_2/5% CO_2. One end of the ileal strip was impaled onto a platinum wire electrode. The other end was tied with a silk suture attached to a Gould Statham Model UC3 force-displacement transducer. Basal tension was set at 0.1–0.3 g, and phasic contractions were elicited by field stimulation pulses (100–150 V, 2.5-ms duration) delivered at a frequency of 0.2 Hz. After an equilibration period of approximately 60 min, tension development was assessed just before and during the steady-state response to the test drug at a concentration of 4 mg/L. Contractile tension in this preparation is due to the electrically stimulated release of acetylcholine from postganglionic parasympathetic nerve terminals and interaction of acetylcholine with postsynaptic receptors. Drug-induced reduction of contractile force, regardless of mechanism, was thus termed parasympatholytic activity.

Chemistry. Melting points were determined on a Thomas-Hoover melting point apparatus and were uncorrected. IR spectra were recorded on a Perkin-Elmer Model 283 spectrophotometer as KBr pellets. NMR spectra were determined on a Varian T-60A spectrometer in $CDCl_3$, Me_2SO-d_6, or CD_3OD with tetramethylsilane as a standard or in D_2O with 4,4-dimethyl-4-silapentane-5-sulfonate as a standard. Elemental analyses were performed either by our Analytical Chemistry Group or by Galbraith Laboratories, Knoxville, TN.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-quinazoline (Changrolin, 1). The compound was prepared in the manner described by Liangquan et al.,[2] mp 188–191 °C (lit.[2] mp 191–193 °C).

4-(4-Hydroxyanilino)quinazoline (2). The compound was prepared in the manner described by Liangquan et al.,[2] mp 249–251 °C (lit.[2] mp 252–254 °C).

1-(4-Hydroxyanilino)phthalazine (3). A mixture of 2.00 g (12.1 mmol) of 1-chlorophthalazine[6] and 2.64 g (24.2 mmol) of *p*-aminophenol in 40 mL of absolute ethanol was heated to reflux for 2 h. The precipitate was collected and successively washed with a saturated solution of $NaHCO_3$ and water. The proudct was crystallized from methanol: mp 245–247 °C. The HCl salt had mp >300 °C; NMR (D_2O) δ 7.03 (d, J = 8 Hz, 2 H), 7.40 (d, J = 8 Hz, 2 H), 8.0–8.6 (m, 4 H), 8.78 (s, 1 H). Anal. ($C_{14}H_{11}N_3O$·HCl) C, H, N, Cl.

1-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-phthalazine (4). A mixture of 4.65 g (19.5 mmol) of **3**, 6.5 mL of a 37% solution of formaldehyde, and 4.5 mL (54 mmol) of pyrrolidine in 3 mL of ethanol was stirred with warming for 3 h. The solvent was removed on a rotary evaporator, the product

(4) Harris, A. S. *Circulation* **1950**, *1*, 1318.
(5) Wolman, M. *Pathobiol. Annu.* **1980**, *10*, 253.
(6) Brasyumas, V.; Podzhyunas, A. *Med. Prom. SSSR* **1959**, *13*, 38; *Chem. Abstr.* **1959**, *53*, 16144*f*.

Table I. Antiarrhythmic and Parasympatholytic Activities of Substituted Phenols

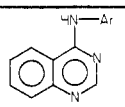
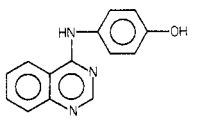
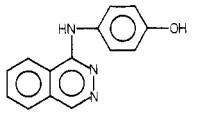
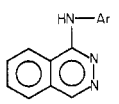
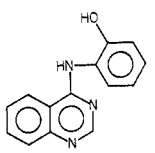
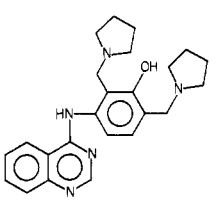
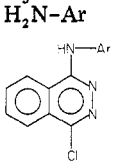
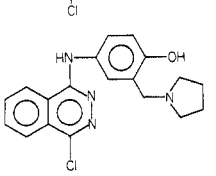
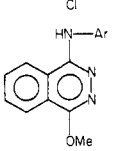
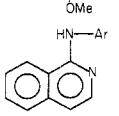
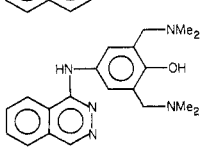
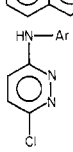
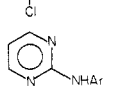
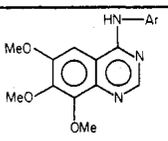
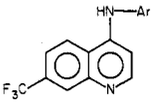
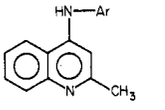
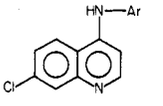
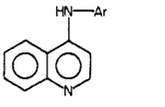
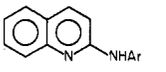
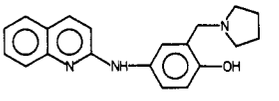
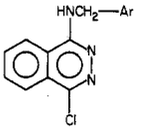
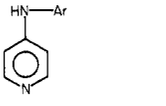
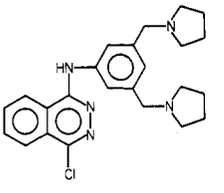
compd	structure	active dose in Harris dog,[a] mg/kg	N^b	% inhibn of guinea pig ileum contractile force at 4 mg/L[c]	N^d
1 (changrolin)		10.3 (4, 9, 19, 9)	4	43 ± 6	7
2		inactive to 30 mg/kg	2	13 ± 2	3
3		inactive to 30 mg/kg	2	23 ± 6	6
4		1.5 (1, 2)	2	83 ± 6	8
5		inactive to 30 mg/kg	2	48 ± 4	3
6		inactive to 22 mg/kg	1	21 ± 4	4
7	H_3CCONH-Ar	inactive to 30 mg/kg	1	X	
8	H_2N-Ar	inactive to 30 mg/kg	2	3 ± 6	3
9		2.5 (2, 3)	2	76 ± 8	6
10		17	1	65 ± 5	6
11		low activity[e]	2	84 ± 4	6
12		1.1 (1.0, 1.2)	6	48 ± 6	5
13		14	1	14 ± 5	3
14		10.5 (10, 11)	2	40 ± 8	8
15		low activity[g]	2	6 ± 1	3

Table I (*Continued*)

compd	structure	active dose in Harris dog,[a] mg/kg	N^b	% inhibn of guinea pig ileum contractile force at 4 mg/L[c]	N^d
16		low activity[f]	2	14 ± 5	3
17		3.0 (3, 3)	2	36 ± 5	3
18		11	1	X	
19		low activity[g]	1	27 ± 6	3
20		low activity[h]	1	19 ± 6	10
21		6 (6, 6)	2	50 ± 4	4
22		11	1	72 ± 12	3
23		4.5 (3, 6)	2	78 ± 5	6
24		8.5 (4, 13)	2	5 ± 0.3	3
25		3 (2, 4)	2	93 ± 3	4

[a] Average of experimental values, which are given in parentheses. [b] Number of Harris dog experiments. [c] Values are means plus or minus the standard error of the mean. X indicates that the experiment was not carried out. [d] Number of guinea pig ileum experiments. [e] Incomplete restoration of normal sinus rhythm up to 2 mg/kg when death occurred. [f] Incomplete or no effect to restore sinus rhythm up to 30 mg/kg. [g] Only partial restoration of normal sinus rhythm up to 12 mg/kg when loss of muscle tone occurred. [h] Only partial restoration of normal sinus rhythm up to 9 mg/kg when death occurred.

was dissolved in $CHCl_3$, and the solution was washed with water, dried ($MgSO_4$), and saturated with dry hydrogen chloride. The solvent was removed, and crystallization was effected with 2-propanol/ether, leaving bright-yellow crystals: mp 183–185 °C; NMR (Me_2SO-d_6) δ 1.7–2.3 (m, 8 H), 3.0–3.7 (m, 8 H), 4.55 (br s, 4 H), 7.88 (s, 1 H), 8.0–8.5 (m, 2 H), 9.0–9.4 (m, 2 H). Anal. ($C_{24}H_{20}N_5O$·3HCl·H_2O) C, H, N, Cl.

4-(2-Hydroxyanilino)quinazoline (5). The compound was prepared in the same manner as **3** by using *o*-aminophenol and 4-chloroquinazoline, in 71% yield. The free base was crystallized from EtOH/DMF. The HCl salt had mp 260–262 °C; NMR (Me_2SO-d_6) δ 6.9–7.6 (m, 4 H), 7.8–8.3 (m, 3 H), 8.9–9.1 (m, 2 H). Anal. ($C_{14}H_{11}N_3O$·HCl) C, H, N, Cl.

4-[2,4-Bis[(*N*-pyrrolidinyl)methyl]-3-hydroxyanilino]-quinazoline (6). The intermediate was prepared in the same manner as **3** by using *m*-aminophenol and 4-chloroquinazoline, in 85% yield, mp 231–233 °C. Aminomethylation was carried out as for **4**, yielding pale yellow crystals of the HCl hydrate: mp 230–232 °C; NMR (free base) ($CDCl_3$) δ 1.7–2.2 (m, 8 H), 2.3–2.8 (m, 8 H), 3.67 (s, 2 H), 3.73 (s, 2 H), 6.70 (s, 1 H), 7.2–8.0 (m, 4 H), 8.18 (s, 1 H), 8.65 (s, 1 H), 8.8–9.4 (m, 1 H). Anal. ($C_{24}H_{25}N_5O$·3HCl·1.75H_2O) C, H, N, Cl.

3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyacetanilide (7). The compound was prepared by aminomethylating 4-acetamidophenol in the same manner as **4**, in 67% yield: mp 93–96 °C. The HCl salt was white hydroscopic crystals: mp 73–76 °C; NMR (D_2O) δ 1.6–2.4 (m, 8 H), 2.2 (s, 3 H), 2.6–3.8 (m, 9 H), 4.45 (s, 4 H), 7.55 (s, 2 H). Anal. ($C_{18}H_{27}N_3O_2$·2.4HCl·0.5H_2O) C, H, N, Cl.

2,6-Bis[(*N*-pyrrolidinyl)methyl]-4-aminophenol (8). A solution of 100.0 g (0.315 mol) of **7** in 200 mL of 6 M HCl was heated to reflux for 3 h. The solution was basified with solid KOH to pH 11. The resulting solid was collected by filtration and washed with water and cold ether. Crystallization from ether

afforded a 42% yield of product as pale yellow needles: mp 105–106 °C. The HCl salt formed white crystals: mp 219–221 °C; NMR (Me_2SO-d_6) δ 1.6–2.2 (m, 8 H), 2.8–3.4 (m, 8 H), 4.23 (br s, 4 H), 7.32 (s, 2 H). Anal. ($C_{16}H_{25}N_3O$) C, H, N.

1-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-4-chlorophthalazine (9). The intermediate was prepared in the same manner as **3** by using 1,4-dichlorophthalazine. Aminomethylation of the intermediate as for **4** afforded the product as pale yellow crystals after medium-pressure liquid chromatography (MPLC) on silica gel (EtOAc/MeOH/NH_4OH, 9:1:0.01): mp 169–170 °C; NMR (CD_3OD) δ 1.6–2.1 (m, 8 H), 2.3–2.5 (m, 8 H), 3.75 (s, 4 H), 7.40 (s, 2 H), 7.9–8.6 (m, 4 H). Anal. ($C_{24}H_{28}ClN_5O$) C, H, N.

1-[3-[(*N*-Pyrrolidinyl)methyl]-4-hydroxyanilino]-4-chlorophthalazine (10). The compound was a byproduct from the synthesis of **9**: mp 157–158 °C; NMR ($CDCl_3$) δ 1.6–2.0 (m, 4 H), 2.4–2.8 (m, 4 H), 3.76 (m, 2 H), 6.3–8.2 (m, 9 H). Anal. ($C_{19}H_{19}N_4OCl$) C, H, N.

1-[3,4-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilinol]-4-methoxyphthalazine (11). A mixture of 2.7 g (6.2 mmol) of **9** and 3.7 g (69 mmol) of freshly prepared NaOMe (1.58 g of Na and MeOH) was heated to 120 °C under a nitrogen atmosphere for 18 h. The product was purified by MPLC (EtOAc/MeOH/NH_4OH, 1:1:0.01) and crystallized from $CHCl_3$/EtOAc, affording yellow crystals: mp 178–179 °C; NMR ($CDCl_3$) δ 1.6–2.2 (m, 8 H), 2.4–2.9 (m, 8 H), 3.77 (s, 4 H), 4.18 (s, 3 H), 7.1–7.5 (m, 2 H), 7.5–8.4 (m, 5 H). Anal. ($C_{25}H_{31}N_5O_2{\cdot}H_2O$) C, H, N.

1-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-isoquinoline (12). The compound was prepared in the same manner as **4** by using 1-chloroisoquinoline[7] in place of 1-chlorophthalazine: mp 95 °C; NMR (Me_2SO-d_6) δ 1.6–2.2 (m, 8 H), 2.8–3.4 (m, 8 H), 4.28 (s, 4 H), 5.4–7.0 (m, 5 H), 7.15 (d, J = 6 Hz, 1 H), 7.4–8.0 (m, 6 H), 8.4–8.8 (m, 1 H). Anal. ($C_{25}H_{30}N_4O{\cdot}HCl{\cdot}H_2O$) C, H, N.

1-[3,5-Bis[(dimethylamino)methyl]-4-hydroxyanilino]-phthalazine (13). The product was prepared in the same manner as **4**, by using dimethylamine in place of pyrrolidine: mp 195 °C (HCl salt); NMR (D_2O) δ 2.68 (s, 12 H), 4.18 (s, 4 H), 7.53 (s, 1 H), 7.9–9.0 (m, 4 H). Anal. ($C_{20}H_{25}N_5O{\cdot}3HCl$) C, H, N.

3-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-6-chloropyridazine (14). The compound was prepared in the same manner as **4**, by using 3,6-dichloropyridazine in place of 1-chlorophthalazine: mp 150–151 °C; NMR (Me_2SO-d_6) δ 1.4–2.0 (m, 8 H), 2.2–2.7 (m, 8 H), 3.7 (2, 4 H), 3.92 (s, 2 H), 7.07 (d, J = 9 Hz, 1 H), 7.33 (s, 2 H), 7.13 (d, J = 9 Hz, 1 H). Anal. ($C_{20}H_{26}N_5OCl$) C, H, N.

2-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]pyrimidine (15). The compound was prepared in the same manner as **4**, by using 2-chloropyrimidine in place of 1-chlorophthalazine: mp 171–172 °C; NMR (Me_2SO-d_6) δ 1.5–2.2 (m, 8 H), 2.3–2.8 (m, 8 H), 3.67 (s, 4 H), 4.0–4.8 (m, 2 H), 6.70 (t, J = 5 Hz, 1 H), 7.37 (s, 2 H), 8.37 (d, J = 5 Hz, 2 H). Anal. ($C_{20}H_{27}N_5O$) C, H, N.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-6,7,8-trimethoxyquinazoline (16). The compound was prepared in the same manner as **4**, by using 4-chloro-6,7,8-trimethoxyquinazoline in place of 1-chlorophthalazine: mp 189–191 °C; NMR (D_2O) δ 1.9–2.5 (m, 8 H), 3.1–3.9 (m, 8 H), 4.13 (s, 9 H), 4.45 (s, 4 H), 7.67 (s, 1 H), 7.80 (s, 2 H), 8.63 (s, 1 H). Anal. ($C_{27}H_{35}N_5O_4{\cdot}4HCl$) C, H, N.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-7-(trifluoromethyl)quinoline (17). The compound was prepared in the same manner as **4** by using 4-chloro-7-(trifluoromethyl)quinoline in place of 1-chlorophthalazine: mp 56–58 °C; NMR (D_2O) δ 1.8–2.7 (m, 8 H), 2.9–4.1 (m, 8 H), 4.67 (s, 4 H), 7.03 (d, J = 7 Hz, 1 H), 7.78 (s, 2 H), 8.0–8.8 (m, 4 H). Anal. ($C_{26}H_{29}N_4OF_3{\cdot}4HCl{\cdot}H_2O$) C, H, N.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-2-methylquinoline (18). A mixture of 5.0 g (18 mmol) of **8** and 3.23 (18.0 mol) of 2-ethyl-4-chloroquinoline was heated to between 130 and 145 °C for 1 h, making certain that the temperature did not exceed 145 °C. The product was purified by MPLC ($CHCl_3$/MeOH/NH_4OH, 9:1:0.01) and recrystallized from *i*-PrOH, yielding yellow crystals: mp 150–155 °C (HCl salt); NMR (free base) ($CDCl_3$) δ 1.6–2.0 (m, 8 H), 2.4–2.8 (m, 8 H), 2.48 (s, 3 H), 3.72 (s, 4 H), 6.50 (s, 1 H), 6.93 (s, 2 H), 7.3–8.0 (m, 4 H). Anal. ($C_{26}H_{32}N_4O{\cdot}HCl$) C, H, N.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-7-chloroquinoline (19). The compound was prepared in the same manner as **18** by using 4,7-dichloroquinoline in place of 2-methyl-4-chloroquinoline: mp 92 °C; NMR (D_2O) δ 1.7–2.5 (m, 8 H), 2.8–4.0 (m, 8 H), 4.53 (s, 4 H), 7.1–8.0 (m, 4 H), 8.0–8.6 (m, 2 H). Anal. ($C_{25}H_{29}N_4OCl{\cdot}4HCl{\cdot}3H_2O$) C, H, N.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-quinoline (20). The compound was prepared in the same manner as for **18** by using 4-chloroquinoline in place of 2-methyl-4-chloroquinoline: mp 67 °C; NMR (D_2O) δ 1.5–2.4 (m, 8 H), 2.6–3.8 (m, 8 H), 4.45 (s, 4 H), 7.1–8.5 (m, 8 H). Anal. ($C_{25}H_{20}N_4O{\cdot}4HCl{\cdot}2H_2O$) C, H, N.

2-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-quinoline (21). The compound was prepared in the same manner as **4**, by using 2-chloroquinoline in place of 1-chlorophthalazine: mp 64–66 °C; NMR (D_2O) δ 1.9–2.4 (8 H), 3.1–3.7 (m, 8 H), 4.53 (s, 4 H), 7.4–8.3 (m, 8 H). Anal. ($C_{25}H_{30}N_4O{\cdot}3HCl{\cdot}3H_2O$) C, H, N.

2-[3-[(*N*-Pyrrolidinyl)methyl]-4-hydroxyanilino]quinoline (22). The compound was a byproduct from the synthesis of **21**: mp 139–149 °C; NMR ($CDCl_3$) δ 1.6–2.0 (m, 4 H), 2.3–2.7 (m, 4 H), 3.75 (s, 2 H), 6.5–7.7 (m, 9 H). Anal. ($C_{20}H_{21}N_3O{\cdot}0.5H_2O$) C, H, N.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxyanilino]-pyridine (24). The compound was prepared in the same manner as **4** by using 4-chloropyridine in place of 1-chlorophthalazine: mp 158–159 °C; NMR ($CDCl_3$) δ 1.6–2.1 (m, 8 H), 2.3–2.8 (m, 8 H), 3.72 (s, 4 H), 6.00 (br s, 2 H), 6.5–6.7 (m, 2 H), 6.92 (s, 2 H), 7.7–8.3 (m, 2 H). Anal. ($C_{21}H_{28}N_4O$) C, H, N.

4-[[3,5-Bis[(*N*-pyrrolidinyl)methyl]-4-hydroxybenzyl]-amino]-1-chlorophthalazine (23). *p*-Hydroxybenzylamine was formed by heating to reflux *p*-methoxybenzylamine in concentrated HBr. The solution was neutralized with solid KOH, and the product was collected by filtration. The compound was prepared in the same manner as **3** by using *p*-hydroxybenzylamine and 1,4-dichlorophthalazine: mp 197–199 °C; NMR (Me_2SO-d_6) δ 1.5–2.3 (m, 8 H), 2.7–3.6 (m, 8 H), 4.43 (br s, 4 H), 7.72 (s, 2 H), 8.0–8.4 (m, 3 H), 9.1–9.4 (m, 1 H). Anal. ($C_{25}H_{30}N_5OCl{\cdot}3HCl{\cdot}1.5H_2O$) C, H, N.

4-[3,5-Bis[(*N*-pyrrolidinyl)methyl]anilino]-1-chlorophthalazine (25). By the procedure of Weinreb[3] a solution of 6.5 mL of pyrrolidine in 100 mL of CH_2Cl_2 under a nitrogen atmosphere was treated with 39 mL (78 mmol) of trimethylaluminum. After gas evolution had ceased, 8.2 g (39 mmol) of dimethyl 5-aminoisophthalate (5-aminoisophathalic acid in HCl/MeOH) was added, and the solution was heated to reflux for 38 h. The cooled solution was slowly added to ice–water. The aqueous mixture was filtered, the filtrate was and extracted with $CHCl_3$. The combined extracts were dried ($MgSO_4$), and the solvent was removed, leaving 8.9 g of solid product: NMR ($CDCl_3$) δ 1.6–2.0 (m, 8 H), 2.9–3.6 (m, 8 H), 6.67 (s, 2 H), 6.77 (s, 1 H).

A mixture of 5.0 g (16 mmol) of crude product and 2.4 g (6.3 mmol) of lithium aluminum hydride in 100 mL of ether under a nitrogen atmosphere was heated to reflux for 4 h. The solution was cooled in an ice bath and quenched with water. The aqueous mixture was filtered, and the filtrate was extracted with ether. The combined extracts were dried ($MgSO_4$), and the solvent was removed, leaving a yellow oil. Distillation with a Kugelrohr apparatus (90 °C oven temperature, 0.1 mm) afforded a colorless oil: NMR ($CDCl_3$) δ 1.4–2.1 (m, 8 H), 2.1–2.7 (m, 8 H), 3.47 (s, 4 H), 3.4–4.0 (m, 2 H), 6.4–6.7 (m, 3 H).

A mixture of 5.00 g (19.3 mmol) of the product and 3.84 g (19.3 mmol) of 1,4-dichlorophthalazine under a nitrogen atmosphere was heated to 160 °C (oil bath temperature) for 3 h. Purification of the product by silica gel column chromatography ($CHCl_3$/MeOH/NH_4OH, 9:1:0.05) afforded **25** as yellow crystals: mp 180–183 °C; IR (KBr) 1620, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.4–2.0 (m, 8 H), 2.1–2.7 (m, 8 H), 3.57 (s, 4 H), 6.8–8.4 (m, 8 H). Anal. ($C_{24}H_{28}H_5Cl$) C, H, N.

Registry No. **2**, 34923-98-3; **3**, 85236-43-7; **3**·HCl, 85236-44-8; **4**·3HCl, 85236-45-9; **5**, 85236-46-0; **5**·HCl, 85236-47-1; **6**, 85236-48-2; **6**·3HCl, 85236-49-3; **7**, 81079-95-0; **7**·HCl, 85236-50-6; **8**, 85236-51-7;

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8·HCl, 85236-52-8; **9**, 85236-53-9; **10**, 85236-54-0; **11**, 85236-55-1; **12**·HCl, 85236-56-2; **13**·3HCl, 85236-57-3; **14**, 85236-58-4; **15**, 85236-59-5; **16**·4HCl, 85236-60-8; **17**·4HCl, 85236-61-9; **18**·HCl, 85236-62-0; **19**·4HCl, 85236-63-1; **20**·4HCl, 85236-64-2; **21**·3HCl, 85236-65-3; **22**, 85236-66-4; **23**·3HCl, 85236-67-5; **24**, 85236-68-6; **25**, 85236-69-7; 3,5-bis[(*N*-pyrrolidinyl)carbonyl]benzenamine, 85236-70-0; 3,5-bis[(*N*-pyrrolidinyl)methyl]benzenamine, 85236-71-1; 1-chlorophthalazine, 5784-45-2; *p*-aminophenol, 123-30-8; pyrrolidine, 123-75-1; 4-chloroquinoazoline, 5190-68-1; *o*-aminophenol, 95-55-6; *m*-aminophenol, 591-27-5; 4-acetamidophenol, 103-90-2; 1,4-dichlorophthalazine, 4752-10-7; 1-chloroisoquinoline, 19493-44-8; 3,6-dichloropyridazine, 141-30-0; 4-chloro-6,7,8-trimethoxyquinazoline, 33371-00-5; 4-chloro-7-(trifluoromethyl)-quinoline, 346-55-4; 2-ethyl-4-chloroquinoline, 7176-10-5; 4,7-dichloroquinoline, 86-98-6; 4-chloroquinoline, 611-35-8; 2-chloroquinoline, 612-62-4; 4-chloropyridine, 626-61-9; *p*-hydroxybenzylamine, 696-60-6; *p*-methoxybenzylamine, 2393-23-9; 5-aminoisophathalic acid, 99-31-0; changrolin, 72063-47-9.

1-(Aminomethyl)-6,7-dihydroxytetralin Derivatives: Synthesis and Assessment of Dopamine-Like Effects

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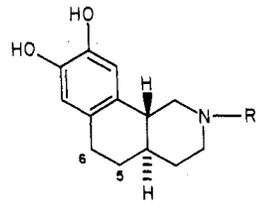
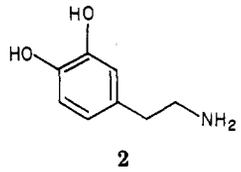
The title compounds were designed as flexible congeners of *trans*-octahydrobenz[*h*]isoquinoline, in which the dopamine moiety can exist in the α conformation. Extremely low dopamine-like effects in the title series in the cat cardioaccelerator nerve assay paralleled low activity in the *trans*-octahydrobenz[*h*]isoquinoline compounds and was consistent with a prior proposal of the presence of a bulky region on the dopamine receptor(s).

In a prior paper,[1] rigid congeners of the α conformer of dopamine derived from a *trans*-octahydrobenz[*h*]isoquinoline system, **1**, were reported to exhibit an extremely



1, R = H, Me, Et, *n*-Pr

low order of potency in inhibition of transmission in the cat cardioaccelerator nerve, an assessment of peripheral presynaptic dopaminergic effect. The compounds lowered blood pressure and heart rate in anesthetized cats, effects that were prevented by haloperidol. It was speculated[1] that carbons 5 and 6 of **1** represent a region of molecular bulk not present in molecules of other systems that are potent dopaminergic agonists and that also represent α conformations of dopamine: dopamine itself (**2**), 2-



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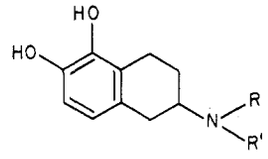

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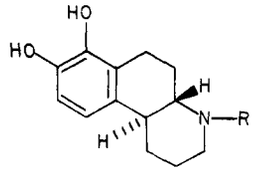

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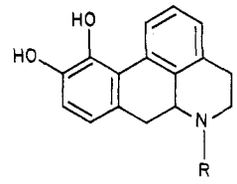
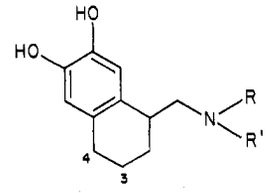


4

aminotetralins (**3**), apomorphine homologues (**4**), and octahydrobenzo[*f*]quinolines (**5**). This region of bulk in **1** may prevent optimal interaction of the molecule with dopamine receptors, and it was inferred[1] that the complementary region of the dopamine receptor includes some degree of physical bulk.

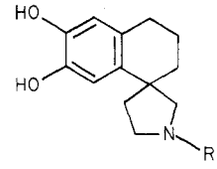
Further, to assess the low biological activity of series **1**, we designed a simpler system, the 6,7-dihydroxy-1-(aminomethyl)tetralin (**6**). Reasonable conformations exist for



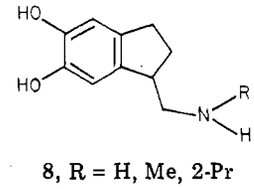
6, R, R′ = combinations of H, Me, Et, *n*-Pr, and 2-Pr

6 in which the dopamine moiety assumes an α conformation, with appropriate torsion angles very similar to those observed in **1**. Carbons 3 and 4 in the target system **6** are analogous to carbons 5 and 6 in **1**.

Crooks et al.[2] reported that the spirotetralin system **7**



7, R = H, Me



8, R = H, Me, 2-Pr

showed only extremely weak dopamine-like effects. Dreiding models reveal that the dopamine moiety in **7** cannot attain the catechol ring-amino nitrogen antiperiplanar disposition characteristic of the biologically significant α conformer of dopamine. Gaino et al.[3] claimed adrenergic β_2 activity for the 1-(aminomethyl)indan derivatives **8**. However, no pharmacological data for these could be found in the literature. Nichols et al.[4] have re-

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(3) Gaino, M.; Yamamura, S.; Saito, J.; Ohashi, M. Japanese Patent 7 805 146 (Cl.CO7C87/06), 1978; *Chem. Abstr.* **1978**, *88*, 169822.

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