port, as well as the excellent technical assistance of F. Garcia, M. Charon, and P. Bucau-Varlet, in the biological assays and N. Chi-Hung and M. Rautureau in the chemical syntheses. F.W., P.T., and J.M.L. are supported by INSERM (Unités 22 and 219).

Registry No. **1a**, 69022-46-4; **1b**, 65222-35-7; **1c**, 83947-99-3; **1d**, 83948-00-9; **1e**, 83948-01-0; **1g**, 83948-02-1; **1h**, 83948-03-2; **1k**, 83948-04-3; **1m**, 83948-05-4; **2b**, 73323-33-8; **2i**, 73323-34-9; **3a**, 72237-96-8; **3b**, 72238-00-7; **3c**, 83948-06-5; **3e**, 83948-07-6; **3f**, 83948-08-7; **3h**, 83948-09-8; **3i**, 83948-10-1; **4a**, 72237-98-0; **4b**, 72238-02-9; **4c**, 83948-11-2; **4d**, 83948-12-3; **4h**, 83948-13-4; **7a**, 83947-90-4; **7b**, 83948-14-5; **7i**, 83948-15-6; **7k**, 83948-16-7; **8a**, 83947-91-5; **8b**, 83948-17-8; **8i**, 83948-18-9; **8k**, 83948-19-0; **9b**, 83948-20-3; **10b**, 83948-21-4; **10c**, 83948-22-5; **10i**, 83948-23-6; **12**, 72237-94-6; **13**, 72238-06-3; **14**, 83947-93-7; **15**, 83947-92-6; **16**, 83947-94-8; **17**, 83947-95-9; **18**, 83947-96-0; **19**, 83947-97-1; **20**, 83947-98-2; **21b**, 72238-04-1; **22b**, 72238-05-2.

Synthesis and Antileishmanial Activity of 6-Methoxy-4-methyl-*N*-[6-(substituted-1-piperazinyl)hexyl]-8-quinolinamines and Related Compounds[1,2]

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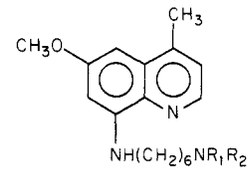
The 8-quinolinamine, 4-[6-[(6-methoxy-4-methyl-8-quinolinyl)amino]hexyl]-1-piperazineethanol (**1b**), has been shown to be highly effective against *Leishmania donovani* infections in hamsters. In an effort to obtain a more potent, less toxic 8-quinolinamine, a series of analogues (**2**) was prepared that examined particularly the structural requirements of the terminal piperazine moiety. Of the substituted piperazines and alternative heterocycles prepared, as well as those quinoline analogues with ring insertion of a methyl group in the 2-position or an aryloxy substituent in the 5-position, an increase in potency was achieved only with the 2-hydroxypropyl analogue (**2f**).

Leishmaniasis is a disease of tropical and subtropical areas caused by intracellular protozoan parasites of the genus *Leishmania* and is transmitted by the bite of phlebotomine flies (sandflies). It displays four general clinical forms: cutaneous, mucocutaneous, chiclero ulcer, and visceral, which are caused, respectively, by *L. tropica*, *L. braziliensis*, *L. mexicana*, and *L. donovani*. In the first three forms the parasites invade the cutaneous tissues in various parts of the body, causing disfiguring lesions of differing severity. In the visceral form of the disease, the phagocytic cells of the spleen, liver, and bone marrow are invaded, often resulting in death. Antimonials and the antibiotic Amphotericin B are used to treat the disease but are often of limited efficacy and the cause of host toxicity;[3,4] thus, the need for a better drug is real and ongoing.

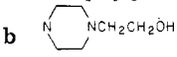
Although a multitude of 8-quinolinamines have been examined for antimalarial activity, relatively little information is available, and apparently only limited effort has been expended toward the development of an agent for *Leishmaniasis* from this class of compounds.

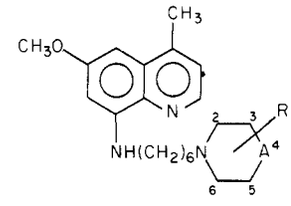
A series of 4-unsubstituted 8-quinolinamines containing side chains related to that in **1b** had been reported to be active against *L. donovani* and *L. tropica* infections in hamsters.[5-8] More recently, the presence of a methyl group in the 4-position has been shown to enhance activity, and *N*,*N*-diethyl-*N*-(6-methoxy-4-methyl-8-quinolinyl)-1,6-hexanediamine (**1a**) was the most potent compound examined, exhibiting a *G* index[9] of 474[3] against *L. donovani* infections in hamsters. Since an analogue with a piperazine side chain (**1b**) prepared in the course of our previous investigations proved to be quite active (*G* = 104) in this experimental model, we undertook the preparation of analogues with the aim of providing a more potent, less toxic 8-quinolinamine structure.



NR_1R_2

1a $N(C_2H_5)_2$

b 



2, A = NR', $S(O)_n$, O

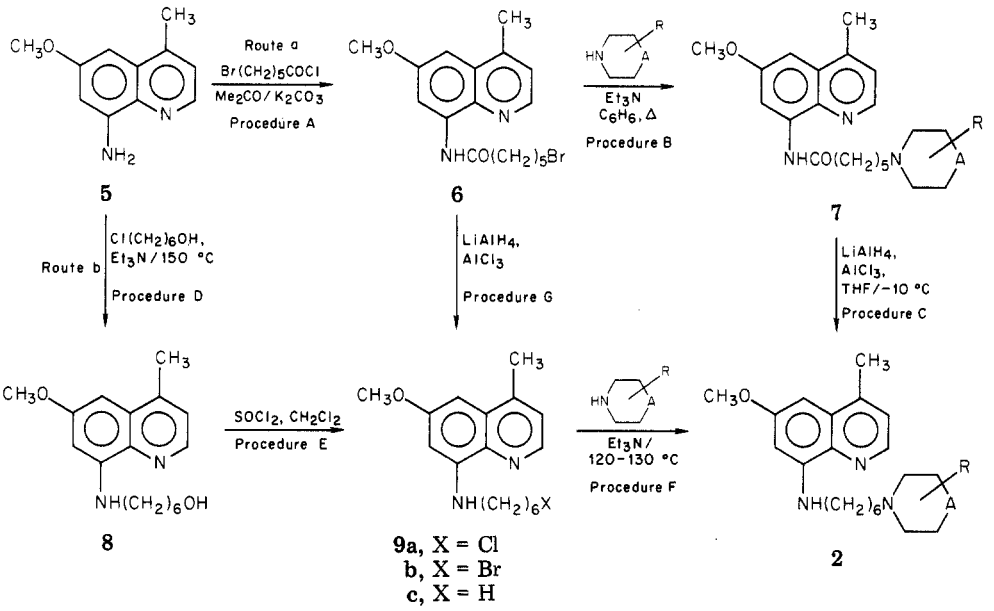
Our primary goal was the modification of **1b** by variation of and substitution on the piperazine moiety as represented in structure **2**.

Recent efforts to develop a less toxic 8-quinolinamine for malaria therapy have revealed that the introduction of a 5-phenoxy group reduced toxicity while retaining activity in murine and primate antimalarial models.[10]

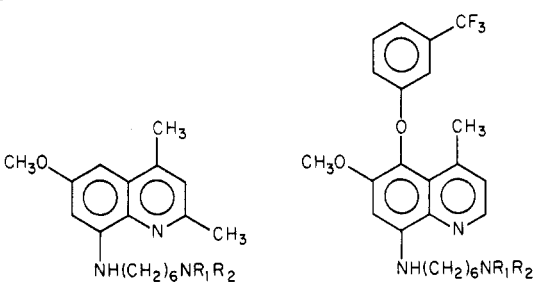
(1) This investigation was supported by the U.S. Army Medical Research and Development Command Contract DAMD 17-79-C-9122. This is contribution no. 1552 to the Army Research Program on Antiparasitic Drugs.
(2) A preliminary report of this work has been presented; see "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, NY, Aug 1982, American Chemical Society, Washington, DC, 1982, Abstr MEDI 25.
(3) K. E. Kinnamon, E. A. Steck, P. S. Loiseaux, W. L. Hanson, W. L. Chapman, and V. B. Waits, *Am. J. Trop. Med. Hyg.*, **27**, 751 (1978).
(4) E. A. Steck, *Progr. Drug Res.*, **18**, 290 (1974).
(5) L. P. Walls, British Patents 834 300 (1960); 1 153 471 (1969).
(6) P. A. Barrett, A. G. Caldwell, and L. P. Walls, German Patent 1 237 121 (1963).
(7) P. A. Barrett, A. G. Caldwell, and L. P. Walls, U.S. Patent 3 142 679 (1964); West German Patent 1 132 557 (1962).
(8) P. A. Barrett, A. G. Caldwell, and L. P. Walls, *J. Chem. Soc.*, 2404 (1961).
(9) *G* index = the SD_{90} for meglumine antimoniate (standard drug) divided by the SD_{90} for the test compound, where SD_{90} is defined as the dose providing 90% suppression of parasitemia.
(10) E. H. Chen, A. J. Saggiomo, K. Tanabe, B. L. Verma, and E. A. Nodiff, *J. Med. Chem.*, **20**, 1107 (1977).

0022-2623/83/1826-0185$01.50/0

Scheme I



Thus, several nuclear-substituted analogues of **1** as represented by structures **3** and **4** were also included in this study.



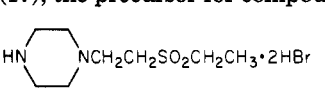
3 **4**

Chemistry. Many of the 6-methoxy-4-methyl-*N*-[6-(substituted-1-piperazinyl)hexyl]-8-quinolinamines and related compounds (**2**) were prepared as shown in Scheme I.[11] In route a, acylation of 6-methoxy-4-methyl-8-quinolinamine (**5**)[12] with 6-bromohexanoyl chloride (procedure A) afforded 6-bromo-*N*-(6-methoxy-4-methyl-8-quinolinyl)hexanamide (**6**), which was allowed to react with the requisite piperazine or related heterocycle to give the corresponding substituted hexanamide **7** (procedure B; Table I). This material was then reduced with lithium aluminum hydride/aluminum chloride (3:1) to provide **2** (Table II, procedure C). The nuclear analogues **3** and **4** (Tables III and IV) also were prepared in this manner.

Although the above sequence was clean and provided the final products in reasonably good yield, it was unacceptable in those cases in which the terminal heterocycle contained an acyl group that would also be reduced by the $LiAlH_4/AlCl_3$ reduction. Another disadvantage when large numbers of analogues are being prepared is that two steps are required from the common intermediate **6** to the final product **2**. Therefore, a modification (route b) was employed in which the products **2** were obtained by the reaction of the appropriate piperazine or related heterocycle with *N*-(6-halohexyl)-6-methoxy-4-methyl-8-quinolinamine (**9a** or **9b**) at 120–130 °C (procedure F). Initially, *N*-(6-chlorohexyl)-6-methoxy-4-methyl-8-quinolinamine (**9a**) was prepared as the requisite intermediate by the alkylation of **5** with 6-chlorohexanol to provide **8** (procedure D), followed by chlorination with thionyl chloride (procedure E). Because of the inefficient alkylation reaction and the resultant difficult chromatographic separation, a second approach to **9** was investigated, wherein the hexanamide **6** was reduced with $LiAlH_4/AlCl_3$ (3:1) to afford a mixture containing approximately 9 parts of the desired **9b** (64% yield) and 1 part of the dehalogenated material **9c** (procedure G). The mixture was utilized directly in the next reaction, and the product, **2**, was separated readily from **9c** by chromatography.

Finally, several of the products, **2f, h, i, v–cc**, were prepared by simply alkylating or acylating **2a** with the appropriate reagents (Scheme II, procedures I–K). The reaction of **9a** or **9b** with piperazine to obtain **2a** was complicated by the simultaneous formation of the bisadduct **2dd**, and the resultant mixture was difficult to purify (procedure H). We eliminated this problem by allowing **9** to react with phenylmethyl 1-piperazinecarboxylate[13,14] (**10**) to afford **2u**, which was hydrolyzed cleanly to **2a** in a hydrobromic/acetic acid mixture (Scheme II, procedures L, M).

We prepared 1-[2-(ethylsulfonyl)ethyl]piperazine dihydrobromide (**17**), the precursor for compound **2e** by first

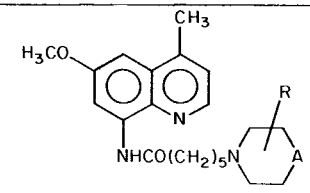


17

allowing 2-hydroxy-2-(ethylsulfonyl)ethyl 4-methylbenzenesulfonate[15] to react with the sodium salt of phenylmethyl 1-piperazinecarboxylate (**10**) to provide phe-

(11) Modified procedure of P. A. Barrett et al.[8]
(12) K. N. Campbell, A. H. Sommers, J. F. Kerwin, and B. K. Campbell *J. Am. Chem. Soc.*, **68**, 1556 (1946).
(13) W. O. Foye and L. R. Fedor, *J. Am. Pharm. Assoc.*, **48**, 412 (1959).
(14) H. G. Kazmirowski, E. Carstens, and D. Lehman, East German Patent 130658, Apr 19, 1978.
(15) M. W. Miller, H. L. Howes, Jr., R. V. Kasubick, and A. R. English, *J. Med. Chem.*, **13**, 849 (1970).
(16) Tests were performed by Dr. W. L. Hanson, University of Georgia, Athens, GA.
(17) W. L. Hanson, W. L. Chapman, Jr., and K. E. Kinnamon, *Int. J. Parasitol.*, 7, 443 (1977).
(18) Test results were supplied through the courtesy of Col. D. A. Davidson and Dr. E. A. Steck of the Walter Reed Army Institute of Research.

Table I. *N*-(6-Methoxy-4-methyl-8-quinolinyl)-substituted-1-piperazinehexanamides and Related Compounds



no.		mp, °C	purified yield, %	reaction solvent/time	purification solvent	formula	anal.
7a	4-Me-P[a]	104–105	53	C_6H_6/44 h	hexane + toluene	$C_{22}H_{32}N_4O_2 \cdot 0.2H_2O$	C, H, N, H_2O
7b	4-cyclohexyl-P[a,b]	109–110	75	C_6H_6/40 h	2-PrOH/H_2O	$C_{27}H_{40}N_4O_2$	C, H, N
7c	*N*-(3,4-Cl_2-C_6H_3)-P[a,b]	99–100	62	C_6H_6/46 h	2-PrOH	$C_{27}H_{32}Cl_2N_4O_2$	C, H, N, Cl
7d	*N*-(2-pyridyl)-P[a]	120–121	85	toluene/2.5 h	2-PrOH	$C_{26}H_{33}N_5O_2 \cdot 0.2H_2O$	C, H, N, H_2O[c]
7e	3,5-$(CH_3)_2$-P[a]	94–96	83	C_6H_6/25 h	hexane + toluene	$C_{23}H_{34}N_4O_2$	C, H, N
7f	bis-1,4-substituted-P[f]	169–171	52	toluene, Et_3N/28 h	toluene + 2-PrOH	$C_{38}H_{50}N_6O_4$	C, H, N
7g	4-Me-D[a]	74–77	45	toluene/20 h	hexane	$C_{23}H_{34}N_4O_2$	C, H, N
7h	*trans*-3,5-Me_2-TM[a,d]	75–77	26	C_6H_6/11 h	hexane	$C_{23}H_{33}N_3O_2S$	C, H, N
7i	*cis*-3,5-Me_2-TM[a,d]	61–63	43	C_6H_6/11 h	hexane	$C_{23}H_{33}N_3O_2S$	C, H, N
7j	thiomorpholine	89–91	89	C_6H_6/37 h	2-PrOH	$C_{21}H_{29}N_3O_2S$	C, H, N, S
7k	3,5-Me_2-M	87–90	55	C_6H_6/26 h	hexane	$C_{23}H_{33}N_3O_3 \cdot 0.2C_6H_{14}$[e]	C, H, N

[a] P = piperazine; M = morpholine; TM = thiomorpholine; D = perhydro-1,4-diazepine. [b] The starting piperazines for these compounds were obtained from the Warner-Lambert files. References for these compounds are as follows: **7b**, H. G. Morren, Belgian Patent 549 420, 1957; **7c**, D. R. Maxwell and W. R. Wragg, British Patent 943 739, 1963. [c] H_2O: Calcd, 0.80; found, 0.31. [d] The mixture of *cis*- and *trans*-2,6-dimethylthiomorpholine used to prepare **7h** and **7i** was prepared by Gary Larsen according to D. Harman and W. E. Vaughan, *J. Am. Chem. Soc.*, **72**, 632 (1950). The cis and trans products were isolated by chromatography and identified by NMR techniques. [e] The presence of hexane was demonstrated by NMR. [f] The precursor to **2dd** (Scheme II).

nylmethyl 4-[2-(ethylsulfonyl)ethyl]-1-piperazinecarboxylate and then hydrolyzing this with 48% hydrobromic acid in acetic acid.

Antileishmanial Activity. Most of the side-chain analogues (**2**, Table V) are more potent than the reference standard and the 2-hydroxypropyl analogue (**2f**) is more potent (G = 143) than **1b** (Table V). However, even the closely related 3-hydroxypropyl (**2g**) and the 2,3-dihydroxypropyl (**2h**) compounds are less active and none of the compounds is superior to **1a**.

Insertion of a methyl group at the 2-position of the quinoline ring results in a 10-fold loss of activity (**3b–c**, Table III) compared with **1a**. Although further testing at lower dose levels is required to compute G values on compounds **4a–c** (Table IV), it is clear that the intent to reduce toxicity by the attachment of the 5-[3-(trifluoromethyl)-phenoxy] group has not been realized.

Conclusion

The nature of the terminal amine function in this system is surprisingly specific with regard to antileishmanial potency. Clearly, replacement of a simple dialkyl substituent with a piperazine or more complex hetero ring system will not achieve the desired result of higher potency and lower toxicity among the 8-quinolinamines.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus. Satisfactory IR and NMR spectra were obtained for all compounds. Anhydrous $MgSO_4$ was used to dry solutions.

Procedure A (Scheme I). 6-Bromo-*N*-(6-methoxy-4-methyl-8-quinolinyl)hexanamide (6). To a mixture of 18.8 g (0.10 mol) of 6-methoxy-4-methyl-8-quinolinamine (**5**)[12,19] and 17.0 g (0.16 mol) of Na_2CO_3 in 350 mL of acetone was added dropwise a solution of 21.4 g (0.10 mol) of 6-bromohexanoyl chloride in 100 mL of acetone. The mixture was heated under reflux for 3 h and allowed to cool, and then Et_3N was added dropwise to the stirred mixture until the yellow color disappeared. The mixture was filtered and the filter cake was washed with acetone and then with CH_2Cl_2. The acetone filtrate and wash were concentrated to dryness, and the residue was combined with the CH_2Cl_2 wash. The solution was washed with H_2O and with brine, dried, and concentrated to dryness to provide 38.7 g. Recrystallization from EtOH afforded 31 g (65%) of the product, **6**, mp 114–116 °C. Anal. ($C_{17}H_{21}BrN_2O_2$) C, H, N.

6-Bromo-*N*-(6-methoxy-2,4-dimethyl-8-quinolinyl)hexanamide (Table III, 11) and 6-bromo-*N*-[6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxy]-8-quinolinyl]hexanamide (Table IV, 16) were obtained similarly from 6-methoxy-2,4-dimethyl-8-quinolinamine[19,20] and 6-methoxy-4-methyl-5-[3-(trifluoromethyl)phenoxyl-8-quinolinamine.[19]

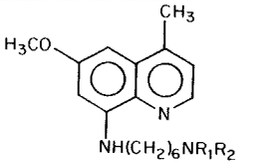
Procedure B (Scheme I). *N*-(6-Methoxy-4-methyl-8-quinolinyl)-4-methyl-1-piperazinehexanamide Hydrate (1:0.2) (7a, Table I). A mixture of 5.5 g (0.015 mol) of 6-bromo-*N*-(6-methoxy-4-methyl-8-quinolinyl)hexanamide (**6**) and 1.8 g (0.018 mol) of 1-methylpiperazine in 70 mL of benzene was heated under reflux for 20 h, treated with 2 mL of Et_3N, and heated for an additional 24 h. The mixture was allowed to cool and then filtered, and the filtrate was washed with H_2O, dried, and concentrated to dryness in vacuo. The residue was recrystallized twice from *n*-hexane containing a little toluene and then dried in vacuo at 68 °C to afford 3.1 g (53%) of the title compound, mp 104–107 °C.

See Tables I and III for compounds prepared similarly. Some were obtained as oils and are not reported in the tables but were used without further purification in the next step.

Procedure C (Scheme I). 6-Methoxy-4-methyl-*N*-[6-(4-methyl-1-piperazinyl)hexyl]-8-quinolinamine Trihydro-

(19) Provided by the Walter Reed Army Institute of Research.
(20) F. I. Carroll, B. D. Berrang, and C. P. Linn *J. Med. Chem.*, **23**, 581 (1980).

Table II. 6-Methoxy-4-methyl-*N*-[6-(substituted-1-piperazinyl)hexyl]-8-quinolinamines and Related Compounds

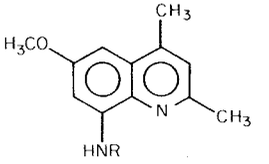


no.	NR_1R_2	mp, °C	procedure(s)	yield purified,[a] %	reaction solvent	reaction time, h/temp, °C	purification solvent	formula	anal.
2a	piperazine (P)[r]	245–247	D, E, H	60	toluene	110–130	HCl/2-PrOH	$C_{21}H_{32}N_4O\cdot 3HCl\cdot 0.2C_3H_8O\cdot 0.5H_2O$[b]	C, H, N, Cl^-, H_2O
2b	4-Me-P[r]	241–244 dec	A, B, C	74	THF	3/−20 to 0	HCl/2-PrOH[c]	$C_{22}H_{34}N_4O\cdot 3HCl\cdot 1.4H_2O\cdot 0.3C_3H_8O$[b]	C, H, N, Cl^-, H_2O
2c	4-[$(CH_2)_{11}CH_3$]-P[r]	53–55	D, E, F[d]	22	neat[e]	3/130	2-PrOH	$C_{33}H_{56}N_4O$	C, H, N
2d	4-cyclohexyl-P[r]	68–70	A, B,[d] C	43	THF	3/−20 to 0	2-PrOH	$C_{27}H_{42}N_4O$	C, H, N
2e	4-($CH_2CH_2SO_2C_2H_5$)-P[r]	70–72	D, E, F	61	DMF + Et_3N	5/120	hexane–2-PrOH (3:2)	$C_{25}H_{40}N_4O_3S\cdot 0.2C_6H_{14}$[f]	C, H, N
2f	4-($CH_2CHOHCH_3$)-P[r]	245 dec	D, E, F	46	neat	3/130	HCl/2-PrOH	$C_{24}H_{38}N_4O_2\cdot 3HCl\cdot 1.3H_2O$	C, H, N, Cl^-, H_2O
2g	4-($CH_2CH_2CH_2OH$)-P[r]	100–102	A, B, C	49	THF	2/−10 to 0	2-PrOH	$C_{24}H_{38}N_4O_2$	C, H, N
2h	4-($CH_2CHOHCH_2OH$)-P[r]	237–241	I	23	neat[e]	5/130	HCl/2-PrOH	$C_{24}H_{38}N_4O_3\cdot 2.9HCl\cdot 0.5H_2O$	C, H, N, Cl^-, H_2O
2i	4-[$CH_2CHOHCH_2N(C_2H_5)_2$]-P[r]	241–244	I[g]	30	neat	4/100	HCl/2-PrOH	$C_{28}H_{47}N_5O_2\cdot 3.9HCl\cdot 0.9H_2O\cdot 0.2C_3H_8O$[b]	C, H, N, Cl^-, H_2O
2j	4-[$(CH_2)_3N(CH_3)_2$]-P[r]	255–258 dec	D, E, F[h]	32	neat	4/120	EtOH	$C_{26}H_{43}N_5O\cdot 4HCl\cdot 0.3H_2O\cdot 0.2C_2H_6O$[i]	C, H, N, Cl^-, H_2O
2k	4-[$CH_2CH_2OCH(C_6H_5)_2$]-P[r]	138–145	A, B,[d] C	81	THF	2/−20 to 0	HCl/2-PrOH[c]	$C_{36}H_{46}N_4O_2\cdot HCl\cdot 0.3H_2O$	C, H, N, Cl, H_2O
2l	4-[$CH(C_6H_5)(4\text{-}Cl\text{-}C_6H_4)$]P[r]	180–185 dec	A, B,[d] C	38	THF	3/−20 to 0	HCl/2-PrOH[c]	$C_{34}H_{41}ClN_4O\cdot 2.2HCl$	C, H, N, Cl, Cl^-
2m	4-(3,4-Cl_2-C_6H_3)-P[r]	92–94	A, B,[d] C	81	THF	3/−20 to 0	2-PrOH	$C_{27}H_{34}Cl_2N_4O$	C, H, N
2n	4-(2-pyridyl)-P[r]	78–81	A, B, C	66	THF	3/−20 to 0	2-PrOH	$C_{26}H_{35}N_5O$	C, H, N
2o	2-CH_3-4-[$CH_2CH_2CH(CH_3)_2$]-P[r]	175–200 indef	A, B,[d] C	60	THF	3/−20 to 0	HCl/2-PrOH[c]	$C_{27}H_{44}N_4O\cdot 2.7HCl\cdot 0.5H_2O$	C, H, N, Cl^-, H_2O
2p	3,5-$(CH_3)_2$-P[r]	120–180 dec	A, B, C	41	THF	1/−20 to 0	HCl/2-PrOH	$C_{23}H_{36}N_4O_6\cdot 1.1H_2O\cdot 0.4C_3H_8O$[b]	C, H, N, Cl, H_2O[j]
2q	1(2*H*)-3,4-H_2-Q[r]	92–94	N	92	H_2SO_4	18/22	2-PrOH	$C_{25}H_{32}N_4O$	C, H, N
2r	4-($SO_2C_6H_5$)-1(2*H*)-3,4-H_2-Q[r]	134–137	G, F[h]	22	neat[e]	3/130	EtOH	$C_{31}H_{36}N_4O_3S$	C, H, N
2s	4-($SO_2C_2H_5$)-P[r]	72–74	D, E, F[d]	68	neat	1/130	2-PrOH	$C_{23}H_{36}N_4O_3S$	C, H, N
2t	4-($CO_2C_2H_5$)-P[r]	59–60	D, E, F	21	neat	3/135	2-PrOH–H_2O	$C_{24}H_{36}N_4O_3$	C, H, N
2u	4-($CO_2CH_2C_6H_5$)-P[r]	143–150 prior sintering	G, L	67 6	neat[e]	2/150	HCl/2-PrOH	$C_{29}H_{38}N_4O_3\cdot 2HCl\cdot 0.4H_2O$	C, H, N, Cl^-, H_2O
2v	4-[$COCH(C_2H_5)_2$]-P[r]	250–253 dec	J	33	acetone	1.5/reflux	HCl/2-PrOH	$C_{27}H_{42}N_4O_2\cdot 2HCl\cdot 0.1C_3H_8O$[b]	C, H, N, Cl^-
2w	4-($CONHC_2H_5$)-P[r]	100–130 indef	K	29	THF	3/RT	HCl/2-PrOH[c]	$C_{24}H_{37}N_5O_2\cdot 2HCl\cdot 0.7H_2O\cdot 0.5C_3H_8O$[b]	C, H, N, Cl^-, H_2O[l]
2x	4-[$CON(CH_2CH_3)_2$]-P[r]	226–228 dec	J	50	acetone	2/reflux	HCl/2-PrOH[c]	$C_{26}H_{41}N_5O_2\cdot 2HCl\cdot 0.4H_2O$	C, H, N, Cl^-, H_2O
2y	4-[$CON(CH_2CH_2CH_3)_2$]-P[r]	210–213	J	65	acetone	1/reflux	HCl/2-PrOH	$C_{28}H_{45}N_2O_2\cdot 2HCl\cdot 0.3H_2O$	C, H, N, Cl^-, H_2O

2z	4-[$CON(C_6H_5)_2$]-P[r]	90–110	J	45	acetone	2/reflux	acetone/2-PrOH[c]	$C_{34}H_{41}N_5O_2 \cdot 2.5H_3PO_4 \cdot 0.2C_3H_8O \cdot 0.8H_2O$[b]	C, H, N, P, H_2O
2aa	4-($CSNHC_2H_5$)-P[r]	110–125 indef	K	30	THF	12/RT	HCl/2-PrOH	$C_{24}H_{37}N_5OS \cdot 2HCl \cdot 0.8H_2O \cdot {}^1/_3C_3H_8O$[b]	C, H, N, Cl^-, S, H_2O[m]
2bb	4-[$C(=NCN)SCH_3$]-P[r]	97–99	K[n]	66	toluene	64/22	2-PrOH	$C_{24}H_{34}N_6OS$	C, H, N, S
2cc	4-[$CON(CH_2)_4$]-P[r]	190–192 dec	J	27	acetone	2/reflux	2-butanone	$C_{26}H_{39}N_5O_2 \cdot HCl \cdot 0.4H_2O$	C, H, N, Cl^-, H_2O
2dd	bis-1,4-substituted-P[r,s]	126–128	A, B, C	43	THF	18/−15 to RT	2-PrOH/MeOH (2:3)	$C_{38}H_{54}N_6O_2 \cdot 0.2C_3H_8O$[b]	C, H, N
2ee	4-Me-D[r]	137–139	A, B, C	45	THF	3/−10 to 0	2-PrOH[o]	$C_{23}H_{36}N_4O \cdot 2.4C_4H_4O_4$[o]	C, H, N
2ff	*trans*-3,5-Me_2-TM[r]	68–80	A, B, C	67	THF	3/−10 to 0	EtOH/H_2O	$C_{23}H_{35}N_3OS \cdot 2C_7H_6O_3 \cdot 0.5H_2O$[p]	C, H, N, S, H_2O
2gg	*cis*-3,5-Me_2-TM[r]	217–219 dec	A, B, C	74	THF	3/−10 to 0	$(CH_3)_2CO$[c]	$C_{23}H_{35}N_3OS \cdot 2HCl \cdot 0.7H_2O$	C, H, N, Cl^-, H_2O
2hh	thiomorpholine (TM)[r]	257–259 dec	A, B, C	82	THF	3/−10 to 0	HCl/2-PrOH	$C_{21}H_{31}N_3OS \cdot 2HCl \cdot 0.2C_3H_8O$[b]	C, H, N, Cl^-
2ii	TM[r] *S*-oxide	252–255	O	43	30% H_2O_2/AcOH	18/RT	HCl/2-PrOH[c]	$C_{21}H_{31}N_3O_2S \cdot 2HCl \cdot 0.2H_2O \cdot 0.5H_2O$	C, H, N, S, Cl^-, H_2O
2jj	TM,[r] *S,S*-dioxide	92–94	D, E, F[d]	72	toluene	6/120–140	2-PrOH	$C_{21}H_{31}N_3O_3S$	C, H, N
2kk	3,5-Me_2-M[r]	223–226 dec	A, B, C	53	THF	3/−20 to 0	HCl/2-PrOH	$C_{23}H_{35}N_3O_2 \cdot 2HCl \cdot 0.3C_3H_8O \cdot 0.3H_2O$[b]	C, H, N, Cl^-, H_2O
1b[q]	4-(CH_2CH_2OH)-P[r]	243–245 dec	A, B, C	65	THF	4/−20 to 0	EtOH/MeOH (5:1)	$C_{23}H_{36}N_4O_2 \cdot 2.8HCl \cdot 0.5H_2O$	C, H, N, Cl^-, H_2O

[a] Yield given for last step. [b] The presence of 2-PrOH was confirmed by NMR. [c] By trituration. [d] The requisite intermediate heterocycles were obtained from the private inventory of these laboratories. References for these compounds are **2e**: J. S. Buck and R. Baltzly, U.S. Patent 2 415 785, 1947; **2d**: see Table I; **2k**: H. G. Morren et al. *Ind. Chim. Belg.*, **19**, 76 (1954); **2l**: H. G. Morren et al. *Bull. Soc. Chim. Belg.*, **60**, 282 (1951); **2m**: see Table I; **2o**: J. G. Duff and D. J. Jung, *Can. Pharm. J.*, **95**, 256 (1962); **2s**: R. M. Jacob, U.S. Patent 2 507 408, (1950); **2jj**: R. Gehm and J. Dehnert, British Patent 874 519 (1961). [e] Triethylamine was added toward the end of the reaction period. [f] Presence of hexane was demonstrated by NMR. [g] The intermediate, *N,N*-diethyloxiranemethanamine, was prepared according to Gilman et al. *J. Am. Chem. Soc.*, **68**, 1261 (1946). [h] The requisite 1-[3-(dimethylamino)propyl]piperazine was prepared according to A. S. Tomcufcik, P. F.Fabio, and A. M. Hoffman, Belgian Patent 637 271 (1964). [i] NMR confirmed the presence of ethanol. [j] H_2O: calcd, 3.68; found, 3.25. [k] The requisite 1,2,3,4-tetrahydro-1-(phenylsulfonyl)quinoxaline was prepared according to J. C. Cavagol and F. W. Wiselogle, *J. Am. Chem. Soc.*, **69**, 795 (1947). [l] H: calcd, 8.24; found, 7.68. [m] H_2O: calcd, 2.62; found, 3.08. [n] See ref 21. [o] Product precipitated by addition of solution of (*Z*)-2-butenedioic acid in methanol. The NMR confirms the presence of (*Z*)-2-butenedioic acid. [p] NMR confirms the presence of 2-hydroxybenzoic acid. [q] This compound was prepared under U.S. Army Medical Research and Development Command Contract DADA-17-72-2077. [r] P = piperazine; Q = quinoxaline; TM = thiomorpholine; M= morpholine; D = perhydro-1,4-diazepine. [s] See Scheme II.

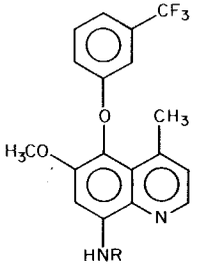
Table III. Physical Properties and Antileishmanial Activity of 2-Methyl Analogues of 1



no.	R	mp, °C	yield, %	purification solvent	formula	anal.	G^a
11[b]	$CO(CH_2)_5Br$	82–83	76	EtOH–H_2O	$C_{18}H_{23}BrN_2O_2$	C, H, N	
12[b]	$CO(CH_2)_5N[(CH_2)_2]_2NCH_2CH_2OH$	237–240 dec	52	HCl/2-PrOH	$C_{24}H_{36}N_4O_3 \cdot 3HCl \cdot 1.2H_2O$	C, H, N, Cl^-, H_2O	
3a	$(CH_2)_6N[(CH_2)_2]_2NCH_2CH_2OH$	257–259 dec	44	EtOH + MeOH	$C_{24}H_{38}N_4O_2 \cdot 3HCl \cdot 1.2H_2O$	C, H, N, Cl^-, H_2O	
13[b]	$CO(CH_2)_5N(C_2H_5)_2$	117–119	65	HCl/2-PrOH	$C_{22}H_{33}N_3O_2 \cdot 2HCl \cdot 1.3H_2O$	C, H, N, Cl^-, H_2O[c]	
3b	$(CH_2)_6N(C_2H_5)_2$	208–210 dec	60	HCl/2-PrOH	$C_{22}H_{35}N_3O \cdot 2HCl \cdot 0.2H_2O \cdot 0.1C_3H_8O$[d]	C, H, N, Cl^-, H_2O	32
14[b]	$CO(CH_2)_5NHCH(CH_3)C_2H_5$	220–224 dec	54	HCl/2-PrOH	$C_{22}H_{33}N_3O_2 \cdot 2HCl \cdot 0.3H_2O \cdot 0.1C_3H_8O$[d]	C, H, N, Cl^-, H_2O	
3c	$(CH_2)_6NHCH(CH_3)C_2H_5$	208–210 dec	64	HCl/2-PrOH	$C_{22}H_{35}N_3O \cdot 2HCl \cdot H_2O$	C, H, N, Cl^-, H_2O	28
15[b]	$CO(CH_2)_5NHCH(CH_3)_2$	246–248 dec	69	HCl/2-PrOH	$C_{21}H_{31}N_3O_2 \cdot 2.1HCl \cdot 0.2C_3H_8O$[d]	C, H, N, Cl^-	
3d	$(CH_2)_6NHCH(CH_3)_2$	250–252 dec	73	HCl/2-PrOH	$C_{21}H_{33}N_3O \cdot 2HCl \cdot 0.3H_2O \cdot 0.3C_3H_8O$[d]	C, H, N, Cl^-, H_2O	42

[a] G = glucan time index; glucan time is the proprietary name for meglumine antimoniate. [b] Precursor; see Scheme I. [c] H: calcd, 8.10; found, 7.6. [d] The presence of 2-propanol was confirmed by NMR.

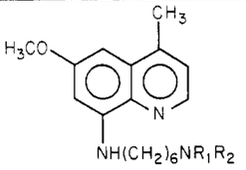
Table IV. Physical Properties and Antileishmanial Activity of 5-[3-(Trifluoromethyl)phenoxy] Analogues of 1



no.	R	mp, °C	yield, %	purification solvent	formula	anal.	% suppression: *L donovani* (hamster), (mg/kg)/day 208	52	13
16	$CO(CH_2)_5Br$[a]	126–128	91	2-PrOH	$C_{24}H_{24}BrF_3N_2O_3$	C, H, N			
4a	$(CH_2)_6N[(CH_2)_2]_2NCH_2CH_2OH$	224–228 dec	50	CH_3CN/2-PrOH (5:1)[b]	$C_{30}H_{39}F_3N_4O_3 \cdot 2.9HCl$	C, H, N, Cl^-	T	99.1	98.0
4b	$(CH_2)_6N(C_2H_5)_2$	110–160 indefinite	48	EtOH[c]	$C_{36}H_{36}F_3O_2 \cdot 2H_2PO_4$	C, H, N	T	100	99.6
4c	$(CH_2)_6NHCH(CH_3)_2$	62–65	35	2-PrOH–H_2O	$C_{27}H_{34}F_3N_3O_2$	C, H, N	T	T	98.6

[a] Precursor, see Scheme I. [b] Trituration. [c] The free base was treated with 85% phosphoric acid in ethanol and triturated with acetone.

Table V. Effects of 6-Methoxy-4-methyl-*N*-[6-(substituted-1-piperazinyl)hexyl]-8-quinolinamines and Related Compounds against *Leishmania donovani* Infections in Hamsters



compd	% suppression: *L. donovani* (hamster), (mg/kg)/day[a] 208	52	13	3.25	0.81	0.2	0.05	*G*[a]
2a	NA[b]							
2b	99.7 (4T)[c]	100	99.7, 99.4	99.3	64.7			26
2c	I[d]							
2d	I							
2e	99.9	99.5	99.7	99.6	21.1			19
2f	T	99.7	99.1	99.4	99.8	75.7	35	143
2g	T	97.8	96.3					38
2h	T	99.9	100	99.98	98.5, 89.6	25.8		57
2i	T	99.9	99.7	32.6				6
2j	T	99.7	65.8					2
2k	100	99.5	83.5					5
2l	T	96.8	99.4, 100	100	70			23
2m	77.8	I						<1
2n	97.5	97.8	95.9, 49.1	24.4	18.9			5
2o	T	99.8	98.9, 100	100	96.6	57.3		72
2p	T	100	100, 99.8	99.8	97.9, 87.7	1.3		72
2q	I							
2r	I							
2s	99.9	99.8	94.8, 95.9, 97.0	I				4
2t	99.5 (1T)	99.9	99.9	99.1	23.9			33
2u	T	98.0	54.6					2.3
2v	98.6 (5T)	99.3	56.6					2.6
2w	T	100	99.2, 99.6	84.1	35.9			9
2x	T	98.6 (5T)	98.8, 100	72.2				8
2y	100	99.4	89.7					6
2z	I							
2aa	NA							2
2bb	NA							
2cc	100	99.8	100	98.8	4.6			2.3
2dd	I							
2ee	98.6	99.4	99.8	91.2	61			12
2ff	98.2 (5T)	65	21.4					0.4
2gg	T	93.7	81.1					1.5
2hh	T	100	99.8	59.9	27.61			6.4
2ii	T	92.8	84.8					3
2jj	100	67.6	35					0.5
2kk	T	99.1	99.1, 99.9	98.7	61			24
1a	T	100	100		100	99.6	83.7	474
1b		100	100	97	85.8			104
meglumine antimoniate		91.3 at 104 mg/kg	42	I				1

[a] See ref 17; *G* = glucantime index; glucantime is the proprietary name for meglumine antimoniate. [b] NA = data not available. [c] T = toxic. [d] I = inactive.

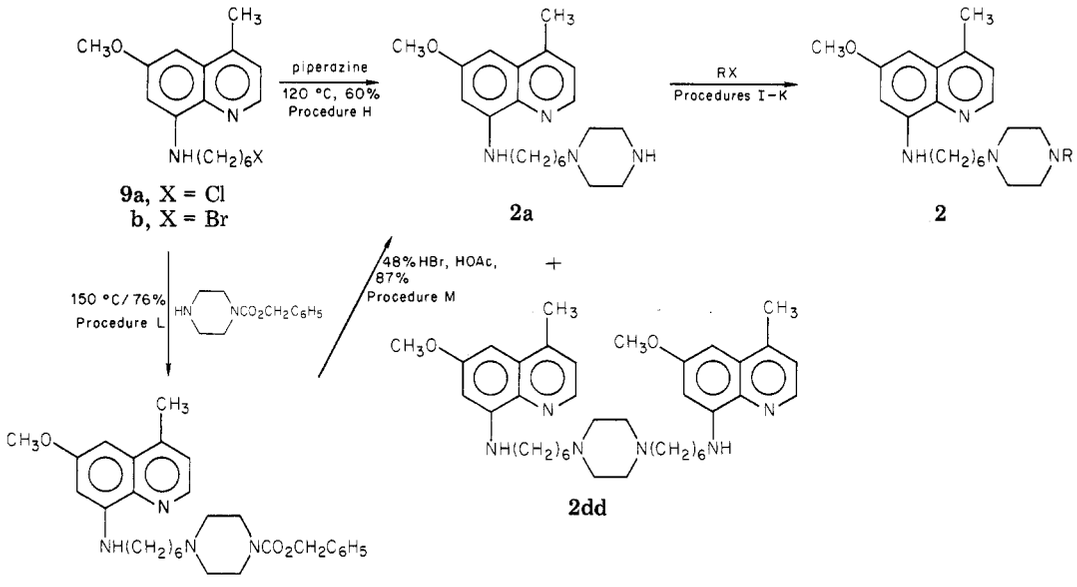
chloride 2-Propanolate (1:03) Hydrate (1:1.4) (2b). A cold (−40 °C) slurry of 1.0 g (0.0015 mol) of anhydrous $AlCl_3$ in 60 mL of THF was added to a cold (−40 °C) suspension of 0.8 g (0.02 mol) of $LiAlH_4$ in 40 mL of THF. The mixture was stirred and allowed to warm to −20 °C. To it was added dropwise a solution of 2.0 g (0.005 mol) of *N*-(6-methoxy-4-methyl-8-quinolinyl)-4-methyl-1-piperazinehexanamide (**7a**) in 50 mL of THF. The mixture was stirred for 1 h and stored at 4 °C overnight. To it was added dropwise 4 mL of 30% NaOH solution and enough water to clarify the supernatant. The supernatant was decanted and the residual sticky precipitate was washed with THF. The wash and supernatant were combined, concentrated in vacuo to remove the THF, and taken up in CH_2Cl_2 and H_2O. The CH_2Cl_2 layer was separated, washed with H_2O and brine, dried, and filtered, and the filtrate was concentrated to dryness in vacuo.

A solution of the residue in 2-PrOH was treated with a saturated solution of HCl in 2-PrOH. The resulting gelatinous precipitate was collected, washed with 2-PrOH and ether, dried overnight at 55 °C in vacuo, and allowed to air-equilibrate to afford 2.0 g (74%) of the title compound, mp 241–244 °C. NMR confirmed the presence of 0.3 mol of 2-PrOH.

See Tables II–IV for compounds prepared similarly.

Procedure D (Scheme I). 6-[(6-Methoxy-4-methyl-8-quinolinyl)amino]-1-hexanol (8). To a stirred mixture of 1.9 g (0.01 mol) of 6-methoxy-4-methyl-8-quinolinamine (**5**) and 1.4 g (0.01 mol) of 6-chlorohexanol at 150 °C was added portionwise over 1 h 1.4 mL (0.01 mol) of Et_3N. The mixture was stirred for 1 h at the same temperature, and then 0.8 g (0.006 mol) of 1-chlorohexanol was added, followed by the portionwise addition of 0.8 mL (0.008 mol) of Et_3N. The mixture was stirred for 1 h, and the procedure was repeated with 0.5 g (0.004 mol) of 1-chlorohexanol and 0.5 mL of Et_3N. After the mixture was stirred an additional hour, the mixture was allowed to cool, diluted with acetone, and filtered, and the filtrate was concentrated to dryness in vacuo. The residue was dissolved in CH_2Cl_2 and chromatographed over 70 g of silica gel first with 500 mL of CH_2Cl_2 and then with the following solutions of EtOAc in CH_2Cl_2: 5% (500 mL), 10% (1 L), 15% (500 mL), and finally 20% (500 mL). Fractions of the 20% eluant containing the product, R_f (silica–EtOAc) 0.3, were combined and concentrated to dryness in vacuo.

Scheme II



Recrystallization from 2-PrOH afforded 1.6 g (55%) of the title compound, mp 97–99 °C. Anal. ($C_{17}H_{24}N_2O_2$) C, H, N.

Procedure E (Scheme I). *N*-(6-Chlorohexyl)-6-methoxy-4-methyl-8-quinolinamine (9a). To a cold (0–5 °C) suspension of 23.2 g (0.8 mol) of 6-[(6-methoxy-4-methyl-8-quinolinyl)-amino]-1-hexanol (**8**) in 275 mL of CH_2Cl_2 was added dropwise 6.2 mL (0.85 mol) of $SOCl_2$ in 30 mL of CH_2Cl_2. The stirred mixture was allowed to warm to room temperature overnight, treated with an additional 4 mL of $SOCl_2$, stirred for 4 h, and then concentrated to dryness under vacuum. The residue was taken up in ice–H_2O and CH_2Cl_2 and treated with saturated Na_2CO_3 solution until the aqueous layer was weakly alkaline. The CH_2Cl_2 layer was separated, washed, dried, and filtered, and the filtrate was concentrated to dryness. The residual oil was chromatographed over 800 g of silica gel with CH_2Cl_2 to provide 18 g of material, which was recrystallized from hexane to afford 17.1 g (70%) of **9a**, mp 68–72 °C. Anal. ($C_{17}H_{23}ClN_2O$) C, H, N, Cl.

Procedure F (Scheme I). 4-(Ethylsulfonyl)-*N*-(6-methoxy-4-methyl-8-quinolinyl)-1-piperazinehexanamine (2s). A mixture of 1.5 g (0.005 mol) of *N*-(6-chlorohexyl)-6-methoxy-4-methyl-8-quinolinamine (**9a**) and 2.7 g (0.015 mol) of 1-(ethylsulfonyl)piperazine was heated at 130 °C for 50 min, allowed to cool, and taken up in CH_2Cl_2 and H_2O. The organic layer was washed again, dried, and concentrated to dryness in vacuo. The residue was chromatographed over 70 g of silica gel, first with EtOAc and then with 2% MeOH in EtOAc. The eluant-containing product, R_f (silica–EtOAc) 0.05, was concentrated to dryness in vacuo. Recrystallization of the residue from 2-PrOH afforded 1.5 g (68%) of **2s**, mp 72–74 °C.

See Table II for other compounds prepared in this fashion.

Procedure G (Scheme I). *N*-(6-Bromohexyl)-6-methoxy-4-methyl-8-quinolinamine–*N*-Hexyl-6-methoxy-4-methyl-8-quinolinamine (9b and 9c, 9:1). Under N_2, a cold (−30 °C) slurry of 3.1 g (0.02 mol) of anhydrous $AlCl_3$ in 50 mL of THF was added to an equally cold mixture of 2.6 g (0.07 mol) of $LiAlH_4$ in 50 mL of THF. The stirred mixture was allowed to warm to −10 °C and to it was added dropwise a solution of 7.3 g (0.02 mol) of 6-bromo-*N*-(6-methoxy-4-methyl-8-quinolinyl)hexanamide (**6**) in 150 mL of THF. The mixture was stirred at −10 to −5 °C for 2 h, and then to it was added dropwise 13 mL of 30% aqueous NaOH and enough H_2O to clarify the supernatant. The mixture was filtered through supercell, concentrated under vacuum to remove the THF, diluted with CH_2Cl_2, washed with H_2O, dried, and concentrated to dryness. The residue was recrystallized from a 6:1 mixture of hexane–2-PrOH to afford 5 g (64%) of the desired *N*-(6-bromohexyl)-6-methoxy-4-methyl-8-quinolinamine (**9b**) contaminated with *N*-hexyl-6-methoxy-4-methyl-8-quinolinamine (**9c**) (9:1), mp 67–70 °C. The NMR spectrum confirmed the presence of approximately 0.1 mol of the debrominated product. Anal. ($C_{17}H_{23}BrN_2O \cdot 0.1C_{17}H_{24}N_2O$) C, H, N, Br.

In one instance the above mixture was subjected to chromatography on silica gel with toluene to afford purified samples of **9b**, mp 74 °C, R_f (SiO_2–tol) 0.14, and **9c**, mp 51–52 °C, R_f 0.21. Anal. ($C_{17}H_{23}BrN_2O$ and $C_{17}H_{24}N_2O$) C, H, N.

Procedure H (Scheme II). 6-Methoxy-4-methyl-*N*-[6-(1-piperazinyl)hexyl]-8-quinolinamine Trihydrochloride 2-Propanolate (1:0.2) Hemihydrate (2a). A solution of 6.2 g (0.02 mol) of crude *N*-(6-chlorohexyl)-6-methoxy-4-methyl-8-quinolinamine (**9a**) in 75 mL of toluene was added dropwise to a stirred, hot suspension of 25 g (0.29 mol) of piperazine in 25 mL of toluene. The mixture was distilled until the internal temperature rose to 130 °C, and then it was allowed to cool and taken up in a mixture of H_2O and CH_2Cl_2. The organic layer was separated, washed again, dried, and concentrated to dryness in vacuo. The residual brown oil was chromatographed over 200 g of silica gel, first with EtOAc and then with 500 mL each of the following solutions of MeOH in EtOAc: 4%, 8%, 12%, 16%, 20%, and 25%. The eluant, which appeared to contain only the product, R_f (silica; MeOH–EtOAc–Et_3N, 25:75:1) 0.05, was concentrated to dryness in vacuo. The residue was triturated with Et_2O and filtered to remove 1 g of the bis product (**2dd**), mp 126–128 °C, and concentrated again. The residue was dissolved in hot 2-PrOH and filtered to remove haze, and the filtrate was treated with a saturated solution of HCl in 2-PrOH. The resulting precipitate was collected, dried overnight at 60 °C in vacuo, asnd allowed to air-equilibrate to afford 5.8 g (60%) of **2a**, mp 245–247 °C dec with prior sintering at 125 °C. The NMR spectrum confirmed the presence of 2-PrOH.

Procedure I (Scheme II). 4-[6-[(6-Methoxy-4-methyl-8-quinolinyl)amino]hexyl]-α-methyl-1-piperazineethanol Trihydrochloride Hydrate (1:1.3) (2f). A solution of 2.0 g (0.004 mol) of 6-methoxy-4-methyl-*N*-[6-(1-piperazinyl)hexyl]-8-quinolinamine trihydrochloride 2-propanolate (1:0.2) hemihydrate (**2a**) in water was made basic with NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 was washed, dried, and filtered, and the filtrate was concentrated to dryness in vacuo. A mixture of the residual brown oil and 1.3 mL (0.016 mol) of 1-chloro-2-propanol was heated at 130 °C for 3 h, allowed to cool, and taken up in a mixture of CH_2Cl_2 and dilute NH_4OH. The CH_2Cl_2 was washed, dried, and concentrated to dryness in vacuo. The residual oil was chromatographed over 70 g of silica gel with 14% MeOH in EtOAc to afford 0.8 g of the product, R_f (silica; EtOAc–MeOH–Et_3N, 75:25:1) 0.33. A solution of this material in 2-PrOH was treated with a saturated solution of HCl in 2-PrOH. The resulting precipitate was collected, washed with 2-PrOH and ether, dried in vacuo at 45 °C for 55 h, and allowed to air-equilibrate for 18 h to afford 1.0 g (46%) of **2f**, mp 80–100 °C, resolidify, 245 °C dec.

See Table II for compounds prepared similarly.

Procedure J (Scheme II). *N*,*N*-Diethyl-4-[6-[(6-methoxy-4-methyl-8-quinolinyl)amino]hexyl]-1-piperazinecarboxamide Dihydrochloride Hydrate (1:0.4) (2x). To a mixture of 2.4 g (0.007 mol) of 6-methoxy-4-methyl-*N*-[6-(1-piperazinyl)hexyl]-8-quinolinamine (**2a**) and 1.7 g (0.016 mol) of Na_2CO_3 in 50 mL of acetone was added a solution of 1.8 g (0.007 mol) of diethylcarbamoyl chloride in 20 mL of acetone. The mixture was stirred under gentle reflux for 2 h, allowed to cool, and filtered, and the filtrate was concentrated to dryness in vacuo. A solution of the residue in CH_2Cl_2 was washed with H_2O, dried, and filtered, and the filtrate was concentrated to dryness. Chromatography of the residue over 70 g of silica with 10% MeOH in EtOAc afforded 2 g of product, R_f 0.3. The material was triturated with 2-PrOH containing excess HCl. The resulting yellow precipitate was collected, washed with 2-PrOH and then Et_2O, dried in vacuo at 52 °C overnight, and air-equilibrated to afford 1.8 g (50%) of product, mp 226–228 °C dec.

Compounds **2v,y,z,cc** were prepared similarly by the reaction of **1** with, respectively, 2-ethylbutyryl chloride, dipropylcarbamoyl chloride, diphenylcarbamoyl chloride, and 1-pyrrolidinecarbonyl chloride.

Procedure K (Scheme II). *N*-Ethyl-4-[6-[(6-methoxy-4-methyl-8-quinolinyl)amino]hexyl]-1-piperazinecarboxamide Dihydrochloride 2-Propanolate (2:1) Hydrate (10:7) (2w). A solution of 15.5 g (0.025 mol) of 6-methoxy-4-methyl-*N*-[6-(1-piperazinyl)hexyl]-8-quinolinamine trihydrobromide 2-propanolate (1:03) hemihydrate (**2a**) in water was made alkaline with dilute NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 was washed with a NaCl solution, which was prepared by diluting a saturated NaCl solution with an equal volume of H_2O, dried, filtered, and concentrated to dryness under vacuum to afford 8.1 g (92%) of the starting material as the base. To a solution of 2.8 g (0.08 mol) of this material in 50 mL of THF was added a solution of 0.62 mL (0.007 mol) of ethyl isocyanate in 3 mL of THF. The solution was stirred for 3 h and then concentrated to dryness under vacuum. A solution of the residue in CH_2Cl_2 was washed with H_2O, dried, and concentrated. The residue was triturated with a 10% solution of HCl in 2-PrOH. The resulting solid was collected, washed with 2-PrOH and Et_2O, and dried under vacuum at 60 °C to afford 1.2 g (29%) of the title compound, mp indefinite 100–130 °C dec. The presence of 0.5 mol of 2-PrOH was confirmed by NMR spectroscopy.

***N*-Ethyl-4-[6-[(6-methoxy-4-methyl-8-quinolinyl)amino]hexyl]-1-piperazinecarbothioamide dihydrochloride 2-propanolate (3:1) hydrate (5:4) (2aa)** was prepared similarly from **2a** and ethyl isothiocyanate.

Methyl *N*-cyano-4-[6-[(6-methoxy-4-methyl-8-quinolinyl)amino]hexyl]-1-piperazinecarboximidothioate (2bb) was prepared from **2a** and dimethyl cyanocarbonimidodithioate[21] in toluene.

Procedure L (Scheme II). Phenylmethyl 4-[6-[(6-Methoxy-4-methyl-8-quinolinyl)amino]hexyl]-1-piperazinecarboxylate (2u). A mixture of 15.4 g (0.05 mol) of *N*-(6-chlorohexyl)-6-methoxy-4-methyl-8-quinolinamine (**9a**) and 12.1 g (0.055 mol) of phenylmethyl 1-piperazinecarboxylate[13,14] (**10**) was heated at 148–150 °C for 4 h. After 2 h of heating, 10 mL of Et_3N was added slowly. The reaction mixture was allowed to cool, diluted with CH_2Cl_2, washed first with dilute NH_4OH and then with H_2O, dried, and concentrated under vacuum. The concentrate was chromatographed over 500 g of silica gel, first with CH_2Cl_2 and then with a 1% solution of MeOH in CH_2Cl_2, and finally with a 2% solution of MeOH in CH_2Cl_2 to afford 20 g of crude product, R_f (silica; EtOAc) 0.27. Trituration with a 10:1 mixture of cyclohexane–2-PrOH afforded 18.6 g (76%) of the desired product, mp 73–73.5 °C. Anal. ($C_{29}H_{38}N_4O_3$) C, H, N.

In a separate experiment, the residue from the column was dissolved in 2-PrOH and heated with 15 mL of a 12% solution of hydrogen chloride in 2-PrOH. The solution was chilled overnight to afford the product as the dihydrochloride, mp 143–150 °C with prior softening.

Procedure M (Scheme II). 6-Methoxy-4-methyl-*N*-[6-(1-piperazinyl)hexyl]-8-quinolinamine Trihydrobromide 2-Propanolate (1:0.3) Hemihydrate (2a·HBr). A mixture of 0.55 g (0.001 mol) of phenylmethyl 4-[6-[(6-methoxy-4-methyl-8-quinolinyl)amino]hexyl]-1-piperazinecarboxylate (**2u**) and 0.5 mL of 45% HBr in 4 mL of HOAc was heated on a steam bath for 2 h, allowed to cool, and diluted with Et_2O. The resulting gum was triturated with additional Et_2O and then with 2-PrOH. The gold precipitate that formed was collected, washed with 2-PrOH and Et_2O, dried under vacuum at 75 °C, and allowed to equilibrate in air to afford 0.6 g (87%) of the desired compound, mp 240–242 °C dec. The NMR spectrum confirmed the presence of about 0.3 mol of 2-PrOH. Anal. ($C_{21}H_{32}N_4O\cdot3HBr\cdot0.3C_3H_8O\cdot0.5H_2O$) C, H, N, Br, H_2O.

Procedure N. 3,4-Dihydro-*N*-(6-methoxy-4-methyl-8-quinolinyl)-1(2*H*)-quinoxalinehexanamine (2q). A solution of 3.3 g (0.006 mol) of 3,4-dihydro-*N*-(6-methoxy-4-methyl-8-quinolinyl)-4-(phenylsulfonyl)-1(2*H*)-quinoxalinehexanamine (**2r**) in 8 mL of concentrated H_2SO_4 was allowed to stand overnight at room temperature, chilled by the addition of ice, made basic with NaOH, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried, and concentrated to dryness under vacuum. Recrystallization of the residue from 2-PrOH afforded 2.2 g (92%) of **2q**, mp 92–94 °C.

Procedure *O*. 6-Methoxy-4-methyl-*N*-[6-(4-thiomorpholinyl)hexyl]-8-quinolinamine *S*-Oxide Dihydrochloride 2-Propanolate (1:0.2) Hydrate (1:0.2) (2ii). A mixture of 1.5 g (0.003 mol) of 6-methoxy-4-methyl-*N*-[6-(4-thiomorpholiny)hexyl]-8-quinolinamine dihydrochloride 2-propanolate (1:0.2) (**2hh**) and 5 mL of 30% H_2O_2 in 50 mL of HOAc and 5 mL of H_2O was stirred overnight, combined with ice, made basic with 50% NaOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed, dried, and concentrated to dryness in vacuo. The residue was triturated with a solution of HCl in 2-PrOH to afford 0.6 g (43%) of **2ii**, mp 253–256 °C dec.

Preparation of 1-[2-(Ethylsulfonyl)ethyl]piperazine Dihydrobromide (17), Precursor for Compound 2e. To a solution of 6.6 g (0.03 mol) of phenylmethyl 1-piperazinecarboxylate[13,14] (**10**) in 100 mL of DMF was added, in portions, 1.44 g (0.03 mol) of a 50% NaH suspension in mineral oil. The mixture was heated at 50 °C for 1 h and allowed to cool slightly. To it was added dropwise a solution of 8.8 g (0.003 mol) of 2-(ethylsulfonyl)ethanol 4-methylbenzenesulfonate[15] in 30 mL of DMF. The mixture was heated at 50 °C for 1 h, allowed to cool, concentrated under vacuum to one-half the original volume, allowed to stand for 4 days, and then concentrated to a paste. The paste was diluted with Et_2O, and the suspension was filtered to remove insoluble salts. The filtrate was concentrated and chromatographed over 250 g of silica gel with 1 L each of the following solutions of MeOH in EtOAc: 1.5%, 3%, and 15%. That portion of the eluant containing the product, R_f (silica; 10% MeOH–EtOAc) 0.7, was concentrated to dryness under vacuum to afford 8.3 g (81%) of phenylmethyl 4-[2-(ethylsulfonyl)ethyl]-1-piperazinecarboxylate as an oil. The IR and NMR spectra was consistent with the assigned structure. A solution of 0.6 g (0.002 mol) of this material in 4 mL of HOAc and 1 mL of 48% HBr was heated on the steam bath for 35 min and allowed to cool, to afford 0.5 g (79%) of 1-[2-(ethylsulfonyl)ethyl]piperazine dihydrobromide (**17**), mp 265–267 °C dec. Anal. ($C_8H_{18}N_2O_2S\cdot2HBr$) C, H, N, Br, S.

Antileishmanial Evaluation. The 8-quinolinamines were tested for antileishmanial activity against *L. donovani* in hamsters.[16,17] Male hamsters (seven per group) were inoculated intracardially with 10^7 amastigotes (*L. donovani* Khartoum). After 3 days, the test compounds were administered twice daily for 4 days by the intramuscular route. The animals were sacrificed 1 day later, their livers were removed, the parasites were determined by impression smears, and the percent suppression and *G* values were calculated. The results[18] are reported in Tables III–V.

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(21) Dimethyl cyanocarbonimidodithioate [NCN = $C(SMe)_2$] was prepared by Jack Hinkley of these laboratories according to A. Hantsch and M. Wolvkamp, *Justis Liebigs Ann. Chem.*, **331**, 265 (1904).

Registry No. **1a**, 57695-04-2; **1b**, 75464-77-6; **1b**·HCl, 83547-43-7; **2a**, 83547-39-1; **2a**·3HCl, 83546-65-0; **2a**·3HBr, 83547-38-0; **2b**·3HCl, 83546-66-1; **2c**, 83546-67-2; **2d**, 83546-68-3; **2e**, 83546-69-4; **2f**·3HCl, 83546-70-7; **2g**, 83546-71-8; **2h**·HCl, 83546-72-9; **2i**·HCl, 83546-73-0; **2j**·4HCl, 83546-74-1; **2k**·HCl, 83560-59-2; **2l**·HCl, 83546-75-2; **2m**, 83546-76-3; **2n**, 83546-77-4; **2o**·HCl, 83546-78-5; **2p**, 83546-79-6; **2q**, 83546-80-9; **2r**, 83546-81-0; **2s**, 83546-82-1; **2t**, 83546-83-2; **2u**, 83547-40-4; **2u**·2HCl, 83546-84-3; **2v**·2HCl, 83546-85-4; **2w**·2HCl, 83546-86-5; **2x**·2HCl, 83546-87-6; **2y**·2HCl, 83546-88-7; **2z**·2.5H_3PO_4, 83546-89-8; **2aa**·2HCl, 83546-91-2; **2bb**, 83546-92-3; **2cc**·HCl, 83546-93-4; **2dd**, 83546-94-5; **2ee**·$C_4H_4O_4$, 83546-96-7; **2ff**, 83546-97-8; **2gg**·2HCl, 83546-98-9; **2hh**·2HCl, 83546-99-0; **2ii**·2HCl, 83547-00-6; **2jj**, 83547-01-7; **2kk**·2HCl, 83547-02-8; **3a**·3HCl, 83547-17-5; **3b**·2HCl, 83547-18-6; **3c**·2HCl, 83547-19-7; **3d**·2HCl, 83547-20-0; **4a**·HCl, 83547-21-1; **4b**·2H_3PO_4, 83547-23-3; **4c**, 83547-24-4; **5**, 57514-21-3; **6**, 75464-75-4; **7a**, 83547-03-9; **7b**, 83547-04-0; **7c**, 83547-05-1; **7d**, 83547-06-2; **7e**, 83547-07-3; **7f**, 83547-08-4; **7g**, 83547-09-5; **7h**, 83547-10-8; **7i**, 83547-11-9; **7j**, 83547-12-0; **7k**, 83560-60-5; **8**, 83547-13-1; **9a**, 83547-14-2; **9b**, 83547-15-3; **9c**, 83547-16-4; **10**, 31166-44-6; **11**, 83547-25-5; **12**·3HCl, 83547-26-6; **13**·2HCl, 83547-27-7; **14**·2HCl, 83547-28-8; **15**·HCl, 83547-29-9; **16**, 83547-30-2; **17**·2HBr, 83547-41-5; $Cl(CH_2)_6OH$, 2009-83-8; $Br(CH_2)_5COCl$, 22809-37-6; P, 110-85-0; 1-Me-P, 109-01-3; 1-[$(CH_2)_{11}CH_3$]-P, 54722-40-6; 1-cyclohexyl-P, 17766-28-8; 1-($CH_2CH_2SO_2C_2H_5$)-P, 83547-31-3; 1-($CH_2CHOHCH_3$)-P, 1074-54-0; 1-($CH_2CH_2CH_2OH$)-P, 5317-32-8; 1-($CH_2CHOHCH_2OH$)-P, 7483-59-2; 1-[$CH_2CHOHCH_2N(C_2H_5)_2$]-P, 4232-58-0; 1-[$(CH_2)_3N(CH_3)_2$]-P, 877-96-3; 1-[$CH_2CH_2OCH(C_6H_5)_2$]-P, 60703-69-7; 1-[$CH(C_6H_5)(4\text{-}Cl\text{-}C_6H_4)$]-P, 303-26-4; 1-(3,4-$Cl_2$-$C_6H_3$)-P, 57260-67-0; 1-(2-pyridyl)-P, 34803-66-2; 3-CH_3-1-[$CH_2CH_2CH(CH_3)_2$]-P, 83547-32-4; 2,6-$(CH_3)_2$-P, 108-49-6; 1(2*H*)-3,4-H_2-Q, 3476-89-9; 1-($SO_2C_6H_5$)-1(2*H*)-3,4-H_2-Q, 6344-73-6; 1-($SO_2C_2H_5$)-P, 14172-55-5; 1-($CO_2C_2H_5$)-P, 120-43-4; 1-($CO_2CH_2C_6H_5$)-P, 31166-44-6; 1-[$COCH(C_2H_5)_2$]-P, 83547-33-5; 1-($CONHC_2H_5$)-P, 75529-72-5; 1-[$CON(CH_2CH_3)_2$]-P, 119-54-0; 1-[$CON(CH_2CH_2CH_3)_2$]-P, 41340-64-1; 1-[$CON(C_6H_5)_2$]-P, 1804-36-0; 1-($CSNHC_2H_5$)-P, 83547-34-6; 1-[C(=NCN)SCH_3]-P, 83547-35-7; 1-[$CON(CH_2)_4$]-P, 73331-93-8; 1-Me-D, 4318-37-0; *trans*-3,5-Me_2-TM, 83547-36-8; *cis*-3,5-Me_2-TM, 83547-37-9; TM, 123-90-0; TM *S*-oxide, 39213-13-3; TM *S,S*-dioxide, 39093-93-1; 3,5-Me_2-M, 123-57-9; 1-(CH_2CH_2OH)-P, 103-76-4; 2-(ethylsulfonyl)ethanol 4-methylbenzenesulfonate, 19387-92-9; phenylmethyl 4-[2-(ethylsulfonyl)ethyl]-1-piperazinecarboxylate, 83547-42-6.

Buspirone Analogues. 1. Structure–Activity Relationships in a Series of *N*-Aryl- and Heteroarylpiperazine Derivatives

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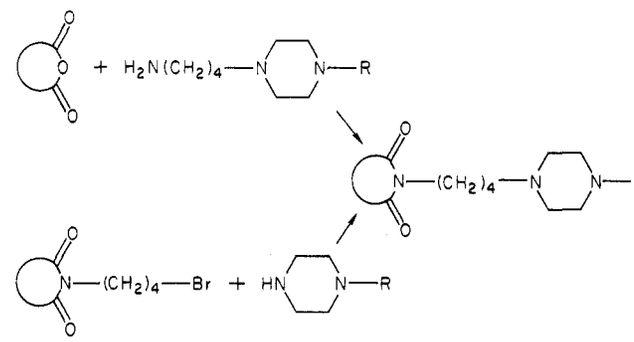
A series of analogues of buspirone was synthesized in which modifications were made in the aryl moiety, alkylene chain length, and cyclic imide portion of the molecule. These compounds were tested in vitro for their binding affinities to rat brain membrane sites labeled by either the dopamine antagonist [^{3}H]spiperone or the α_1-adrenergic antagonist [^{3}H]WB-4101. Compounds were also tested in vivo for tranquilizing properties and induction of catalepsy. Potency at the [^{3}H]spiperone binding site was affected by alkylene chain length and imide portion composition. Nonortho substituents on the aryl moiety had little effect on [^{3}H]spiperone binding affinity. Structure–activity relationships of ortho substituents demonstrated only modest correlations between the receptor binding data and physical parameters of the substituents. The complex nature of the drug–receptor interactions may be understood in terms of the fit of buspirone to a hypothetical model of the dopamine receptor.

Buspirone (**1**), a member of a series of previously reported *N*-(4-arylpiperazin-1-yl)alkyl cyclic imides,[1,2] has shown anxiolytic activity in several conflict behavioral paradigms[3] and calming effects in aggressive rhesus monkeys.[4] Clinical studies of buspirone have demonstrated it to have a unique anxioselective profile; i.e., its efficacy in the treatment of anxiety neuroses is comparable to that of diazepam but without benzodiazepine-related side effects.[5,6] Such side effects are well-known and documented.[7,8]

Earlier pharmacological studies of buspirone[9,10] led to its evaluation in schizophrenia; however, the drug exhibited only transient activity even at high doses.[11] Subsequent pharmacological investigation, directed at determining its mechanism of action, have demonstrated that while buspirone is without effect upon benzodiazepine binding and GABA binding or uptake, it may possess both agonist and antagonist activity at dopaminergic receptors.[12-19] This profile of mixed agonist and antagonist properties may be relevant to buspirone's mechanism of anxioselective action in which no sedation, anticonvulsant, or muscle relaxant properties are associated with the drug.

In addition to in vivo studies, we have employed the receptor-binding methodology used to characterize buspirone to both investigate a number of newer buspirone analogues and to reexamine previously described members of the series.

Scheme I



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