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Synthesis and Pharmacological Activities of 3-Phenyl-2-(1-piperazinyl)quinolines and Related Compounds

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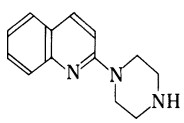
Various 3-phenyl-2-piperazinylquinolines and their 3-methyl analogs were synthesized and the effects of these compounds on the central nervous system were evaluated pharmacologically in mice. Some compounds having a 3-phenyl group showed potent antagonism of maximal electroshock seizures, but the 3-methyl analogs had no significant activity in any of the tests.

Keywords——3-phenyl-2-piperazinylquinoline; 3-methyl-2-piperazinylquinoline; anticonvulsant activity; anti-maximal electroshock seizure activity; central nervous system activity; structure–activity relationship; phosphorus pentachloride

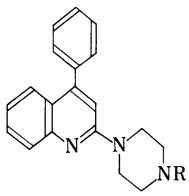
It has been reported that 2-(1-piperazinyl)quinoline (I) (quipazine) acts on the central nervous system (CNS), showing some activity in common with tricyclic antidepressants.[1] We have reported the potential antidepressant activity of 4-phenyl-2-piperazinylquinolines (II)[2] in mice. Among these compounds, 2-(4-ethyl-1-piperazinyl)-4-phenylquinoline dihydrochloride (IIa, AD-1308) was examined by Karasawa *et al.* of this laboratory, in order to establish the mechanism of its antidepressant action compared with that of tricyclic antidepressants.[3] Recently the effect on the antidepressant activity caused by replacing the piperazinyl group in IIa with either NH, NCH_3, O or S having an open chain (dialkylamino)alkyl group has been examined, and it was confirmed that the 2-piperazinyl moiety caused the optimal antagonistic effect on reserpine-induced hypothermia.[4]

We were interested in synthesizing 3-phenyl-2-piperazinylquinolines (III, $R^2 = Ph$), which have a phenyl group at the 3 position instead of the 4 position, in the hope of finding compounds having a new profile of activity, and also determining the structure–activity relationships in this class of compounds acting on the CNS. Such compounds have never previously been reported. This paper deals with the synthesis of the above compounds and their 3-methyl analogs (III, $R^2 = CH_3$), and the results of primary evaluation of their pharmacological activity on the CNS.

Catalytic hydrogenation of (*E*)-*o*-nitro-α-phenylcinnamic acid (**1**)[5] over Pd–C afforded

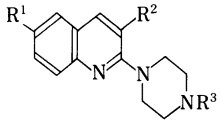


I



II

IIa : R = Et



III

Chart 1

3,4-dihydro-3-phenylcarbostyril (**3a**) in good yield. The reaction of **3a** with bromine afforded the 6-bromo derivative (**3b**) accompanied with a trace amount of 6-bromocarbostyril (**4b**). The Schmidt reaction of 2-methylbenzocyclopentan-1-one (**5**),[6] on the other hand, gave 3,4-dihydro-3-methylcarbostyril (**6a**) although in rather low yield. The reaction of **6a** with bromine gave the 6-bromo derivative (**6b**).

Treatment of the dihydrocarbostyrils (**3a**, **b** and **6a**, **b**) with phosphorus pentachloride (PCl_5) afforded a mixture of three products, 3-chloro-3,4-dihydrocarbostyrils (**7a**, **b** and **8a**, **b**), carbostyrils (**4a**, **b** and **9a**, **b**) and 2-chloroquinolines (**10a**, **b** and **11a**, **b**), respectively. 3-Phenylcarbostyril (**4a**) was identical with the compound obtained by the cyclization of **2**, which was prepared by the selective hydrogenation of the nitro group of **1**, with acetic anhydride and concentrated sulfuric acid.[7] The structures of these products were determined on the basis of spectroscopic and chemical evidence. On treatment with potassium carbonate (K_2CO_3), the α-chlorolactams (**7a** and **8b**) lost hydrogen chloride with ease to give the carbostyrils (**4a** and **9b**). The conversion of **4a** into **10a** was incomplete on treatment with PCl_5 and phosphorus oxychloride ($POCl_3$), but with the Vilsmeier reagent, this conversion proceeded in an excellent yield. On the other hand, the treatment of the 3-methyl analogs (**9a** and **9b**) with $POCl_3$ readily gave the 2-chloro derivatives (**11a** and **11b**). The chlorides (**10a**, **b**

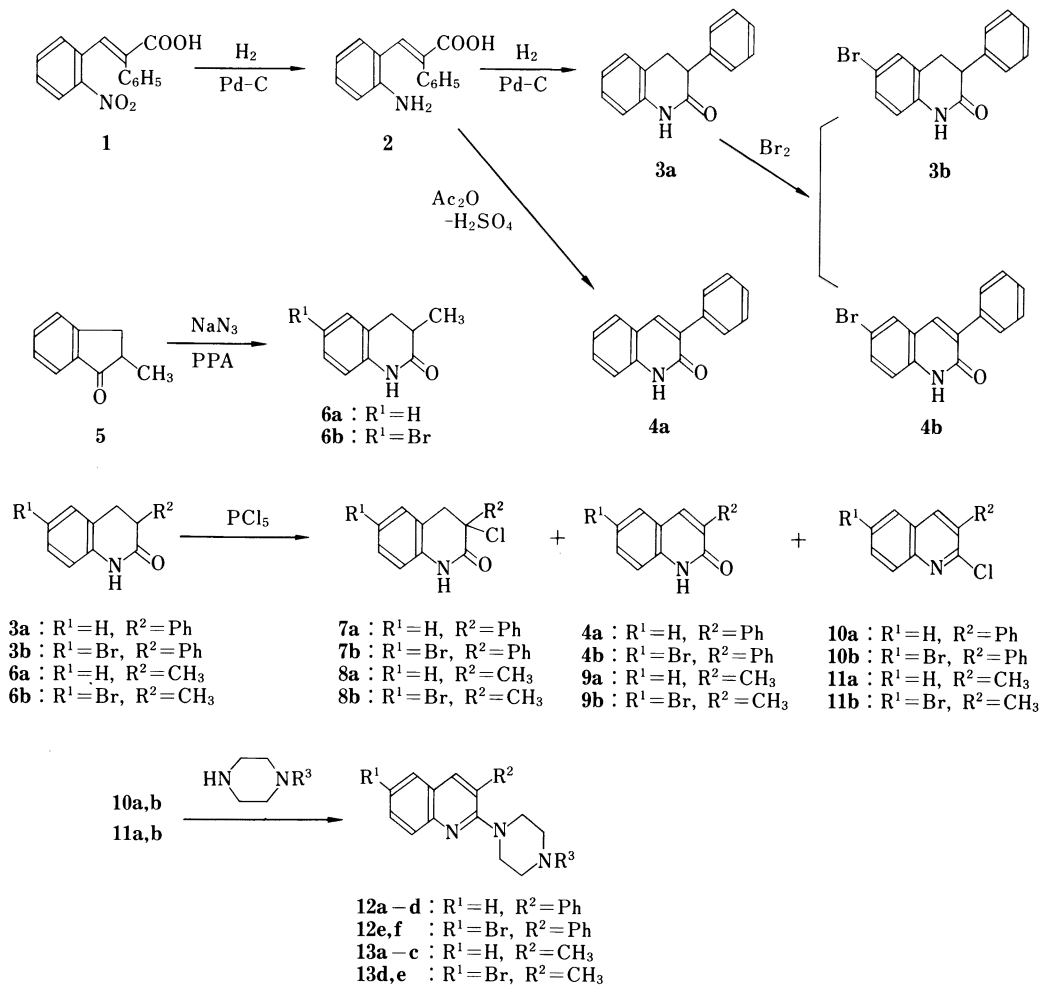


Chart 2

TABLE I. Physicochemical Properties and Analytical Data of Intermediates, **3b**, **4b**, **6b**, **7a**, **7b**, **8a**, **8b**, **9b**, **10b**, and **11b**

Compd. No.	mp (°C)	Recryst. solvent[a]	Formula	Analysis (%) Calcd (Found)				
				C	H	Br	Cl	N
3b	175	C–E	$C_{15}H_{12}BrNO$	59.62	4.00	26.45		4.64
				(59.70	3.89	26.57		4.60)
4b	258	C–E	$C_{15}H_{10}BrNO$	60.02	3.36	26.62		4.67
				(60.27	3.21	26.48		4.69)
7a	188—189	C–Al	$C_{15}H_{12}ClNO$	69.90	4.69		13.76	5.44
				(69.66	4.44		13.59	5.23)
7b	190	E–H	$C_{15}H_{11}BrClNO$	53.52	3.29	23.74	10.53	4.16
				(53.47	3.09	23.71	10.77	4.10)
10b	144—145	E–H	$C_{15}H_9BrClN$	56.55	2.85	25.08	11.13	4.40
				(56.78	2.73	25.18	11.18	4.47)
6b	157—159	C–E	$C_{10}H_{10}BrNO$	50.02	4.20	33.28		5.83
				(49.86	4.20	33.11		5.73)
8a	175—177	Ac–H	$C_{10}H_{10}ClNO$	61.37	5.15		18.12	7.16
				(61.19	5.24		18.16	7.09)
8b	194—195	C–H	$C_{10}H_9BrClNO$	43.74	3.30	29.11	12.91	5.10
				(43.98	3.12	29.10	12.95	5.01)
9b	248—251	C–H	$C_{10}H_8BrNO$	50.45	3.39	33.57		5.88
				(50.32	3.23	33.34		5.81)
11b	146	Ac–H	$C_{10}H_8BrClNO$	46.82	2.75	31.15	13.82	5.46
				(46.79	2.68	31.18	13.84	5.54)

a) Recrystallization solvents used were as follows: Ac, acetone; Al, EtOH; C, $CHCl_3$; E, Et_2O; H, hexane.

and **11a**, **b**) were allowed to react with various piperazines to give the desired 2-piperazinyl derivatives (**12a**—**f** and **13a**—**e**). The results are summarized in Tables I and II.

Pharmacology

The compounds listed in Table II were examined for CNS activities in mice at 100 mg/kg *p.o.* in a set of primary tests and the results are summarized in Table III in comparison with those for IIa (which has potent antidepressant activity) and quipazine (I). Compounds **12b**—**d**, **f** having a 3-phenyl group, but not **12a** or **12e**, exhibited potent anticonvulsant activity as measured in terms of protection against maximal electroshock seizure (MES), and the potency was comparable to that of the antiepileptic drug, carbamazepine. Neither antagonistic effect against reserpine-induced hypothermia nor neuroleptic-like properties were shown by **12a**—**f**. This is in contrast to the activity profile of the 4-phenyl isomers.[2] Some of the compounds (**12a**—**d**) showed a mild antagonizing effect on tremor induced by tremorine, comparable to that of IIa or quipazine. The 3-methyl derivatives (**13a**—**e**) showed weak or no activities in the above tests. Weak activity was observed only in the anti-reserpine (**13a**, **b**) and anti-MES (**13d**, **e**) tests.

From these results, all the compounds examined in this study proved to have different CNS pharmacological activity profiles from those of the potentially antidepressive 4-phenyl derivatives and quipazine. It appears that the phenyl group at the 4 position but not the 3 position in the quinoline nucleus, in combination with the 2-piperazinyl moiety, is essential for potent antidepressant activity, and that the aromatic group conjugating with the quinoline nucleus plays an important role in modifying the biological response. Structural modification of biologically active compounds by introducing such a group seems to be a useful strategy for finding compounds with different activity profiles.

TABLE II. Physicochemical Properties and Analytical Data of 2-Piperazinylquinolines (**12** and **13**)

Compd. No.	R^1	R^2	R^3	mp (°C) Recryst. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	Br	Cl	N
12a	H	Ph	H	184—186	83	$C_{19}H_{19}N_3 \cdot$	68.13	5.72			10.36
				Al		$C_4H_4O_4$[b]	(68.37	5.93			10.34)
12b	H	Ph	CH_3	258—260	76	$C_{20}H_{21}N_3 \cdot$	60.91	6.39		17.98	10.66
				Al–Ac		$2HCl \cdot H_2O$	(60.70	6.26		17.70	10.69)
12c	H	Ph	C_2H_5	240—242	72	$C_{21}H_{23}N_3 \cdot$	61.76	6.67		17.56	10.29
				Al–Ac		$2HCl \cdot H_2O$	(61.63	6.68		17.78	10.21)
12d	H	Ph	CH_2CH_2OH	184—189	75	$C_{21}H_{23}N_3O \cdot$	59.43	6.41		16.71	9.90
				Al		$2HCl \cdot H_2O$	(59.34	6.31		16.55	9.82)
12e	Br	Ph	CH_3	147	87	$C_{20}H_{20}BrN_3$	62.83	5.27	20.95		10.99
				E–H			(63.08	5.31	20.90		10.80)
12f	Br	Ph	CH_2CH_2OH	250—255	80	$C_{21}H_{22}BrN_3O \cdot$	50.12	5.21	15.88	14.09	8.35
				Al		$2HCl \cdot H_2O$	(49.98	5.37	15.71	13.95	8.32)
13a	H	CH_3	CH_3	241—243	67	$C_{15}H_{19}N_3 \cdot$	50.14	7.29		19.74	11.69
				Al		$2HCl \cdot 5/2\,H_2O$	(50.37	6.99		19.51	11.77)
13b	H	CH_3	C_2H_5	220—225	40	$C_{16}H_{21}N_3 \cdot$	49.11	7.73		18.12	10.74
				Al		$2HCl \cdot 7/2\,H_2O$	(49.01	7.76		17.89	10.77)
13c	H	CH_3	CH_2CH_2OH	225—229	55	$C_{16}H_{21}N_3O \cdot$	55.82	6.73		20.60	12.20
				Al		$2HCl$	(55.92	6.91		20.41	12.17)
13d	Br	CH_3	CH_3	97—98	88	$C_{15}H_{18}BrN_3$	56.26	5.66	24.96		13.12
				E–H			(56.27	5.55	24.86		13.04)
13e	Br	CH_3	CH_2CH_2OH	103	87	$C_{16}H_{20}BrN_3O$	54.86	5.76	22.82		12.00
				E			(54.99	5.74	22.76		11.91)

a) For abbreviations of recrystallization solvents, see footnote *a*) in Table I. *b*) Maleate.

TABLE III. Results of Primary Tests at 100 mg/kg, *p.o.* in Mice

Compd. No.	Anti-MES activity[a]	Anti-reserpine activity (%)	Anti-tremorine activity (%)
12a	0/5	−14	20
12b	4/5	−21	47
12c	5/5	−21	33
12d	5/5	−9	33
12e	1/5	−40	0
12f	5/5	−6	0
13a	0/5	21	0
13b	0/5	19	0
13c	0/5	7	0
13d	1/5	−7	0
13e	2/5	−3	0
Carbamazepine	5/5		
Quipazine (I)		46	40
IIa	0/5	85	53

a) Number of positive effects/number of mice tested.

Experimental

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Proton magnetic resonance (^{1}H-NMR) spectra were taken on a Varian HA-100 or Varian A-60 spectrometer using

tetramethylsilane as an internal standard. Abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. The chemical shifts are given as δ (ppm). Mass spectra (MS) were taken on a JEOL JMS-D300 spectrometer and infrared (IR) spectra were recorded on a Hitachi EPI-S2 spectrometer in KBr disks. Organic extracts were dried over magnesium sulfate.

3,4-Dihydro-3-phenylcarbostyril (3a)——Compound **1**[5] (6.4 g) was hydrogenated with 5% Pd–C (0.5 g) in MeOH at room temperature under atmospheric pressure. The theoretical amount of hydrogen (4 mol eq) was absorbed during about 6 h. The catalyst and the solvent were removed, and the residue was recrystallized to give **3a** (4.5 g, 85%), mp 170—171 °C ($CHCl_3$–EtOH) (lit. mp 170—172 °C).[8] IR: 1680 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.25 (2H, d, J=7 Hz, 4-H_2), 3.86 (1H, dd, J=7, 7 Hz, 3-H), 6.6—7.3 (4H, m, –C_6H_4–), 7.26 (5H, s, C_6H_5), 8.60 (1H, NH).

3-Phenylcarbostyril (4a)——a) Compound **1**[5] (26.9 g) was hydrogenated with 5% Pd–C (2 g) in MeOH at room temperature under atmospheric pressure. The theoretical amount of hydrogen (3 mol eq) was absorbed during about 40 min. The catalyst and the solvent were removed to give crude **2** as a crystalline residue. MS m/z: 239 (M^+). Without further purification, this crude product was treated with acetic anhydride and concentrated sulfuric acid as reported[7] to give **4a** (16 g, 73%), mp 235 °C ($CHCl_3$–EtOH) (lit. mp 228 °C).[7] ^{1}H-NMR (DMSO-d_6) δ: 8.09 (1H, s, 4-H), 7.0—7.9 (9H, m, Ar-H), 11.97 (1H, NH).

b) A mixture of **7a** (77 mg), K_2CO_3 (46 mg, 1.1 mol eq) and MeOH (10 ml) was refluxed for 30 min. After being cooled, the reaction mixture was diluted with water and the resulting precipitates were collected and recrystallized to give **4a** (62 mg, 94%).

The Reaction of 3,4-Dihydro-3-phenylcarbostyril (3a) with Bromine——A mixture of **3a** (2.23 g), $CHCl_3$ (30 ml) and Br_2 (1.92 g, 1.2 mol eq) was refluxed for 6 h. The reaction mixture was concentrated *in vacuo* and the residue was chromatographed on silica gel with $CHCl_3$. The first eluate afforded **3b** (2.68 g, 89%) after recrystallization. IR: 1690 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.18 (2H, d, J=8 Hz, 4-H_2), 3.83 (1H, t, J=8 Hz, 3-H), 6.86 (1H, d, J=9 Hz, 8-H), 7.26 (5H, s, C_6H_5), 7.35 (1H, m, 7-H), 7.41 (1H, d, J=2 Hz, 5-H), 10.46 (1H, NH). The second eluate gave **4b** (155 mg, 5%) after recrystallization. ^{1}H-NMR (DMSO-d_6) δ: 7.2—7.9 (7H, m, C_6H_5, 7-H and 8-H), 7.97 (1H, d, J=2 Hz, 5-H), 8.07 (1H, s, 4-H), 12.08 (1H, NH).

3,4-Dihydro-3-methylcarbostyril (6a)——NaN_3 (17.2 g, 1.1 mol eq) was added portionwise to a mixture of 5[6] (35 g) and polyphosphoric acid (370 g) at 65—70 °C, and the reaction mixture was stirred for 3 h at the same temperature. After being cooled, the reaction mixture was poured into ice and water, and extracted with AcOEt. The extracts were washed with water and dried, and the solvent was evaporated off. The residue was recrystallized to give **6a** (13.7 g, 32%), mp 129—130 °C (acetone–hexane) (lit. mp 129—130 °C).[9] IR: 1665 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, J=6.5 Hz, CH_3), 2.4—3.2 (3H, m, 3-H and 4-H_2), 6.7—7.3 (4H, m, Ar-H), 9.10 (1H, NH).

6-Bromo-3,4-dihydro-3-methylcarbostyril (6b)——A mixture of **6a** (1.61 g), $CHCl_3$ (30 ml) and Br_2 (1.92 g, 1.2 mol eq) was refluxed for 4 h. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized to give **6b** (2.14 g, 89%). IR: 1670 (C=O) cm^{-1}.

The Reaction of 3,4-Dihydro-3-phenylcarbostyril (3a) with PCl_5——A mixture of **3a** (1.12 g), PCl_5 (2.5 g, 2.5 mol eq) and benzene (3 ml) was refluxed for 4 h. After being cooled, the reaction mixture was diluted with water and extracted with $CHCl_3$. The extracts were washed with water and dried, and the solvent was evaporated off. The residue was chromatographed on silica gel with $CHCl_3$ to give firstly **10a** (0.48 g, 40%) as an oil. MS m/z: 239 (M^+) (lit. bp 175 °C/1.1 mm).[10] The second fraction gave **7a** (80 mg, 6%) after recrystallization. MS m/z: 257 (M^+). IR: 1680 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.52 and 3.98 (1H each, both d, J=16 Hz, 4-H_2), 6.7—7.7 (9H, m, Ar-H), 10.70 (1H, NH). The third fraction afforded **4a** (0.38 g, 41%) after recrystallization.

The Reaction of 6-Bromo-3,4-dihydro-3-phenylcarbostyril (3b) with PCl_5——Compound **3b** (2.41 g) was treated in the same manner as described for the reaction of **3a** to give the following three compounds. **10b** (0.13 g, 5%): MS m/z: 317 (M^+). **7b** (0.62 g, 23%): MS m/z: 335 (M^+). IR: 1690 (C=O) cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 3.53 and 4.07 (1H each, both d, J=17 Hz, 4-H_2), 6.87 (1H, d, J=8.5 Hz, 8-H), 7.2—7.8 (7H, m, C_6H_5, 5-H and 7-H), 10.90 (1H, NH). **4b** (1.27 g, 53%).

The Reaction of 3,4-Dihydro-3-methylcarbostyril (6a) with PCl_5——A mixture of **6a** (3.2 g), PCl_5 (10.4 g, 2.5 mol eq) and benzene (5 ml) was refluxed for 3 h. After being cooled, the reaction mixture was diluted with water and extracted with AcOEt. The extracts were washed with water and dried, and the solvent was evaporated off. The residue was chromatographed on silica gel. The eluate with benzene gave **11a** (3.2 g, 90%) after recrystallization. mp 83 °C (ether–hexane) (lit. mp 83—84 °C).[11] ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, d, J=1 Hz, CH_3), 7.4—7.9 (4H, m, benzene ring H), 7.92 (1H, q, J=1 Hz, 4-H). The eluate with benzene–$CHCl_3$ (1:1) gave **8a** (0.21 g, 5%) after recrystallization. MS m/z: 195 (M^+). IR: 1690 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.91 (3H, s, CH_3), 3.29 (2H, s, 4-H_2), 6.8—7.4 (4H, m, Ar-H), 9.25 (1H, NH). The eluate with $CHCl_3$ gave **9a** (50 mg, 2%) after recrystallization. mp 240—242 °C ($CHCl_3$–hexane) (lit. mp 238—240 °C).[11] IR: 1650 (C=O) cm^{-1}.

The Reaction of 6-Bromo-3,4-dihydro-3-methylcarbostyril (6b) with PCl_5——Compound **6b** (4.1 g) was treated in the same manner as described for the reaction of **6a** to give the following three compounds. **11b** (1.88 g, 43%): MS m/z: 255 (M^+). **8b** (1.65 g, 35%): MS m/z: 273 (M^+). IR 1680 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.79 (3H, s, CH_3), 3.37 (2H, br s, 4-H_2), 6.90 (1H, d, J=9 Hz, 8-H), 7.41 (1H, q, J=9, 2 Hz, 7-H), 7.48 (1H, d, J=2 Hz, 5-H), 10.05 (1H,

NH). **9b** (0.19 g, 5%). IR: 1665 (C=O) cm^{-1}.

6-Bromo-3-methylcarbostyril(9b)——A mixture of **8b**(1.37 g), K_2CO_3(0.76 g) and MeOH(30 ml) was refluxed for 15 min. After being cooled, the reaction mixture was diluted with water and the resulting precipitates were collected and recrystallized to give **9b** (1.15 g, 97%).

2-Chloro-3-phenylquinoline (10a)——a) A mixture of **4a** (2.21 g), $CHCl_3$ (40 ml), $SOCl_2$ (6 ml) and dimethylformamide (DMF) (1.3 ml) was refluxed for 1 h and concentrated *in vacuo*. The residue was diluted with water and extracted with ether. The extracts were washed with water, dried and evaporated to give **10a** (2.27 g, 95%) as a residual oil.

b) A mixture of **4a** (4.42 g), PCl_5 (20.8 g) and $POCl_3$ (20 ml) was refluxed for 18 h. After being cooled, the reaction mixture was poured into ice and water, and extracted with $CHCl_3$. The residue was recrystallized to give the starting **4a** (2.8 g) and the mother liquor was chromatographed on silica gel with $CHCl_3$ to give **10a** (1.2 g, 25%) as an oil.

6-Bromo-2-chloro-3-phenylquinoline (10b)——A mixture of **4b** (60 mg), $CHCl_3$ (5 ml), $SOCl_2$ (0.1 ml) and DMF (0.1 ml) was refluxed for 1 h and concentrated *in vacuo*. The residue was diluted with water and extracted with AcOEt. The extracts were washed with water and dried, and the solvent was evaporated off. The residue was recrystallized to give **10b** (56 mg, 88%).

2-Chloro-3-methylquinoline (11a)——A mixture of **9a** (160 mg) and $POCl_3$ (5 ml) was refluxed for 2.5 h and concentrated *in vacuo*. The residue was dissolved in ether and the solution was washed with water, dried and concentrated, then the residue was recrystallized to give **11a** (150 mg, 85%).

6-Bromo-2-chloro-3-methylquinoline (11b)——Compound **9b** (1.15 g) was treated in the same manner as described for **11a** to give **11b** (1.17 g, 95%) after recrystallization.

3-Phenyl-2-piperazinylquinolines (12a—f) and 3-Methyl-2-piperazinylquinolines (13a—e)——General Procedure: A mixture of the 2-chloro derivatives (**10a**, **b** and **11a**, **b**) and 3 mol eq of the piperazine was stirred for 4—12 h at 130 °C. The reaction mixture was dissolved in a mixture of ether and water, and the organic layer was washed with water and dried, then the solvent was evaporated off. The residue was recrystallized from an appropriate solvent directly or after the conversion into a salt. The results are summarized in Table II.

Pharmacological Methods——Male Std-ddY strain mice (Shizuoka Lab. Animal Center, SLAC, Shizuoka, Japan), weighing 20—25 g, were employed in the experiments. Test compounds were dissolved or suspended in 0.5% aqueous tragacanth and orally administered to a group of five mice.

Antagonistic Effect on Maximal Electroshock Seizure: This experiment was carried out according to the method of Masuda *et al.*[12] Test compounds were evaluated for ability to prevent the hind-limb extensor component of maximal electroshock seizure induced by applying a current of 25 mA at 60 Hz for 0.2 s, delivered through corneal electrodes 2 h after dosing.

Antagonistic Effect on Hypothermia Induced by Reserpine: This experiment was carried out according to the method described in ref. 2. The inhibitory effect was calculated as the average value (percentage), as compared with the control.

Antagonistic Effect on Tremor Induced by Tremorine: This experiment was carried out according to the method described in ref. 2. The inhibitory effect was calculated as a percentage from the scores compared with those of the control mice.

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