Table V. Development of Equation 14

intercept	R_m	R_m^2	I_3	r	s	F	eq
1.853	-0.142			0.086	0.892	0.19	A
1.904		-0.088		0.201	0.877	1.10	B
-2.994	5.546	-1.532		0.645	0.697	8.93	C
1.044			1.418	0.803	0.533	48.28	D
1.105	-0.034		1.415	0.803	0.543	0.03[a]	E
1.155		-0.030	1.398	0.806	0.540	0.33[b]	F
-1.275	2.912	-0.800	1.132	0.855	0.482	3.86[c]	14

[a] This is $F_{1,25}$ obtained by comparison with eq D. [b] This is $F_{1,25}$ obtained by comparison with eq D; the F test showed that neither eq E nor eq F is a significant improvement over eq D. [c] This is $F_{2,24}$ obtained by comparison with eq D. The F test showed that eq 14 is a significant improvement over eq D.

Conflict Behavior Tests. The punished schedule test had been carried out with only 17 compounds (Table IV). The following equations show the development of eq 18.

$$\log (1/C) = -1.106(\pm 1.011) + 1.846(\pm 0.589)R_m \quad (17)$$

$$n = 17;\ r = 0.629;\ s = 0.515;\ F = 9.81;\ p < 0.01$$

$$\log (1/C) = -1.195(\pm 0.648) + 1.593(\pm 0.382)R_m + 0.803(\pm 0.169)I_3 \quad (18)$$

$$n = 17;\ r = 0.876;\ s = 0.330;\ F = 23.17;\ p < 0.005$$

The introduction of the I_3 term into eq 17 improved the correlation coefficient in a significant way. For eq 18, $F_{1,14} = 22.49$ ($F_{1,14;\alpha=0.005} = 11.06$). On the other hand the regression on R_m after I_3 in eq 18 is significant ($F_{1,14} = 17.44$).

Similarly, a regression analysis carried out for the nonpunished schedule yielded eq 19 and 20.

$$\log (1/C) = -0.658(\pm 1.248) + 1.421(\pm 0.728)R_m \quad (19)$$

$$n = 17;\ r = 0.450;\ s = 0.636;\ F = 3.81;\ p < 0.10$$

$$\log (1/C) = -0.777(\pm 0.773) + 1.107(\pm 0.454)R_m + 1.012(\pm 0.202)I_3 \quad (20)$$

$$n = 17;\ r = 0.845;\ s = 0.394;\ F = 17.54;\ p < 0.005$$

The introduction of the I_3 term improved in a significant way the correlation coefficient in eq 20 ($F_{1,14} = 25.06$). The regression on R_m after I_3 in eq 20 is also significant ($F_{1,14} = 5.92$; $F_{1,14;\alpha=0.05} = 4.60$).

In order to compare the QSAR equation for the exploratory behavior test with those for both conflict behavior tests, eq 21 was calculated with the data from the

$$\log (1/C) = 0.361(\pm 0.713) + 0.613(\pm 0.419)R_m + 1.043(\pm 0.186)I_3 \quad (21)$$

$$n = 17;\ r = 0.850;\ s = 0.363;\ F = 18.30;\ p < 0.005$$

exploratory behavior test for the 17 compounds used in calculating eq 17 and 18 and 19 and 20.

The different slopes of the R_m term in eq 18 and 20 might point out a different dependence on lipophilic character for activity in the punished- and in the nonpunished-schedule test. This could suggest that two different mechanisms are involved in the above-mentioned activities; this is in agreement with the hypothesis of Stein et al.,[34] who proposed different neurological structures and biochemical mechanisms for the antianxiety and sedative action of benzodiazepines. However, because of their large confidence limits, eq 18 and 20 do not allow any conclusion.

On the other hand, because of the lower slope of its R_m term, eq 21 seems to be closer to eq 20 than to eq 18. This should be in agreement with the fact that the depressive effect upon the exploratory behavior, i.e., an unspecific depressant effect, should be more related to the sedative effect obtained in the unpunished schedule.

In conclusion, the slope of the R_m term in the QSAR equations might indicate a relationship between lipophilic character and different CNS effects of benzodiazepines. At least one might suggest that the antianxiety effect measured in the punished-schedule test is more dependent on the lipophilic character than the unspecific depressant effect measured in the exploratory behavior test. Moreover, the present data seem to point out the usefulness of R_m values as an expression of the lipophilic character of complex molecules such as benzodiazepines.

(34) L. Stein, C. D. Wise, and J. D. Belluzzi, in "Mechanism of Action of Benzodiazepines", E. Costa and P. Greengard, Eds., Raven Press, New York, 1975.

Antiamebic Amidines and Sulfonamides of 5- and 6-Amino-2,3-bis(4-alkyl-1-piperazinyl)quinoxalines

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A series of amidines and sulfonamides of 5- and 6-amino-2,3-bis(4-alkyl-1-piperazinyl)quinoxalines was synthesized and tested against cecal and hepatic forms of *Entamoeba histolytica* infections in rats and hamsters, respectively. Four compounds (**5**, **6**, **8**, and **9**) were found to have acceptable activity against infections in both species but were too toxic to be considered for use in man.

The current primary drug[2] used in the treatment of human amebiasis, metronidazole, a nitroimidazole, has demonstrated carcinogenicity in test animals.[3,4] In our research efforts to find antiamebic agents which do not

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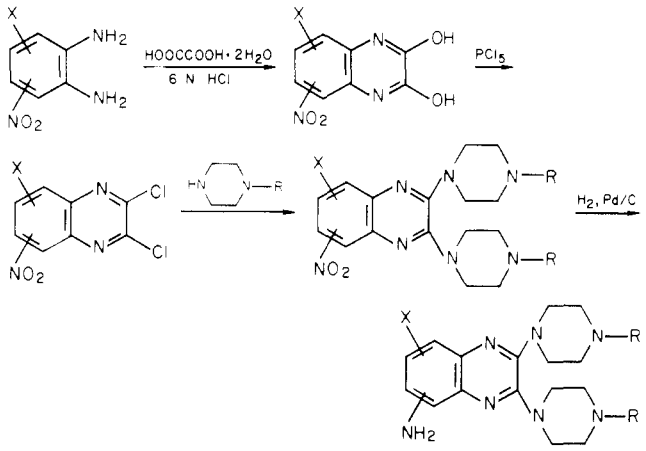
Scheme I



contain a nitro group, we found a number of 5- or 6-substituted 2,3-bis(4-alkyl-1-piperazinyl)quinoxalines[1] (**5**, **6**, **8**, and **9**) which are orally active against both cecal and hepatic amebic infections.

Chemistry. The 5- and 6-aminoquinoxalines were prepared as shown in Scheme I. Nitro-*o*-phenylenediamines were condensed with oxalic acid to give the 5- or 6-nitro-2,3-dihydroxyquinoxalines. Reaction of these intermediates with phosphorus pentachloride gave 2,3-dichloroquinoxalines. Subsequent reaction with *N*-alkylpiperazines gave the 5- or 6-nitro-2,3-bis(4-alkyl-1-piperazinyl)quinoxalines. Reduction of the nitro group was accomplished catalytically (palladium on carbon). The 5- and 6-aminoquinoxalines were transformed into the amidines by one or two of the following methods (Scheme II).

Method A. Aminoquinoxalines are reacted with an *N*,*N*-dialkylamide dialkyl acetal with or without solvent.[5]

Method B. Aminoquinoxalines are reacted with an ortho ester in the presence of sulfuric acid to give an imidate, which is reacted with various amines.[6]

Method C. Aminoquinoxalines are reacted with a complex formed from phosphorus oxychloride and an *N*,*N*-dialkylamide in acetonitrile.[7]

The sulfonamides are prepared by method D (Scheme II) in which an aminoquinoxaline reacts with a sulfonyl chloride in an inert solvent such as chloroform, methylene chloride, or pyridine in the presence of triethylamine.

Biology. The amidines were active in treating cecal and hepatic amebic infections in warm-blooded animals. Two tests which establish this activity are as follows.

Organism. The organism used in both tests was the National Institute of Health 200-μ strain of *E. histolytica*. This strain and an unidentified microorganism were cultured in Cleveland–Collier medium at 37 °C. This medium consisted of a liver infusion agar base overlaid with a horse serum–saline mixture (1:6) to which was added a few milligrams of sterile rice powder. The amebas were transferred to fresh medium twice weekly.

Cecal Infections in Female Albino Wistar Rats. Pooled overlay (0.25 mL) containing large numbers of amebas was injected into the cecum of anesthetized weanling rats during laparotomy. Treatment was begun on the day after inoculation. The compounds were dissolved or suspended in 0.2% aqueous agar and administered once daily, by gavage, for 5 consecutive days. Six days after inoculation of the amebas, the rats were sacrificed and a scraping from the cecal wall of each rat was mixed with a drop of 0.85% saline and examined microscopically for amebas. A rat was considered cured if no amebas were seen. The cure or clearance rate (number cured/number treated) for each regimen was calculated and corrected for nonspecific cures observed in the untreated infected controls. An active dose was the lowest dose, in terms of (mg/kg)/day, which cleared or cured 50% or more of the rats so treated. The results of the compounds of the series appear in Table I, together with results obtained using known effective drugs for comparison.

Hepatic Infections in Female Golden Hamsters. A piece of ameba-laden absorbable sponge (about 5 × 5 × 1 mm) was inserted between the middle lobes of the livers of anesthetized hamsters during laparotomy. Untreated hamsters usually die from the resulting infection about 7 days after inoculation. Treatment was started on the day of inoculation as soon as the hamsters recovered from the surgical anesthetic. The test compounds were dissolved or suspended in 0.2% aqueous agar and administered once daily, by gavage, for 5 consecutive days. Effective regimens prevented mortality. Survival rates were corrected for nonspecific survival observed in untreated groups. An active dose was the lowest dose, expressed in (mg/kg)/day, which protected 50% or more of the hamsters so treated as evidenced by survival 14 days after inoculation. The results of the compounds appear in Table I, together with effective dose of known effective drugs for comparison.

Pharmacology. The compounds were first evaluated against experimental *Entamoeba histolytica* infections in rats at a dosage of 100 mg/kg. Those compounds found active at that dose level in rats were titrated to the lowest active dose and were also evaluated against experimental *E. histolytica* infections in hamsters at a dosage of 100 mg/kg. Active compounds in the hamster were titrated to the lowest active dosage level.

Results and Discussion

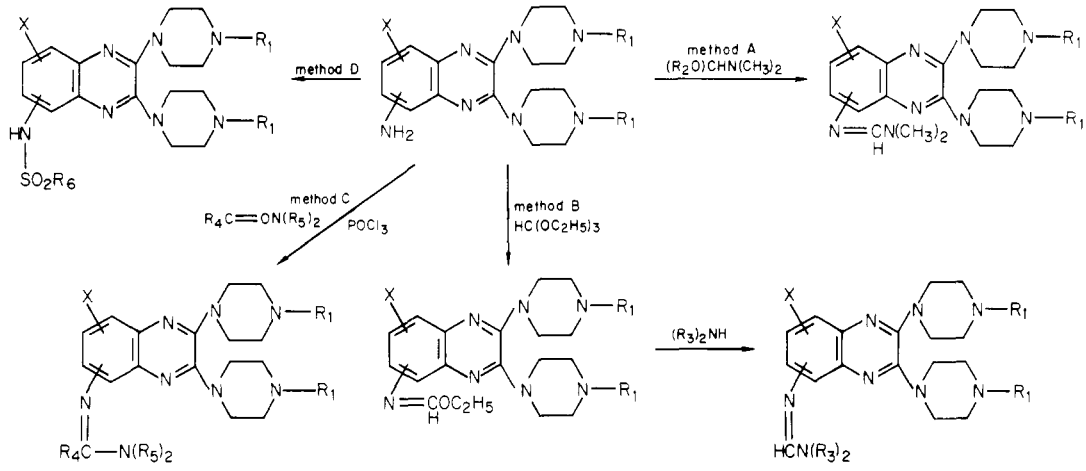
Several amidines and one sulfonamide showed highly effective antiamebic activity against both cecal and hepatic forms of infection. The introduction of a chloro group into the aryl ring led to inactive compounds. Modification of the alkyl group on the piperazinyl moiety gave reduced activity. Our studies indicate that derivatives which possess lower alkyl N substitution in the formamidine series are the most interesting with respect to antiamebic activity. Unfortunately, the studies related to the therapeutic index indicated that, although these drugs were highly effective in the treatment of cecal and hepatic infections in test animals, the gross toxicity excluded the potential use in man.

Experimental Section

Melting points (uncorrected) were determined on a Mel-Temp apparatus. The 2,3-dihydroxy- and 2,3-dichloro-6-nitroquinoxalines were prepared as described by Mager and Berends.[8]

(1) P. F. Fabio, Y.-I. Lin, S. A. Lang, Jr., and A. S. Tomcufcik, U.S. Patent 4 029 788 (June 14, 1977).
(2) (a) R. Elson-Dew, *Adv. Parasitol.*, **6**, 1–62 (1968); (b) *WHO Tech. Rep. Ser.*, **no. 421**, 5–52 (1969); (c) S. J. Powell, *Bull. WHO*, **40**, 953–956 (1969); (d) E. Barrett-Conner, *Calif. Med.*, **114**, 1–6 (1971); (e) L. Goodman and A. Gilman, Ed., "Pharmacological Basis of Therapeutics", 5th ed, MacMillan, New York, N.Y., 1975, Chapter 54, p 1088; (f) I. M. Rollo in ref 2e, Chapter 53, pp 1069–1080.
(3) M. Rutia and P. Shubik, *J. Natl. Cancer Inst.*, **48**, 721–729 (1972).
(4) P. Shubik, *Proc. Natl. Acad. Sci. U.S.A.*, **69**, 1052–1055 (1972).
(5) H. Meerwein, W. Florian, N. Schon, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).
(6) Ciba Geigy, DT-2202942-Q.
(7) H. Bredereck, R. Gompper, K. Klemm, and H. Rempfer, *Chem. Ber.*, **92**, 837 (1959).
(8) H. I. X. Mager and W. Berends, *Recl. Trav. Chim. Pays-Bas*, **78**, 5–21 (1959).

Scheme II



6-Amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (1). To a solution of 18.7 g (0.19 mol) of *N*-methylpiperazine in 150 mL of 2-methoxyethanol was added 9.1 g (0.037 mol) of 2,3-dichloro-6-nitroquinoxaline in several portions (exothermic reaction). The mixture was refluxed with stirring for 16 h. The crude product, 14 g, was recrystallized from 150 mL of 2-methoxyethanol and gave 10.2 g (73.5%) of analytically pure brownish yellow product, 2,3-bis(4-methyl-1-piperazinyl)-6-nitroquinoxaline, mp 230–231 °C. Anal. ($C_{18}H_{25}N_7O_2$) C, H, N.

2,3-Bis(4-methyl-1-piperazinyl)-6-nitroquinoxaline (9.27 g, 0.025 mol) in 100 mL of water plus 12.5 mL of 6 N hydrochloric acid was reduced with 1.0 g of 10% palladium on carbon. The crude product was recrystallized from 300 mL of acetonitrile and gave 5.1 g (60%) of analytically pure yellow product, 6-amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline, mp 208–210 °C. Anal. ($C_{18}H_{27}N_7$) C, H, N.

5-Amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (2). The 2,3-dichloro-5-nitroquinoxaline[8] was converted to 2,3-bis(4-methyl-1-piperazinyl)-5-nitroquinoxaline in the same manner as the corresponding 6-nitroquinoxaline.

From 24.4 g (0.1 mol) of 2,3-dichloro-5-nitroquinoxaline and 50.0 g (0.5 mol) of *N*-methylpiperazine was obtained 31.4 g (84.5%) of product, 2,3-bis(4-methyl-1-piperazinyl)-5-nitroquinoxaline, mp 193–196 °C. An analytically pure sample was obtained by recrystallization from 2B alcohol, mp 195–197 °C. Anal. ($C_{18}H_{25}N_7O_2$) C, H, N.

The reduction was carried out as described for the reduction of 2,3-bis(4-methyl-1-piperazinyl)-6-nitroquinoxaline.

From 25 g (0.067 mol) of 2,3-bis(4-methyl-1-piperazinyl)-5-nitroquinoxaline was obtained 3.3 g (14.5%) of product, 5-amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline, mp 196–199 °C. Anal. ($C_{18}H_{27}N_7$) C, H.

The reduction of the 5-nitroquinoxaline was carried out in much greater yields when the sodium sulfide method was used as in the preparation of 5-amino-7-chloro-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (4).

***N'*-[2,3-Bis(4-methyl-1-piperazinyl)-6-quinoxalinyl]-*N,N*-dimethylformamidine (5). Method A.** A mixture of 6.8 g (0.020 mol) of 6-amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline and 15 mL of *N,N*-dimethylformamide dimethyl acetal was stirred at reflux temperature for 2 h. The solution was cooled at −10 °C to form a solid mass. The solid was slurried with 15 mL of cold diethyl ether, filtered, and washed with 10 mL of cold diethyl ether, followed by 25 mL of petroleum ether. The material was air-dried and dried in vacuo at 60 °C.

The precipitate was dissolved in 200 mL of hot 1:1 benzene/petroleum ether and treated with activated charcoal. The clarified solution was cooled at −10 °C and the precipitate formed was collected and washed with petroleum ether. The solid was dried in vacuo and gave 2.1 g (26.5%) of product, mp 151–152 °C.

2,3-Bis(4-methyl-1-piperazinyl)-6-[[(4-methyl-1-piperazinyl)methylene]amino]quinoxaline (18). Method B. A mixture of 8.0 g (0.020 mol) of ethyl *N*-[2,3-bis(4-methyl-1-piperazinyl)-6-quinoxalinyl]formimidate and 10 g (0.1 mol) of *N*-methylpiperazine was heated for 2 h in an oil bath at 130 °C. The reaction mixture was stripped of volatiles under reduced pressure. The residual solid was washed with hexane, recrystallized from 100 mL of acetonitrile, and gave 3.8 g (42%) of analytically pure product, mp 165–167 °C.

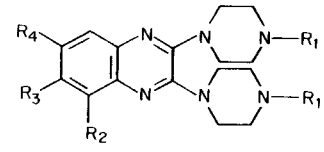
***N'*-[2,3-Bis(4-methyl-1-piperazinyl)-5-quinoxalinyl]-*N,N*-dimethylpropionamidine Dicitrate (19). Method C.** To a solution of 11.3 g (0.112 mol) of *N,N*-dimethylpropionamide in 110 mL of acetonitrile (dried over molecular sieves) was added 8.3 mL of phosphorous oxychloride at 5 to −10 °C. The mixture was stirred at room temperature for 90 min. To the resulting yellow solution was added 13.7 g (0.040 mol) of 5-amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (2) in several portions with stirring. The mixture was placed in an oil bath at 70 °C and stirred for 17 h. The reaction mixture was cooled and poured into 400 mL of ice and water. The mixture was made alkaline to a pH greater than 13 with the addition of 50 mL of 10 N sodium hydroxide and gave 20.3 g of a residual oil. A solution of the residual oil in 50 mL of ethyl acetate was combined with a solution of 8.4 g (0.040 mol) of citric acid monohydrate in 400 mL of ethyl acetate and 10 mL of methanol and gave 17.2 g (53.3%) of product, mp 128 °C (dec).

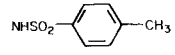
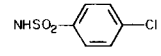
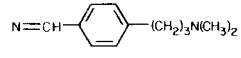
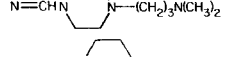
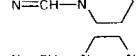
***N*-[2,3-Bis(4-methyl-1-piperazinyl)-6-quinoxalinyl]-*p*-toluenesulfonamide (9). Method D.** A 6.41-g (0.020 mol) portion of 6-amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (1) was dissolved in 200 mL of chloroform. Then 3.0 mL (0.021 mol) of triethylamine was added plus 3.81 g (0.020 mol) of *p*-toluenesulfonyl chloride. The resulting solution was stirred at room temperature for 3 h and was left standing in a sealed flask for 18 h. The solution was washed with water and dried. The solution was stripped of solvent by water-pump evacuation and gave a yellow solid which was recrystallized from 100 mL of benzene and 200 mL of cyclohexane. The solid obtained was recrystallized from 475 mL of acetonitrile and gave 3.2 g (32%) of product, mp 234–237 °C.

Ethyl *N*-[2,3-Bis(4-methyl-1-piperazinyl)-6-quinoxalinyl]formimidate. A mixture of 17 g (0.05 mol) of 6-amino-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (1), 100 mL of triethyl orthoformate, and 5 drops of concentrated sulfuric acid was refluxed for 16 h. The reflux condenser was replaced by a take-off condenser, and 6.5 mL of distillate was collected at bp 80 °C. The reaction mixture was cooled and stripped of volatiles under water-pump pressure. The residual oil (22 g) was combined with 50 mL of hot hexane. The mixture was cooled, and the solid was collected by filtration and washed with hexane. The product was dried and gave 18.5 g (93.1%) of yellow solid, mp 95–105 °C (dec).

6-Amino-2,3-bis(4-propyl-1-piperazinyl)quinoxaline (3). A mixture of 50 g (0.17 mol) of 1-*n*-propylpiperazine dihydrobromide and 60 g (0.71 mol) of sodium bicarbonate in 200 mL of 2-methoxyethanol was stirred for 5 min. To this mixture was added 19.15 g (0.0785 mol) of 2,3-dichloro-6-nitroquinoxaline. The mixture was refluxed for 21 h with stirring. The crude product was obtained by filtration of the cooled reaction mixture, followed

Table I. 2,3-Bis(4-alkyl-1-piperazinyl)quinoxaline



compd[b]	R_1	R_2	R_3	R_4	prepn method	mp, °C	yield purified, %	recrystn solvent	lowest act. dose, (mg/kg)/day: cecal infectn	lowest act. dose, (mg/kg)/day: hepatic infectn[a]
1	CH_3	H	NH_2	H	*c*	208–210	*c*	CH_3CN	50	I[d]
2[e]	CH_3	NH_2	H	H	*c*	196–199	*c*	C_2H_5OH	50	I
3	$CH_2CH_2CH_3$	H	NH_2	H	*c*	143–146	*c*	CH_3CN	I	
4	CH_3	NH_2	H	Cl	*c*	237–240	*c*	$CH_3OCH_2CH_2OH$-H_2O	I	
5	CH_3	H	$N{=}CHN(CH_3)_2$	H	A	151–152	26	C_6H_6–pet. ether	20	50
6[f]	CH_3	$N{=}CHN(CH_3)_2$	H	H	A	184–186	68	CH_3CN	10	50
7	CH_3	$N{=}CHN(CH_3)_2$	H	Cl	A	183–185	73	$CHCl_3$	I	
8	$CH_2CH_2CH_3$	H	$N{=}CHN(CH_3)_2$	H	A	95.5–98	53	$CH_3(CH_2)_4CH_3$	50	100
9	CH_3	H		H	D	234–237	32	CH_3CN	50	100
10	CH_3	H		H	D	242–244	39	CH_3CN	I	
11	CH_3	H		H	B	135–139	39	CH_3CN	50	
12	CH_3	H	$N{=}C(CH_3)N(CH_3)_2$	H	A	160–162	38	CH_3CN	I	
13	CH_3	H	$N{=}CHN(C_2H_5)_2$	H	A	136–138	27	$CH_3(CH_2)_4CH_3$	I	
14	CH_3	H	$N{=}C(C_2H_5)N(C_2H_5)_2$	H	C	114–117	45	CH_3CN	I	
15	$CH_2CH_2CH_3$	H	$N{=}C(CH_3)N(CH_3)_2$	H	C	62–64	75	H_2O[g]	I	
16	CH_3	H		H	B	154–156	71	CH_3CN	I	
17	CH_3	H		H	B	170–172	62	CH_3CN	I	
18	CH_3	H		H	B	165–167	42	CH_3CN	I	
19[h]	CH_3	$N{=}C(C_2H_5)N(CH_3)_2$	H	H	C	128 dec.	53	*i*	I	
20	CH_3	$N{=}C(CH_3)N(CH_3)_2$	H	H	A	174–177	48	CH_3CN	I	
21	CH_3	$N{=}CHN(CH_3)_2$	H	Cl	A	183–185	73	$CHCl_3$	I	
22	CH_3	$N{=}C(CH_3)N(C_2H_5)_2$	H	Cl	C	156.5–158	71	$C_2H_5OC_2H_5$	I	
23	CH_3	$N{=}C(C_2H_5)N(CH_3)_2$	H	Cl	C	152–154	69	$C_2H_5OC_2H_5$	I	
24	CH_3	$NHSO_2(CH_2)_{15}CH_3$	H	Cl	D	94–96	72.5	$CHCl_3$-$CH_3C(=O)CH_3$	I	

25	CH_3	H		H	D	235–238	23	CH_3CN	I	
26	CH_3	H		H	D	136–140	30	CH_3CN	I	
27	CH_3		H	H	D	190–192	72	CH_3CN	I	
28	$CH_2CH_2CH_3$	H		H	D	94–100	32	C_6H_{12}	I	
29	CH_3		H	Cl	D	208–210	71	$CHCl_3$–$CH_3C(=O)CH_3$	I	
30[i]	$CH_2CH_2CH_3$	NH_2	H	H	*c*	110–112	*c*	C_6H_{12}	I	10
metronidazole									10	100
nitroimidazine									20	25
triimidazole									5	

[a] Compounds found inactive in the rat are not tested in the hamster. [b] All new compounds have correct analyses unless otherwise noted. [c] See Experimental Section. [d] Inactive. [e] N: calcd, 28.72; found, 28.11. Product also identified by IR and ^1H NMR. [f] N: calcd, 28.26; found 27.74. Product also identified by IR. [g] Reprecipitated from aqueous acid. [h] Dicitrate salt. [i] The dicitrate salt was isolated from a mixture of ethyl acetate and methanol (see Method C). [j] C: calcd, 66.46; found 65.38. N: calcd, 24.66; found, 23.95. Product has proper ^1H NMR. Analysis is correct for 0.5 hydrate.

by washing with 2-methoxyethanol and water. Analytically pure, yellow 2,3-bis(4-propyl-1-piperazinyl)-6-nitroquinoxaline, mp 127–130 °C, 12.9 g (38.3%), was obtained by recrystallization from a mixture of 200 mL of benzene and 300 mL of hexane. Anal. ($C_{22}H_{33}N_7O_2$) C, H, N.

A 16.6-g (0.0388 mol) portion of the preceding product was reduced in 150 mL of water and 20 mL of 6 N hydrochloric acid with 1.0 g of 10% palladium on charcoal under 50 psi of hydrogen. The solution was filtered, and upon the addition of 17 mL of 10 N sodium hydroxide a solid formed and was collected by filtration, washed thoroughly with water, and air-dried, followed by drying under reduced pressure at 50 °C. The yellow solid was recrystallized from 235 mL of hot acetonitrile and gave 12.0 g (77.8%) of analytically pure yellow product, mp 143–146 °C. Anal. ($C_{22}H_{35}N_7$) C, H, N.

5-Amino-2,3-bis(4-propyl-1-piperazinyl)quinoxaline (30). The method of preparation was the same method used in preparing 6-amino-2,3-bis(4-propyl-1-piperazinyl)quinoxaline (1).

From 19.15 g (0.0785 mol) of 2,3-dichloro-5-nitroquinoxaline, 50 g (0.17 mol) of 1-*n*-propylpiperazine dihydrobromide, and 60 g (0.71 mol) of sodium bicarbonate was obtained 31.9 g of crude product. Recrystallization from 600 mL of hexane gave 14.9 g (44.5%) of analytically pure, yellow 2,3-bis(4-propyl-1-piperazinyl)-5-nitroquinoxaline, mp 95–99 °C. Anal. ($C_{22}H_{33}N_7O_2$) C, H, N.

The reduction was carried out in the manner described for the preparation of 6-amino-2,3-bis(4-propyl-1-piperazinyl)quinoxaline (3).

From 15.7 g (0.0367 mol) of 2,3-bis(4-propyl-1-piperazinyl)-5-nitroquinoxaline was obtained 9.3 g (64%) of crude product. Recrystallization of a 3.3-g sample from 20 mL of ethyl acetate gave 1 g of orange product, mp 110–112 °C. The ^1H NMR spectrum was satisfactory for 5-amino-2,3-bis(4-propyl-1-piperazinyl)quinoxaline (30), although the analysis was below accepted limits.

5-Amino-7-chloro-2,3-bis(4-methyl-1-piperazinyl)-quinoxaline (4). The same procedure was employed as described for the preparation of the other aminoquinoxalines (1, 2, etc.), except for the reduction of the nitroquinoxaline.

From 122 g (0.652 mol) of 5-chloro-3-nitro-*o*-phenylenediamine, 160 g (1.27 mol) of oxalic acid dihydrate, and 2 L of 50% acetic acid was obtained 66.4 g (42%) of 7-chloro-2,3-dihydroxy-5-nitroquinoxaline, mp 315 °C (dec). Recrystallization of a sample from 50% acetic acid gave analytically pure brown product, mp 327–329 °C (dec). Anal. ($C_8H_4N_3ClO_4 \cdot 0.75H_2O$) C, H, N.

From 96.8 g (0.4 mol) of 7-chloro-2,3-dihydroxy-5-nitroquinoxaline and 192 g (0.92 mol) of phosphorus pentachloride was obtained 116 g (100%) of 5-nitro-2,3,7-trichloroquinoxaline, mp 101–106 °C. Recrystallization of a sample from chloroform–hexane gave analytically pure product, mp 107–109 °C. Anal. ($C_8H_2N_3Cl_3O_2$) C, H, N, Cl.

From 119 g (0.427 mol) of 5-nitro-2,3,7-trichloroquinoxaline and 214 g (2.14 mol) of *N*-methylpiperazine was obtained 124.1 g (71.7%) of yellow product, 7-chloro-2,3-bis(4-methyl-1-piperazinyl)-5-nitroquinoxaline, mp 153–155 °C. Recrystallization of a sample from 2-methoxyethanol gave an analytically pure yellow product, mp 153–155 °C. Anal. ($C_{18}H_{24}N_7ClO_2$) C, H, N, Cl.

To a solution of 100 g (0.246 mol) of 7-chloro-2,3-bis(4-methyl-1-piperazinyl)-5-nitroquinoxaline in 600 mL of *p*-dioxane at 80 °C was added a hot solution of 136 g (0.566 mol) of sodium sulfide monohydrate in 600 mL of water. The reaction mixture was stirred at 90 °C for 40 min. The reaction mixture was stored at 4 °C for 16 h after the addition of 600 mL of water. The tan product, 75 g (81.3%), mp 237–239 °C, was collected by filtration, followed by washing and drying. Recrystallization of a 10-g portion from 2-methoxyethanol–water gave 8.0 g of analytically pure yellow product, 5-amino-7-chloro-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (4), mp 237–240 °C.

6-[[[4-[3-(Dimethylamino)propyl]piperidino]-methylene]amino]-2,3-bis(4-methyl-1-piperazinyl)-quinoxaline (11). A 297-g (2.16 mol) amount of 4-pyridinepropanol (practical grade) was added portionwise to 1200 mL of 48% hydrogen bromide solution over a 10-min period with stirring. The resulting solution was refluxed for 19.5 h. The reaction mixture was cooled slightly and stripped of solvent under reduced

pressure. The solid residue was recrystallized from 1100 mL of ethanol after treatment with activated charcoal. The precipitate formed was collected by filtration, washed twice with ethanol, air-dried, and gave 342.9 g of pale yellow solid. The combined filtrate and washings above were reduced to about one-half volume, cooled to 4 °C, filtered, washed with cold ethanol, air-dried, and gave an additional 71.9 g of pale yellow solid. The combined filtrate and washings of the above solid was combined with an equal volume of diethyl ether and cooled to 4 °C. The solid formed was filtered, washed with 100 mL of 1:1 ethanol/ether, air-dried, and gave 84.7 g of a tan solid. The combined weight of 4-(3-bromopropyl)pyridine hydrobromide was 499.5 g (82.4%). To the 499.5 g of the preceding product in 500 mL of benzene was added a solution of 8.0 g of sodium hydroxide in 200 mL of cold water at 10–15 °C with stirring. The two-layered liquid was poured into a separatory funnel and an additional 50 mL of 10 N sodium hydroxide was added with thorough mixing. The aqueous layer (pH 13.0–13.5) was separated from the benzene layer and extracted with 200 mL of benzene. The benzene extracts were combined and dried over anhydrous potassium carbonate and anhydrous magnesium sulfate. The benzene solution was cooled to 5 °C and a total of 226 g of dimethylamine gas was added over a 2.5-h period with stirring. Stirring was continued while the solution was allowed to cool to room temperature overnight. A 300-mL portion of 10 N sodium hydroxide was added to the cooled reaction mixture with stirring, the layers separated and the aqueous layer was extracted with two 250-mL portions of benzene. The combined benzene extract was washed with three 100-mL portions of cold water and dried over anhydrous potassium carbonate and anhydrous magnesium sulfate. The aqueous layer was saturated with potassium carbonate, resulting in separation of an organic top layer which was insoluble in benzene. The organic layer was extracted twice with 250 mL of benzene as was the saturated aqueous layer. The combination of benzene extracts was dried over anhydrous potassium carbonate and anhydrous magnesium sulfate, stripped of solvent by water-pump evacuation, and gave 283.2 g of residual oil, which was distilled through a 15 × 2 cm Podbielniak Helipak filled column at a bath temperature ranging from 150 to 180 °C and controlled pressure of 9.0 to 10.0 mm. The 243.1-g (83%) fraction collected at a distillation temperature of 112–114 °C was 4-[3-(dimethylamino)propyl]pyridine.

A 16.4-g (0.10 mol) portion of the above product was dissolved in 100 mL of 1:1 ethyl alcohol/water and 34.2 mL of 5.85 N hydrogen chloride in isopropyl alcohol and reduced with 1 g of platinum oxide over 40 psi of hydrogen. The reduction mixture was filtered through diatomaceous earth, and the filter cake was washed with 50% aqueous ethanol. The combined filtrate and washings was stripped of solvent by water-pump evacuation. The residue was dried in vacuo over phosphorus pentoxide at 110 °C and gave 4-[3-(dimethylamino)propyl]piperidine dihydrochloride as an off-white solid, mp 233–239 °C (dec).

A mixture of 7.75 g (0.0195 mol) of *N*-[2,3-bis(4-methyl-1-piperazinyl)-6-quinoxalinyl]formimidic acid ethyl ester and 8.5 g (0.050 mol) of the preceding product (free base) above was heated at reflux in an oil bath at about 140 °C for 2.5 h. The condenser was removed and the distillate was allowed to boil off. The reaction mixture was slurried with 150 mL of boiling hexane, cooled at −10 °C, and filtered. The pasty material collected was dissolved in 90 mL of hot acetonitrile. This solution was treated with activated charcoal and filtered. The filtrate was cooled at −10 °C, and the yellow solid formed was collected by filtration, dried in vacuo at 78 °C over phosphorus pentoxide, and gave 3.9 g (38.5%) of 6-[[[4-[3-(dimethylamino)propyl]piperidino]-methylene]amino]-2,3-bis(4-methyl-1-piperazinyl)quinoxaline (**11**), mp 135–139 °C.

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Synthesis and Antiarrhythmic Properties of Some 5-Benzamido-2-methyl-*trans*-decahydroisoquinolines

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An efficient synthetic route to produce exclusively 5-amino-2-methyl-*trans*-decahydroisoquinoline is described. The preparation of ten 5-benzamido-2-methyl-*trans*-decahydroisoquinolines from this precursor has been accomplished, and each has been screened for both antiarrhythmic potency and toxicity. The selection of structures for synthesis was based on our previous report of the significant antiarrhythmic potency of 5-(3,4,5-trimethoxybenzamido)-2-methyl-*trans*-decahydroisoquinoline (**15**). Molecular modifications of this single structure were made in order to ascertain structure–activity relationships in this group of compounds. All the compounds synthesized showed significant antiarrhythmic potency. The lipophilicity of the benzamide moiety appears to play a significant role in developing optimal antiarrhythmic potency. Interestingly and surprisingly, the most potent compound of the present study was **15**, a compound described in our original work. Structure–activity relationships of the series are described.

In a continuing investigation of the antiarrhythmic properties of variously substituted decahydroisoquinolines, a more extensive study was conducted of some of our earlier work related to the 5-substituted decahydroisoquinoline series. The early studies indicated that the more lipophilic trans ring junctured isomers possessed the optimal antiarrhythmic potencies.[2a,b] Subsequent studies on several examples of 6-[3] and 8-substituted[4] decahydroisoquinolines yielded similar conclusions. In addition, the

(1) The work reported constituted a segment of the thesis submitted by R. J. Pennington to the University of Tennessee, Center for the Health Sciences, in partial fulfillment of the Master of Science degree requirements in medicinal chemistry.

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