Design, Synthesis, and Pharmacological Activities of 2-Substituted 4-Phenylquinolines as Potential Antidepressant Drugs†

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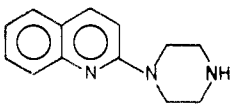
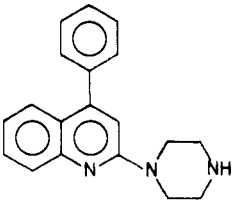
This work represents the design, synthesis, and pharmacological testing of 4-phenylquinoline derivatives as potential antidepressants. Various modifications of substituents at the 2-position of the quinoline ring were tried, and two main series of derivatives were synthesized. In the first series, an open (dialkylamino)alkyl chain is linked to the 2-position of the quinoline ring by isosteres. The second approach involved the synthesis of a novel analogue of trazodone with a 4-phenylquinoline grouping replacing the chlorophenyl group of trazodone. The potential antidepressant activity of these new compounds has been demonstrated by their antagonism to the reserpine-induced hypothermia in mice. Both length of the side chain and isosteric displacements within the side chain affect the value of the ED_{50} obtained. Compounds having three atoms separating the terminal nitrogen from the quinoline ring were found to be more active than those with four atoms. The 2-thia derivatives were devoid of antidepressant activity. Replacement of the open side chain at the 2-position of the quinoline ring by piperazine or substituted piperazines resulted in new compounds that are slightly more potent than imipramine.

For more than two decades, the tricyclic antidepressants, represented by imipramine as the prototype, were the most widely prescribed drugs for treatment of depression. Besides their anticholinergic and cardiotoxic side effects, most of the available tricyclic antidepressants require a long treatment of 3–5 weeks to demonstrate their clinical therapeutic action. In the late 1970s, compounds like iprindole, mianserin, and trazodone were introduced as new drugs with atypical pharmacological profiles, less anticholinergic and cardiotoxic side effects than the typical ones, but still with delayed onset of action.[1,2]

Quipazine (I) was found to have some activities in common with the tricyclic antidepressants.[3,4] Hino and his



I

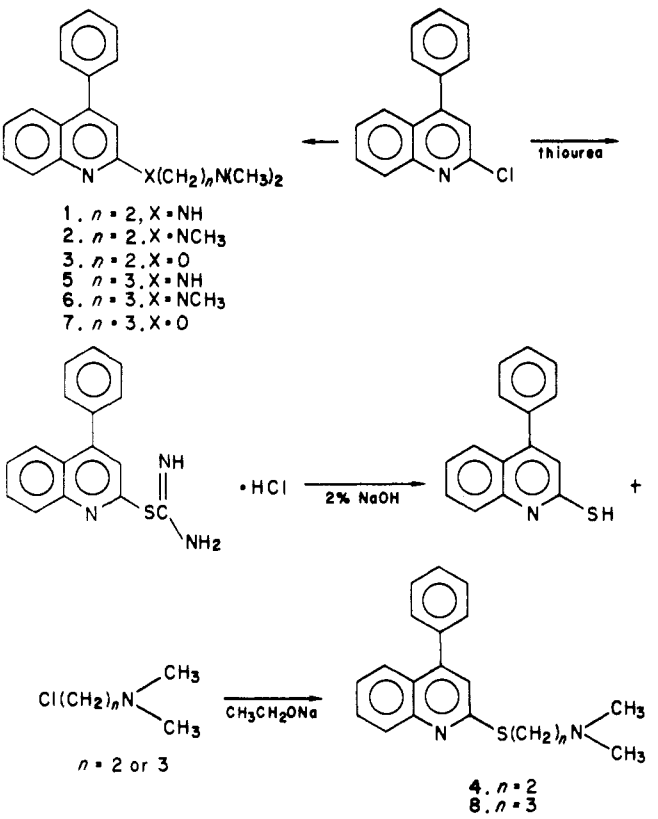


II

group[4] synthesized and determined the antidepressant activities in mice of 2-substituted 4-phenylquinoline derivatives (II). They found that introduction of a phenyl group at the 4-position of the quinoline of quipazine resulted in an increase in pharmacological activity. Moreover, it appears from their studies that the terminal basic nitrogen is essential for antidepressant activity as indicated by the lack of such activity upon replacing the piperazine moiety with morpholine or dimethylamino groups.

These observations have prompted us to design and synthesize two series of compounds that embody the 4-phenylquinoline skeleton and various substitutents at the 2-position of the quinoline ring. In the first series, an open-chain (dialkylamino)alkyl group is linked to the 2-position of the quinoline by either NH, NCH_3, CH_2, O, or S. Besides offering various discriminating physicochemical properties, these modifications will enable the study of the effects on the pharmacological activity of both the isosteric replacement of the atom directly attached to the quinoline ring and the distance between the terminal basic nitrogen (dialkylamino group) and the quinoline ring. The second approach in our work is to synthesize a novel trazodone analogue with the lipophilic 4-phenylquinoline moiety

Scheme I



replacing the chlorophenyl group of trazodone.

Synthesis. The key intermediate is 2-chloro-4-phenylquinoline, which was prepared according to a reported procedure.[6] It was reacted with the appropriate primary or secondary amine, or with the sodium derivative of the amino alcohol to give compounds 1–3 and 5–7 (Scheme I).

Under such conditions, however, the thiols of Scheme I underwent oxidation to the disulfide. An alternative

† Taken in part from: Alhaider, A. A. Ph.D. Dissertation, USC, 1984. A summary of this work was presented at the 131st APhA Meeting, Montreal, Canada, May, 1984.

(1) Hollister, L. E. *Drugs* **1981**, *22*, 129.
(2) Bryant, S. G.; Ereshefsky, L. *Clin. Pharm.* **1982**, *1*, 406.
(3) Rodriguez, R.; Pardo, E. *Psychopharmacologia* **1971**, *21*, 81.
(4) Hino, K. Furukawa, K.; Naga, Y.; Uno, H. *Chem. Pharm. Bull.* **1980**, *28*, 2618.
(5) Houlihan, W. J.; Gogerty, J. H.; Parrino, V. A.; Ryan, E. *J. Med. Chem.* **1983**, *26*, 765.
(6) Kwon, S.; Isagawa, K. *Yoki Gosei Kagaku Shi* **1973**, *31*, 313.

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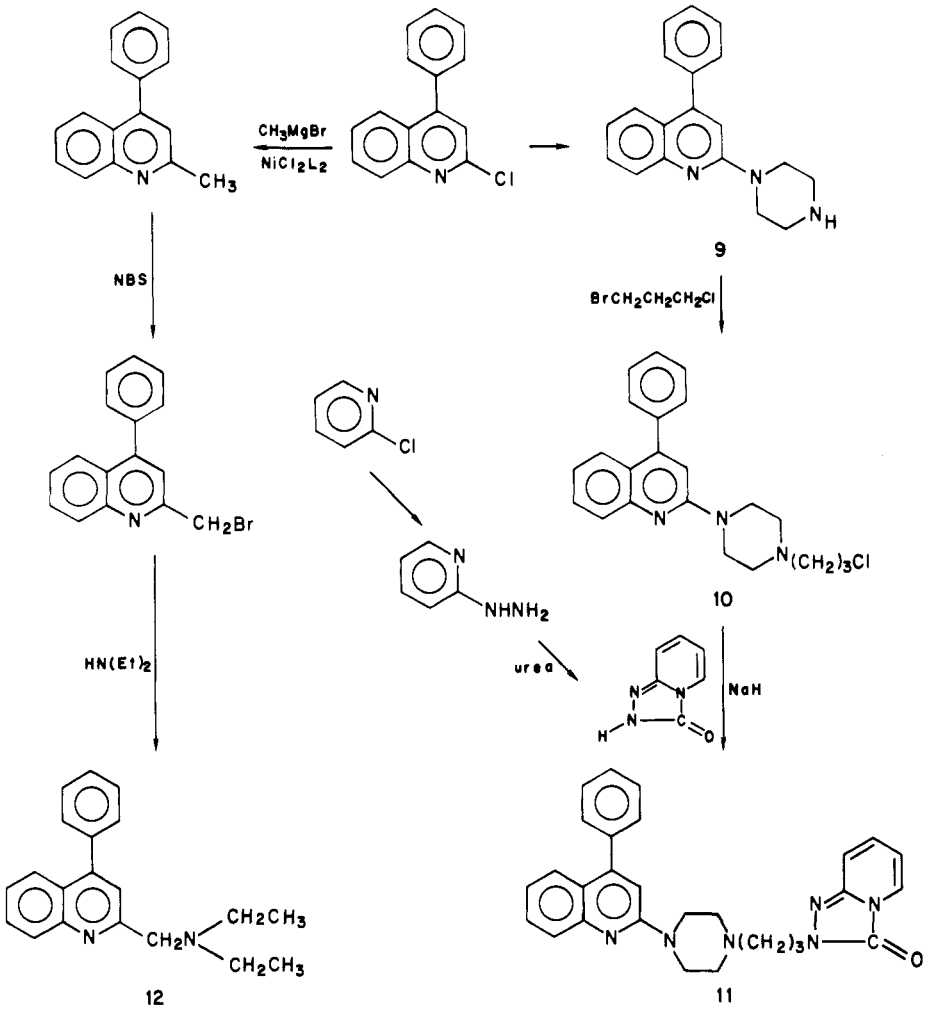
Scheme II



route was thus designed by forming the sodium derivative of the quinoline-2-thiol derivative as a nucleophile that was reacted with the aminoalkyl halide to give compounds **4** and **8**.

For synthesis of Compound **12** (Scheme II), the quinaldine derivative was prepared by cross-coupling of the appropriate Grignard Reagent with the above intermediate, using dichloro[1,3-bis(diphenylphosphino)propane]-nickel(II) (L_2NiCl_2) as a catalyst. Bromination of 4-phenylquinaldine to the corresponding bromomethyl derivative was achieved by the use of *N*-bromosuccinimide (NBS) in carbon tetrachloride. Reaction of the bromomethyl derivative with diethylamine gave the required compound **12**.

The trazodone-type analogue, compound **11** (Scheme II), was obtained through a multistep reaction. A mono N-substituted piperazine, compound **9**, was formed through reaction of the key intermediate with excess piperazine in toluene. The product was then reacted with 3-chloro-1-propane to give the N,N-disubstituted piperazine derivative **10**, which was then condensed with the sodium derivative of triazolopyridine-3-one intermediate to give compound **11**.

Biology. Antidepressant activities of these new compounds were measured by their antagonism to reserpine-induced hypothermia in mice, and the ED_{50} values of seven of these compounds were found to be in the range of 12.0–42.2 mg/kg, ip.

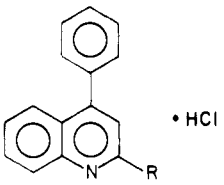
From Table I, it seems that both the distance between the terminal nitrogen and the 4-phenylquinoline nucleus as well as the isosteric displacement of the atom directly attached to the ring play a significant role on antagonizing effects of reserpine-induced hypothermia. Compounds **1–3** are equipotent to or slightly stronger then imipramine, while the thia analogue is less potent. Increasing the length of the side chain resulted in a greater loss of potency as shown by compounds **5–8**. It appears, therefore, that a distance of three atoms between the terminal nitrogen of the side chain and the 4-phenylquinoline skeleton is required for these compounds to show an optimal antagonist effect toward reserpine-induced hypothermia.

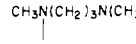
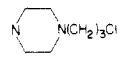
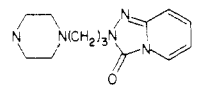
Isosteric replacements of the atoms directly linked to the 2-position of the quinoline ring resulted in analogues that differ not only in their antidepressant activity but also in their acute activity as represented by their LD_{50} values. Thus, although replacement of NH by NCH_3 or O has no significant effect on the ED_{50} value as indicated by the Student's t-test at 95% confidence levels, it offers compound **3**, which has a better therapeutic index (TI) than **1** (10.9 vs. 3.9). The thia analogue, however, has significantly lower antidepressant activity but is also less toxic relative to compounds **1** or **2**.

Compound **9**, originally reported as a potent antidepressant drug by Hino et al.,[4] has a distance of three atoms between the terminal nitrogen and the 4-phenylquinoline skeleton and acts as a reserpine antagonist. Compound **10**, with a 3-chloropropane moiety attached to the secondary nitrogen of **9**, was as effective as **9** in antagonizing the hypothermia induced by reserpine and with a better therapeutic index (TI: 21.3 vs. 12.4).

It seems that the introduction of the phenyl group at the 4-position of the quinoline ring enhances the antihy-

Table I. Pharmacological and Toxicological Activities of Compounds 1–12



compd	R	antihypothermia ED_{50} (ip), mg/kg (95% CL)[a]	LD_{50} (ip), mg/kg (±SD)[b]	therapeutic index[c]
1	$NH(CH_2)_2N(CH_3)_2$	26.0 (19.2–32.8)	102.0 (8.9)	3.92
2	$(CH_3)N(CH_2)_2N(CH_3)_2$	27.0 (22.4–31.6)	98.0 (13.2)	3.63
3	$O(CH_2)_2N(CH_3)_2$	18.5 (11.6–25.4)	202.3 (21.5)	10.94
4	$S(CH_2))_2N(CH_3)_2$	42.1 (35.0–49.2)	198.0 (16.4)	4.70
5	$NH(CH_2)_3N(CH_3)_2$	>50.0	100.0 (17.3)	
6		>50.0	110.0 (12.0)	
7	$O(CH_2)_3N(CH_3)_2$	>50.0	200.0 (18.2)	
8	$S(CH_2)_3N(CH_3)_2$	>50.0	189.0 (12.6)	
9		12.0 (3.4–20.6)	152.0 (23.7)	12.67
10		18.0 (9.6–26.4)	385.0 (18.6)	21.40
11		40.2 (32.5–47.9)	390.0 (21.2)	9.70
12	$-CH_2N(C_2H_5)_2$	>50.0	163.0 (15.0)	7.76
imipramine		21.0 (16.1–25.9)	163.0 (15.0)	7.76
quipazine		35.4 (27.5–43.3)	135 (17.2)	3.81
trazodone		>50.0		

[a] 95% confidence limit. [b] S.D. = standard deviation. [c] LD_{50}/ED_{50}.

pothermic activity. Thus, the removal of such a group from compound 9 offers quipazine (I), which is less potent than **9**. Introduction of a triazolopyridine moiety to **10** offered a trazodone analogue (**11**) with a reduction in the pharmacological activity, but also lower toxicity to a TI of 7.76 for imipramine. Decreasing the distance between the terminal nitrogen and the quinoline ring as shown by **12**, however, resulted in a loss of the antidepressant activity.

In conclusion, some of these new quinoline derivatives have been shown to be as potent or slightly more potent than imipramine as measured by their antagonistic effect toward reserpine-induced hypothermia. Further, in vitro studies that involve the effects of these new drugs on the uptake of norepinephrine and serotonin into the presynaptic cleft as well as behavioral studies are in progress and will be reported elsewhere.

Experimental Section

Proton magnetic resonance (^1H NMR) spectra were obtained with a JEOL FX 90 (Fourier transform) spectrometer using deuteriochloroform or acetone-d_6 as solvents and tetramethylsilane as internal standard. Melting points were determined with a Thomas-Hoover capillary apparatus and are corrected. Infrared spectra were measured on a Beckman IR-4210 spectrophotometer. Elemental analyses were done at the Chan-Shan Institute of Science and Technology, Taiwan. The percentage of carbon, hydrogen, and nitrogen are all within ±0.4% of the theoretical value.

2-Chloro-4-phenylquinoline. This major intermediate was prepared according to the published procedure[6] with an overall yield of 75%.

2-Mercapto-4-phenylquinoline. The procedure of Renerew[7] was adopted, except 2-chloro-4-phenylquinoline was used in lieu of 2-chloroquinoline with an overall yield of 88%.

1-(4-Phenyl-2-quinolyl)-2,2-dimethylethylenediamine (1). A solution of 4.8 g (0.02 mol) of 2-chloro-4-phenylquinoline in 7.04 g (0.08 mol) of *N,N*-dimethylethylenediamine was heated under reflux in an oil bath for 4–6 h. The reaction mixture was cooled to room temperature and was shaken three times with cold water to remove the unreacted amine. The crude product was recrystallized from benzene–hexane to give large white hexagonal crystals: yield 4.74 g (81%); mp 98 °C. Anal. ($C_{19}H_{21}N_3$) C, H, N.

1-(4-Phenyl-2-quinolyl)-1,2,2-trimethylethylenediamine Dihydrochloride (2). To 4.8 g (0.02 mol) of 2-chloro-4-phenylquinoline was added 4.8 g (0.08 mol) of *N,N',N'*-trimethylethylenediamine, and the mixture was kept under reflux on an oil bath for 4–6 h. After cooling, the oily residue was shaken several times with cold distilled water to remove any unreacted diamine. The crude residue was chromatographed over silica gel with benzene followed by chloroform as eluants. The free base was obtained from the chloroform eluate as a thick oil. The hydrochloride salt was obtained by passing dry HCl into an ethereal solution of the product where it precipitated as white crystals that were recrystallized from 2-propanol: yield 4.9 g (87%); mp 100–101 °C. Anal. ($C_{20}H_{23}N_3 \cdot 2HCl \cdot 3^1/_2H_2O$) C, H, N.

4-Phenyl-2-[2,2-(dimethylamino)ethoxy]quinoline Hydrochloride (3). Sodium metal, 1.8 g (0.079 mol), was dissolved in 7.12 g (0.08 mol) of *N,N*-dimethylethanolamine in a 50-mL flask; 4.8 g (0.02 mol) of 2-chloro-4-phenylquinoline was added portionwise to the solution, and the mixture was heated under reflux in an oil bath for 4 h. The reaction mixture was then cooled and washed three times with cold water to remove any unreacted water-soluble starting material. The remaining residue was dissolved in chloroform and chromatographed on silica gel with benzene followed by chloroform. The chloroform fractions were combined and evaporated to dryness, and the thick oil obtained was dissolved in dry ether, and dry HCl gas was passed to produce the hydrochloride salt as a white precipitate. This precipitate was filtered and recrystallized from 2-propanol: 4.3 g (70%); mp 152–153 °C. Anal. ($C_{19}H_{20}N_2O \cdot HCl$) C, H, N.

4-Phenyl-2-quinolyl (*N,N*-Dimethylamino)ethyl Sulfide Hydrochloride (4). 2-Mercapto-4-phenylquinoline, 4.76 g (0.02 mol), was dissolved in sodium ethoxide solutio prepared from 0.70 g (0.03 mol) of Na metal and 100 mL of absolute alcohol. To this solution was added an aqueous alcoholic solution of 10 g (0.08 mol) of 2-(dimethylamino)ethyl chloride dropwise. The cloudy

(7) Renerew, A. *J. Am. Chem. Soc.* **1946**, *68*, 1433.

mixture was clarified by the addition of a few drops of distilled water and was kept under reflux in an oil bath for 6 h. The mixture was cooled, 200 mL of distilled water was added, and the resultant mixture was extracted with chloroform, 3 × 50 mL. The chloroform extract was then washed several times with water, dried over anhydrous $MgSO_4$, and evaporated to dryness. The crude residue was chromatographed over silica gel and eluted with benzene followed by chloroform. The chloroform fractions containing the pure product were combined and evaportated to dryness under reduced pressure. The hydrochloride salt was obtained by passing dry HCl gas into an ethereal solution of the product where it precipitated as yellowish crystals. It was recrystallized from 95% ethanol: yield 5.2 g (72%); mp 216–217 °C. Anal. ($C_{19}H_{20}N_2S$·HCl) C, H, N.

1-(4-Phenyl-2-quinolyl)-3,3-dimethylpropylenediamine Hydrochloride (5). The same procedure mentioned for synthesizing 1 was used, with the exception of not getting the solid base upon attempted crystallization from benzene and hexane. The crude product was, therefore, chromatographed over silica gel with benzene followed by chloroform. The chloroform fractions were mixed together, evaporated to dryness, and dissolved in dry ether. The hydrochloride salt was precipitated by passing dry HCl gas through the ethereal solution of the free base: yield 82%; mp 174–175 °C. Anal. ($C_{20}H_{23}N_3HCl·H_2O$) C, H, N.

1-(4-Phenyl-2-quinolyl)-1,3,3-trimethylpropylenediamine Hydrochloride (6). The same procedure for preparing **2** was followed without any further modification: yield 82%, mp 163–164 °C. Anal. ($C_{21}H_{25}N_3$·HCl·H_2O) C, H, N.

4-Phenyl-2-[3,3-(dimethylamino)propoxy]quinoline Hydrochloride (7). The same method used for the synthesis of **3** was utilized: yield 60%; mp 203–204 °C. Anal. ($C_{20}H_{22}N_2O$·HCl·H_2O) C, H, N.

4-Phenylquinaldine (Scheme II). This compound was synthesized in a manner similar to that used in preparing quinaldine.[8] A three-necked flask filled with septums and a condenser was degassed and flushed with nitrogen several times, and the gas outlet was connected to a mercury trap (U-tube) to relieve the pressure buildup during the reaction. 2-Chloro-4-phenylquinoline, 4.8 g (0.02 mol), and 100 mg of L_2NiCl_2 (L_2 = $(C_6H_5)_2P(CH_2)_3P(C_6H_5)_2$) were mixed with 100 mL of dry ether, and the system was then kept under nitrogen. The flask was cooled in an ice bath, and 2.57 g (0.022 mol) of CH_3MgBr was introduced to the contents through a syringe. The reaction mixture was allowed to come to room temperature, and stirring was continued for 24 h. The mixture was then poured into a saturated solution of ammonium chloride (40 mL), and the ether layer was dried over anhydrous $MgSO_4$ and evaporated to dryness under reduced pressure (water aspirator) at ambient temperature. A violet powder was formed: 4.2 g (86%); mp 88 °C. Anal. ($C_{16}H_{13}N$) C, H, N.

2-(Bromomethyl)-4-phenylquinoline. A solution 2.22 g (0.01 mol) of 4-phenylquinaldine and 3.19 g (0.018 mol) of *N*-bromosuccinimide in 60 mL of dry CCl_4 was heated under reflux for 10–20 h in an oil bath.[9] The precipitate was filtered off and the mother liquor evaporated to dryness under reduced pressure to give the product as a thick oil that was used directly in the next step without further purification.

4-Phenyl-2-[(*N*,*N*-diethylamino)methyl]quinoline Hydrochloride (12). A 2.5-g portion (0.009 mol) of the crude 2-(bromomethyl)-4-phenylquinoline was dissolved in dry toluene, 1.46 g (0.02 mol) of diethylamine was added, and the resultant mixture was heated in an oil bath at 80 °C for 4 h. The solvent was removed under reduced pressure, and the remaining residue was dissolved in chloroform and washed several times with water to remove the unreacted diethylamine. The product was chromatographed on silica gel and eluted with benzene followed by chloroform. The chloroform fractions were combined and evaporated to dryness. The hydrochloride salt of the final product was obtained by passing dry HCl gas into an ethereal solution of the combined fractions to give a brownish precipitate that was recrystallized from alcohol and ether: yield 1.23 g (45%); mp 172–174 °C. Anal. ($C_{20}H_{22}N_2$·HCl) C, H, N.

1-(4-Phenyl-2-quinolyl)piperazine (9). A 4.8-g sample (0.02 mol of 2-chloro-4-phenylquinoline, 6.88 g (0.08 mol) of piperazine, and 1.12 g (0.02 mol) of finely powdered KOH were mixed with 100 mL of toluene. The mixture was heated under reflux in an oil bath for 4 h. After cooling, 200 mL of distilled water was added and the organic layer shaken several times with water to remove unreacted piperazine. The solvent was then removed under reduced pressure, and the precipitate formed was recrystallized from 95% ethanol to give a yellowish powder: yield 5.16 g (85%); mp 98–100 °C. Anal. ($C_{19}H_{19}N_3$) C, H, N.

4-(ω-Chloropropyl)-1-(4-phenyl-2-quinolyl)piperazine Hydrochloride (10). To a solution of 5.81 g (0.02 mol) of 1-(4-phenyl-2-quinolyl)piperazine in 50 mL of toluene were added 12.52 g (0.08 mol) of 3-chloro-1-bromopropane and 1.12 g (0.02 mol) of finely powdered KOH. The mixture was heated under reflux in an oil bath for 4 h. The reaction mixture was shaken three times with water and dried over anhydrous $MgSO_4$, and the solvent was removed under reduced pressure. The crude residue was chromatographed on a silica gel column with benzene–diethylamine (95:5) as an eluant. The product was dissolved in dry ether, and dry HCl gas was passed through the solution to precipitate the hydrochloride salt as white crystals that were then recrystallized from 85% ethanol: yield 5.40 g (85%); mp 257 °C. Anal. ($C_{22}H_{23}N_3$·HCl·H_2O) C, H, N.

2-Pyridylhydrazine (Scheme II). The procedure of Fargher and Furness[10] was utilized with slight modification. A 23-g portion (0.2 mol) of 2-chloropyridine was mixed with a large excess (110 mL) of hydrazine hydrate and the resultant mixture heated under reflux in a water bath for 6 h. After cooling, the mixture was extracted twice with 100 mL of ether. The aqueous layer was evaporated to dryness under reduced pressure to remove unreacted hydrazine hydrate. The remaining residue was mixed with 40 mL of water, and 2 g of KOH was added. The alkaline layer was extracted with 100 mL of ether to take up the reaction product as well as unreacted 2-chloropyridine. The total ether extracts were combined, dried over anhydrous $MgSO_4$, and kept in the freezer. A white crystalline powder of the product was formed that melted at 46–47 °C.

1,2,4-Triazolo[4,3-*a*]pyridin-3(2*H*)-one. This compound was prepared according to the procedure of Kauffmann and his group.[11] The identity of this compound was confirmed by comparison with an authentic sample from Professor Bruno Silvestrini of Angelini Research Institute.

2-[3-[4-[2-(4-Phenylquinolyl)]-1-piperazinyl]propyl]-1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one Hydrochloride (11). A 2-g portion (0.015 mol) of 1,2,4-triazolo[4,3-*a*]pyridin-3(2*H*)-one was dissolved in 40 mL of xylene with the aid of heat, 1 g (0.04 mol) of NaH (50% NaH in oil suspension that was washed three times with dry xylene under nitrogen) was added, and the mixture was heated under reflux in an oil bath for 1 h. A solution of 2 g (0.0055 mol) of 4-(ω-chloropropyl)-1-(4-phenyl-2-quinolyl)-piperazine in 20 mL of xylene was added dropwise to the reaction mixture, and thereafter the mixture was heated under reflux with continuous stirring at 150 °C for 20 h. After cooling, the mixture was filtered and the mother liquor was washed several times with 2% NaOH to remove any unreacted triazolopyridine. The xylene was evaporated under reduced pressure, and the residue was chromatographed on silica gel and eluted first with benzene and then with a mixture of benzene and diethylamine (95:5) followed by chloroform. The chloroform fractions were combined together and evaporated to dryness. The hydrochloride salt of the final product was obtained by passing dry HCl gas into an ethereal solution of the base, resulting in a white precipitate, recrystallized from ethanol: 2 g (76%); mp 178–179 °C. Anal. ($C_{28}H_{28}N_6O$·HCl·H_2O) C, H, N.

Pharmacological Methods. A. Antagonism of Reserpine-Induced Hypothermia. The method of Askew[12] was adopted with some modification. Swiss-Webster mice, 18–26-g body weight, were housed in groups of five in a room with ambient

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(12) Askew, B. M. *Life Sci.* **1963**, *2*, 725.

temperature of 20 °C. Mice were injected with reserpine 3 mg/kg sc, followed immediately by ip injection of the test compound in normal saline. Control rectal temperatures were taken immediately prior to the injection of reserpine. After 4 h, the rectal temperature of each mouse was measured with a microthermometer. ED_{50} was defined as the dose that caused 50% inhibition of reserpine-induced decrease in the rectal temperature.

Our modification of the procedure of Askew involves simultaneous injection of reserpine and the test compound without waiting for 17 h after reserpine injection. Hino et al.[4] have injected the test compound simultaneously with reserpine, and their ED_{50} value for the imipramine was almost identical to ours. The ED_{50} of imipramine obtained by Houlihan et al.[5] was found to be 12.8 mg/kg when imipramine was injected 1 h after reserpine. Unfortunately, no statistics were available to allow comparison with our value. Also, we have noticed the ED_{50} of imipramine to be 18.5 ± 5.7 mg/kg when it was injected 2 h after reserpine. Furthermore, we have found that the rectal temperature of mice dropped from 37.6 ± 0.53 to 26.2 ± 0.49, 25 ± 0.35 °C, and 22.72 ± 0.45 °C at 4, 5, and 6 h after reserpine injection, respectively. Askew reported that the rectal temperature had fallen to the region of 21-24 °C 17 h after reserpine injection. Therefore, it seems that the need for waiting a period of 17 h is not essential as long as the room temperature is kept at 20 ± 1 °C.

B. LD_{50}. The LD_{50} was determined according to the procedure described by Turner[13] by ip injection of the test compound in normal saline into Swiss-Webster mice weighing 12-23 g. LD_{50} was defined as the dose that killed 50% of the mice in 48 h.

Registry No. 1, 97633-84-6; **2**, 97633-87-9; **2** (free base), 97633-86-8; **3**, 97633-89-1; **3** (free base), 97633-88-0; **4**, 97633-91-5; **4** (free base), 97633-90-4; **5**, 97633-93-7; **5** (free base), 97633-92-6; **6**, 97633-95-9; **6** (free base), 97633-94-8; **7**, 97633-97-1; **7** (free base), 97633-96-0; **8**, 97633-99-3; **8** (free base), 97633-98-2; **9**, 72320-58-2; **10**, 97634-04-3; **10** (free base), 97634-03-2; 11, 97634-06-5; 11 (free base), 97634-05-4; **12**, 97634-02-1; **12** (free base), 97634-01-0; $Me_2N(CH_2)_3NH_2$, 109-55-7; $Me_2N(CH_2)_3NHMe$, 4543-96-8; $HO(CH_2)_3NMe_2$, 3179-63-3; $Cl(CH_2)_3NMe_2$, 109-54-6; L_2NiCl_2, 15629-92-2; CH_3MgBr, 75-16-1; 2-chloro-4-phenylquinoline, 5855-56-1; *N,N*-dimethylethylenediamine, 108-00-9; *N,N',N'*-trimethylethylenediamine, 142-25-6; *N,N'*-dimethylethanolamine, 108-01-0; 2-mercapto-4-phenylquinoline, 27309-54-2; 2-(dimethylamino)ethyl chloride, 107-99-3; 4-phenylquinaldine, 1721-92-2; 2-(bromomethyl)-4-phenylquinoline, 97634-00-9; diethylamine, 109-89-7; piperazine, 110-85-0; 3-chloro-1-bromopropane, 109-70-6; 2-pyridylhydrazine, 4930-98-7; 2-chloropyridine, 109-09-1; hydrazine, 302-01-2; 1,2,4-triazolo[4,3-*a*]pyridin-3-(2*H*)-one, 6969-71-7; urea, 57-13-6; thiourea, 62-56-6; *S*-(4-phenyl-2-quinolyl)-isothiourea, 97633-85-7.

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Conformationally Defined Adrenergic Agents. 1. Design and Synthesis of Novel α_2 Selective Adrenergic Agents: Electrostatic Repulsion Based Conformational Prototypes

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A previous report of the adrenergic selectivity of 2- and 6-fluoronorepinephrine prompted us to formulate a hypothesis that accounted for this selectivity on the basis of a conformational preference induced by electrostatic repulsion between the aromatic fluorine atom and the side-chain hydroxyl group. A series of nitrogen-substituted catechol (aminomethyl)benzocyclobutenes, indanes, tetralins, and benzocycloheptenes were prepared, and when their radioligand binding affinities were determined, it was found that the overall pattern of binding affinity results supported the electrostatic repulsion hypothesis. The radioligand binding assay also revealed several highly α_2 selective adrenergic agents among these compounds, with the binding selectivity maximizing for compounds having nitrogen substituted with a group no larger than methyl and having a five-membered carbocyclic ring (i.e., **16**, **17**, and **19**).

Separation of adrenergic effects into two classes mediated by α and β receptors was first suggested by Ahlquist[1] in 1948. Since that time, further work in the area of sympathetic nervous system receptors has led to their subclassification as α_1, α_2[2] and β_1, β_2.[3]

Compounds possessing selective activity at various of these adrenergic receptors may be expected to be of therapeutic value since they are likely to have enhanced efficacy while minimizing the side effects often encountered with less selective agents.

The preparation of norepinephrine (NE) derivatives that in various in vitro preparations show selective α- or β-adrenergic receptor activity has been reported by Kirk[4] et al. They found that 2-fluoronorepinephrine (2-FNE) exhibited β-agonistic activity while 6-fluoronorepinephrine (6-FNE) was an α agonist. Noting that the corresponding fluorinated dopamines did not show adrenergic selectivity,[5] one of the explanations that they offered for their observations invoked the formation of a hydrogen bond between the benzylic hydroxyl group and the aromatic fluorine atom. This was suggested to result in the stabilization of different rotameric conformations for the different FNEs. When the radioligand binding affinity of these compounds was determined,[6] it was found that 6-FNE bound to both α_1 and α_2 receptors but did not bind to β receptors. However, 2-FNE bound strongly to β receptors and modestly to the α_2 receptor but did not show significant binding to the α_1-adrenergic receptor.[7]

It was our belief that the observed adrenergic specificity of the 2- and 6-FNEs may have resulted from a conformational bias induced by the electrostatic repulsion between the side-chain β-hydroxyl group and the fluorine atom attached at the 2- or 6-position of the aromatic ring.

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