From the reaction of *p*-trifluoromethylbenzanilide (55 g, 0.207 mole), dimethylaniline (87.5 g, 0.72 mole), and $POCl_3$ (41.5 g, 0.27 mole) 45 g of a solid product was obtained. It was recrystallized from boiling EtOH and sublimed at reduced pressure. Purification was accomplished by treatment with excess $NaHCO_3$ solution giving a yellow solid, mp 149–152°, positive DNPH test. Recrystallization from boiling EtOH raised the melting point to 153–154° and the compound was chromatographically pure (tlc) and had the correct elemental analysis.

Procedure C. Benzophenone Guanylhydrazone Hydrochloride (1).—Benzophenone (18.2 g, 0.066 mole) and aminoguanidine hydrochloride (13 g, 0.118 mole) in 100 ml of glacial AcOH were refluxed for 64 hr and then cooled. A solid separated, was filtered, washed with cold EtOH, and dried. A white powder was obtained and recrystallized from EtOH, weight 26 g (94.6%), mp 292–295° dec. Recrystallization from H_2O–EtOH (4:1) gave a white crystalline solid which still showed a trace of impurity in tlc, mp 292–294° dec, and had the correct elemental analysis. When H_2O–EtOH was used as a reaction solvent only a 50% yield of the crude product was obtained.

***p*-Chlorobenzophenone Guanylhydrazone Hydrochloride** (**6**).—*p*-Chlorobenzophenone (12.5 g, 0.058 mole) and aminoguanidine hydrochloride (7.0 g, 0.063 mole) in 100 ml of H_2O–EtOH (1:1) and a few drops of concentrated HCl were refluxed for 2 days, after which half of the solvent was removed under reduced pressure. A solid separated, was filtered, washed with a large amount of H_2O then with hot PhH, and dried. The crude material weighed 12.3 g (68.5%), mp 268–271°. The recrystallized product from H_2O–EtOH (5:1) had mp 280–282° dec, showed a trace of impurity in tlc, and had the correct elemental analysis.

Procedure D. 4,4′-Ditrifluoromethylbenzophenone Guanylhydrazone Hydrochloride (**4**).—4,4′-Ditrifluoromethylbenzophenone (6.2 g, 0.02 mole) and aminoguanidine hydrochloride (6.2 g, 0.056 mole) in 15 ml of ethylene glycol and 6 drops of concentrated HCl were refluxed for 0.5 hr. The cooled solution was added to 150 ml of H_2O. A solid separated, was filtered, washed (H_2O, PhH, Et_2O), and dried, 4.9 g. This material was recrystallized (H_2O) yielding 1.9 g (23.8%) of white powder, mp 306–308° dec, chromatographically pure (tlc).

4-Bromo-3′,5′-ditrifluoromethylbenzophenone Guanylhydrazone Hydrochloride (**22**).—4-Bromo-3′,5′-ditrifluoromethylbenzophenone (5.0 g, 0.013 mole) and aminoguanidine hydrochloride (5.0 g, 0.045 mole) in 12 ml of DMAC and 6 drops of concentrated HCl were refluxed for 0.5 hr. The reaction mixture was cooled to room temperature and 100 ml of H_2O was added. A viscous white material separated and was left in the open air for 5 days, after which it solidified, weighing 5.5 g, mp 65–118°, positive $AgNO_3$ test. The crude product was recrystallized from 25 ml of boiling toluene. A crop was obtained which still had a broad melting point range. The material was stirred and boiled for 0.5 hr with 40 ml of PhH and filtered, yielding 1.3 g, mp 190–196°, positive $AgNO_3$ test. The solid was stirred and boiled with 200 ml of $CHCl_3$–$C_6H_5CH_3$ and filtered, yielding 0.8 g (15%) of product, chromatographically pure (tlc).

4-Bromo-4′-trifluoromethylbenzophenone guanylhydrazone *p*-toluenesulfonate (**21**) was prepared according to procedure D. Aminoguanidine *p*-toluenesulfonate was prepared by adding *p*-toluenesulfonic acid (385 g, 2.24 moles) with stirring to 2 l. of H_2O and heating the stirred mixture to approximately 80°. Aminoguanidine bicarbonate (272 g, 2 moles) was added to it and the stirred mixture was brought to boiling, whereupon the solid dissolved. The solution was filtered hot and allowed to cool. Crystals formed, were washed with a large amount of H_2O then with EtOH, and dried, yielding 277 g (68.5%) of a crystalline solid, mp 201–203°. Recrystallization (hot H_2O, EtOH–H_2O (4:1)) raised the melting point to 205–206°, tlc (C_6H_6–EtOH (95:5), 25 min) showing a trace of impurity. *Anal.* ($C_8H_{14}N_4O_3S$) C, H, N, S.

Acknowledgment.—We express our appreciation to Douglas French and Victor Nora for their assistance in the preparation of many compounds, Arvia Hosking and June French for the antitumor evaluations, and Ali Shakoori and Dee J. Glasby for excellent technical assistance. We appreciate the helpful counsel of Drs. Edgar A. Steck and Bing T. Poon.

N-Dialkylaminoalkylbiphenylamines as Antimalarial and Antischistosomal Agents[1]

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Received May 24, 1968

A series of N-dialkylaminoalkylbiphenylamines and N′-substituted N-biphenylpiperazines have been prepared and evaluated as antimalarial and antischistosomal agents. Potentially general procedures were developed for constructing four- and six-carbon aminoalkyl chains on the biphenylamine nuclei, utilizing succinic anhydride and 6-bromohexanoic acid, respectively. No important effects against experimental *Plasmodium berghei* or *Schistosoma mansoni* infections in mice were observed, but several of the compounds displayed significant *in vitro* activity against a series of nonparasitic microorganisms.

We have prepared the series of biphenylamine derivatives listed in Tables I and II as part of a program to develop novel antimalarial and antischistosomal agents. In general, the compounds of Table I are derived from the mirasan[2] series of antischistosomal drugs (*e.g.*, **1**) by three types of modification: replacement of chlorine by phenyl, insertion of a *p*-chlorophenyl group into the open *meta* position of the toluidine ring, and extension of the basic side chain. The compounds of Table II are based on a group of antischistosomal N-(3-chloro-*p*-tolyl)piperazines[2,3] that developed from the mirasan group. The possibility that incorporation of a phenyl fraction into these systems would produce interesting antiparasitic activity was suggested by the marked increase in the antimalarial activity of synthetic quinine analogs when phenyl substituents were inserted into the 2 position.[4] Indeed, one such compound (**2**) has been

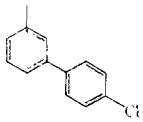
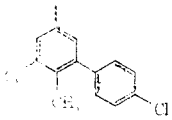
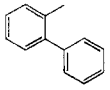
(1) This work was supported by the U. S. Army Medical Research and Development Command under Contract No. DA-49-193-MD-2750. This paper is Contribution No. 394 from the Army Research Program on Malaria.

(2) (a) G. Lammler, *Z. Tropenmed. Parasitol.*, **15**, 337 (1946); (b) O. D. Standen in "Experimental Chemotherapy," Vol. I, R. J. Schnitzer and F. Hawking, Ed., Academic Press, New York, N. Y., 1963, pp 773–775; (c) H. Mauss, H. Kolling, and R. Gonnert, *Med. Chem. Abhandl. Med. Chem. Forschungsstaetten Farbenfabriken Bayer*, **5**, 185 (1956).

(3) (a) N. Katz, J. Pellegrino, C. A. Oliveria, and A. S. Cunha, *J. Parasitol.*, **53**, 1229 (1967); (b) B. DeMeillon, E. C. England, and G. Lammler, *S. African Med. J.*, **30**, 611 (1956); (c) G. Lammler, *Z. Tropenmed. Parasitol.*, **9**, 294 (1958); (d) G. W. Luttermoser, J. I. Bruce, and D. B. McMullen, *Am. J. Trop. Med. Hyg.*, **9**, 39 (1960); (e) E. F. Kimura, R. K. Richards, D. M. Ebert, P. R. Young, and P. M. Bauman, *Toxicol. Appl. Pharmacol.*, **8**, 57 (1966).

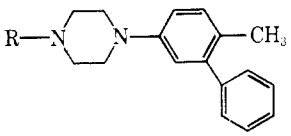
(4) (a) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Monograph No. 9, U. S. Government Printing Office, Washington, D. C., 1953, pp 79–85; (b) F. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," Vol. I, Edwards, Ann Arbor, Mich., 1946, pp 142–148.

TABLE I
N-(ω-DIALKYLAMINOALKYL)BIPHENYLAMINES
$ArNH(CH_2)_nNR_2$

No.	Ar	n	R_2	Mp, °C	Formula	Analyses[a]	Antimalarial assay results[b] 40	160	640
17		2	Et_2	107–108	$C_{19}H_{26}N_2 \cdot H_2C_2O_4$	C, H	0.3	0.1	0.5 (2/5)
18		4	$(CH_2)_4$	135–136.5	$C_{21}H_{28}N_2 \cdot H_2C_2O_4$	C, H; N[c]	0.2	0.6 (2/5)	5/5
19		6	Et_2	120–121	$C_{23}H_{34}N_2 \cdot 2H_2C_2O_4 \cdot H_2O$	C, H, N	0.4	5/5	5/5
20		2	Et_2	136–136.5	$C_{18}H_{23}ClN_2 \cdot H_2C_2O_4$	C, H, N	0.6	1.0	1.8 (3/5)
21		4	$(CH_2)_4$	175–176	$C_{20}H_{25}ClN_2 \cdot H_2C_2O_4$	H; C[d]	1.9	3.1	3.5
							0.0	0.1 (1/5)	0.6 (2/5)
22		2	Et_2	175–176	$C_{19}H_{24}Cl_2N_2 \cdot H_2C_2O_4$	C, H, N	0.2	0.2	0.8 (2/5)
23		4	$(CH_2)_4$	132–134	$C_{21}H_{26}Cl_2N_2 \cdot H_2C_2O_4$	C, H, N	0.7	1.2 (3/5)	5/5
24		6	Et_2	70–75	$C_{23}H_{32}Cl_2N_2 \cdot 2H_2C_2O_4$	C, H, N	0.5	2.3	5/5
25		2	Et_2	129–130	$C_{18}H_{24}N_2 \cdot H_2C_2O_4$	C, H, N	0.2	0.2	0.4
26		4	$(CH_2)_4$	158–160	$C_{20}H_{26}N_2 \cdot H_2C_2O_4$	C, H, N	0.6	1.4	5/5
27		6	Et_2	97–98	$C_{22}H_{32}N_2 \cdot H_2C_2O_4$	C, H, N	0.2	0.3 (1/5)	5/5
Quinine							1.2	3.4	6.5
Chloroquine							4.6	10.0	5/5

[a] Where analyses are indicated by the symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. [b] Figures are increases in survival time (days) of treated mice (dosages of 40, 160, and 640 mg/kg) beyond that of untreated controls. Values in parentheses indicate toxicity deaths *vs.* total mice in treated group. [c] N: calcd, 7.03; found, 7.55. [d] C: calcd, 63.1; found, 63.8.

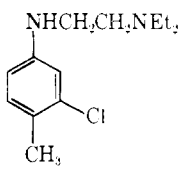
TABLE II
BIPHENYLYLPIPERAZINE DERIVATIVES



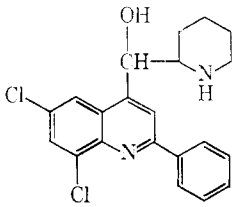
No.	R	Mp, °C	Formula	Analyses[a]	Antimalarial assay results[b] 40	160	640
6	H	210–260 dec	$C_{17}H_{20}N_2 \cdot 2HCl$	C, H, Cl	0.3	0.8 (2/5)	5/5
28	CH_3[c]		$C_{18}H_{22}N_2 \cdot H_2C_2O_4$		0.5	5/5	5/5
7	$CH_2C_6H_5$[c]		$C_{24}H_{28}N_2 \cdot H_2C_2O_4$		0.1	0.1	0.5
29	$COCH{=}CHCOOH$	141.5–142.5	$C_{21}H_{22}N_2O_3$	C, H, N	0.0	0.0	0.4
30	$CH_2CH_2CH_2OC_6H_4$-*t*-Bu-*p*	150–153	$C_{30}H_{38}N_2O \cdot HCl \cdot H_2O$	C, H, N	1.3	2.9	3.5
					0.3	0.3	0.9

[a,b] See corresponding footnotes in Table I. [c] See ref 6.

shown to be effective against both malaria[4] and schistosomiasis[5] in experimental animal systems.

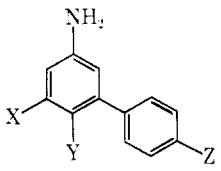


1

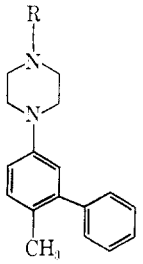


2

Chemistry.—The synthesis of the new compounds resolved itself into two areas: preparation of asymmetric biphenylamines and subsequent attachment of an appropriate side chain to the amine group. Four biphenylamines were employed. One of these, 2-biphenylamine, was commercially available. The synthesis of a second, 6-methyl-3-biphenylamine (**3**), was reported recently.[6] A third, **4**, was obtained by



3, X = Z = H; Y = CH_3
4, X = Y = H; Z = Cl
5, X = Z = Cl; Y = CH_3



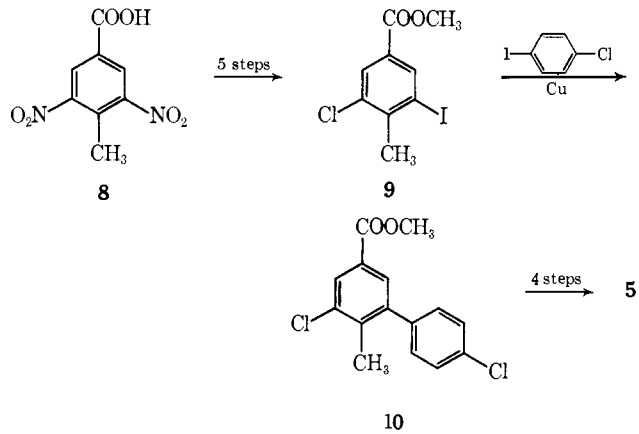
6, R = H
7, R = $CH_2C_6H_5$

(5) W. C. Campbell and A. C. Cuckler, *J. Parasitol*, **49**, 528 (1963).

(6) D. W. Henry, *J. Heterocyclic Chem.*, **3**, 503 (1966).

catalytic reduction of the known precursor, 4-chloro-3-nitrobiphenyl.[7] The preparative procedure for the fourth biphenylamine, **5**, is outlined in Scheme I. The

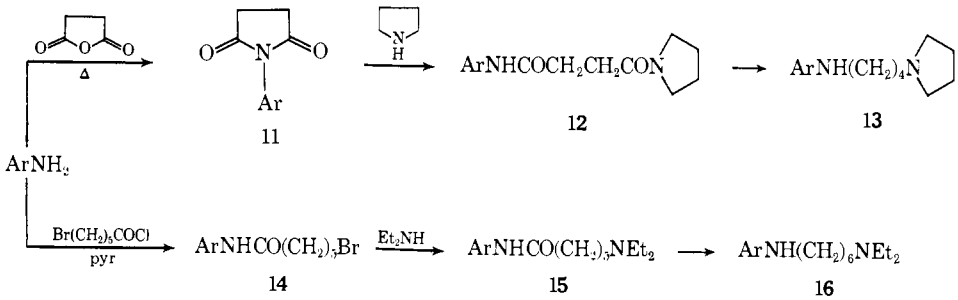
SCHEME I



starting material, 3,5-dinitro-*p*-toluic acid (**8**), was converted to methyl 3-chloro-5-iodo-*p*-toluate (**9**) by a series of reductions and Sandmeyer reactions. Mixed Ullmann coupling of the latter with *p*-chloroiodobenzene provided intermediate biphenyl ester **10** in 25% yield. Ester **10** was converted to the corresponding amide and rearranged to biphenylamine **5** by the Hofmann reaction.

Linear side chains, two, four, and six carbons in length and bearing terminal tertiary aliphatic amino functions, were attached to the amine functions of the biphenylamines to form the compounds of Table I. The two-carbon side chains were readily incorporated in one step by means of commercially available 2-chlorotriethylamine. Convenient and potentially general methods for assembling the four- and six-carbon chains were developed and are outlined in Scheme II. Succinic anhydride, when heated with the biphenylamines, gave N-substituted succinimides (**11**), which opened to succinamides (**12**) upon refluxing with pyrrolidine. Reduction of these with borane–THF or $LiAlH_4$ provided the four-carbon side chain derivatives (**13**).

SCHEME II



The six-carbon side chain series was obtained from 6-bromohexanoic acid *via* the acid chloride. Reaction with the biphenylamines gave 6-bromohexanamides (**14**), which were refluxed with excess diethylamine to give 6-diethylaminohexanamides (**15**). These provided the six-carbon diamines (**16**) upon reduction.

Piperazine derivatives **7** and **28** (Table II) were prepared from biphenylamine **3** by means of a general method that has been reported separately.[6] N-Monosubstituted piperazine **6** was obtained from N′-benzyl precursor **7** by catalytic hydrogenolysis. Compound **6** was converted to maleamide **29** with maleic anhydride and to phenoxypropyl compound **30** by a standard acylation–reduction sequence.

Tables I and II present characterization data on the N-dialkylaminoalkylbiphenylamines and N-biphenylylpiperazines prepared in this study. Almost all of the final products were oils and were characterized and bioassayed as their oxalate salts. The structures of all final products and most intermediates were confirmed by proton magnetic resonance spectroscopy.

Biological Activity.—The compounds were assayed against lethal, blood-induced *Plasmodium berghei* infections in mice[8] as part of the Walter Reed Army Institute of Research malaria program. Tables I and II list the increases in survival time and the toxicities displayed by the compounds prepared in this study. Two compounds, **21** and **30**, appeared to prolong survival times up to 3.5 days at 640 mg/kg and to show a dose–response relationship in initial tests, but this activity could not be confirmed when the tests were repeated. Compound **21** appeared especially variable in its effect, and the two series of results presented in Table I represent the two limiting assays. The majority of compounds were without appreciable beneficial effect and were toxic at the highest doses.[9] Quinine and chloroquine are included for comparison.

Compounds **18**, **20**, **22**, **24–26**, **28**, and **7** were tested for antischistosomal activity in mice infected with lethal inocula of *Schistosoma mansoni* cercariae.[10] All were ineffective at nontoxic doses.

When tested *in vitro*, a number of these compounds were appreciably inhibitory to bacteria, yeast, or a fungus. All compounds of Tables I and II were examined except **17**, **18**, and **6**. Data on those showing significant activity are summarized in Table III; the test employed has been previously described.[11]

(7) C. E. Kaslow and R. M. Summers, *J. Org. Chem.*, **20**, 1738 (1944).

(8) Performed by Dr. Leo Rane at the University of Miami, Miami, Fla; see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

(9) The possibility that the toxicity of these compounds was due to their use as oxalate salts cannot be excluded. If this were the case, the effect was not consistent since two oxalate salts (**7** and **25**) were not toxic. The toxicity of **6** (Table II) as the dihydrochloride suggests that the series possesses at least some intrinsic toxicity.

(10) We are grateful to Colonel William E. Rothe of the Walter Reed Army Institute of Research for communicating these results and providing a description of the test procedure. Lieutenant Colonel Myron G. Radke directed the schistosomiasis assay work.

(11) W. T. Colwell, J. H. Lange, and D. W. Henry, *J. Med. Chem.*, **11**, 282 (1968).

TABLE III

In Vitro ANTIMICROBIAL ACTIVITY OF N-DIALKYLAMINOALKYLBIPHENYLAMINES[a]

	Min inhib conc, μg/ml						
Compd	SA[b]	EC	SM	KA	SC	PN	SS
19	100	1000	1000	1000	10	100	10
21	0.1	100	1000	100	1	10	1
22	10	100	100	1000	1	10	10
23	10	100	...	1000	1	10	10
24	1	1000	1000	1000	1	10	<0.1
Furazolidone	0.1	1	0.1	0.1	1000	10	0.1

[a] A serial, tenfold, tube dilution assay was employed. See ref 11 for a description of the test. [b] SA = *Staphylococcus albus*, EC = *Escherichia coli*, SM = *Serratia marcescens*, KA = *Klebsiella aerobacter*, SC = *Saccharomyces cerevisiae*, PN = *Penicillium notatum*, SS = *Sporobolomyces salmoncolor*.

Experimental Section[12]

4′-Chloro-3-biphenylamine (4).—A suspension of 20.0 g (0.086 mole) of 4-chloro-3′-nitrobiphenyl[7] in 300 ml of EtOH was hydrogenated in the presence of 0.4 g of PtO_2 in a low-pressure Parr apparatus for 0.5 hr. The product, 14.3 g (82%, mp 69–70°), was purified by passage through basic Al_2O_3 ($CHCl_3$ elution) and crystallization from petroleum ether (bp 30–60°). Blakey and Scarborough[13] report a melting point of 82° for this compound.

5-Iodo-3-nitro-*p*-toluic Acid.—The diazonium salt solution, formed by treatment at 0–5° of 196.2 g (1.00 mole) of crude 3-amino-5-nitro-*p*-toluic acid[14] in 1600 ml of 6 *N* HCl with 75.9 g (1.10 moles) of $NaNO_2$ in 150 ml of H_2O, was poured slowly into a stirred solution of 199.2 g (1.2 moles) of KI in 1500 ml of H_2O. N_2 was evolved immediately and the very crude product (246.5 g) precipitated. After partial purification by sublimation at 200° (0.2 mm), the product was used directly in the next step; yield 104.5 g (34%), mp 190–210°. Recrystallization (MeOH–H_2O) gave a pure sample, mp 213–215°. *Anal.* ($C_8H_6INO_4$) C, H.

Methyl 3-Iodo-5-nitro-*p*-toluate.—A solution of the acid (30.7 g, 0.10 mole) and 60 ml of concentrated H_2SO_4 in 350 ml of MeOH was refluxed for 0.5 hr and chilled in ice. The crystalline product (27.5 g, 86%, mp 99–102°) was collected, washed with H_2O, and dried at 60° *in vacuo*. Recrystallized (MeOH–H_2O), it melted at 100–101.5°. *Anal.* ($C_9H_8INO_4$) C, H.

Methyl 3-Amino-5-iodo-*p*-toluate.—Catalytic reduction (27 hr) of methyl 3-iodo-5-nitro-*p*-toluate (32.1 g, 0.10 mole) with Raney Ni in warm MeOH (400 ml) in a low-pressure Parr apparatus provided this product. The filtered reaction mixture was chilled to give 26.1 g (90%, mp 131–134°). Recrystallized (MeOH–H_2O), it melted at 135–136.5°. *Anal.* ($C_9H_{10}INO_2$) C, H.

Methyl 3-Chloro-5-iodo-*p*-toluate (9).—A well-stirred suspension of methyl 3-amino-5-iodo-*p*-toluate hydrochloride salt, prepared by diluting a solution of 62.8 g (0.216 mole) of the amine in 300 ml of DMF with 110 ml of 6 *N* HCl, was treated slowly at 0° with a solution of 16.4 g (0.238 mole) of $NaNO_2$ in 40 ml of H_2O. The diazonium salt solution was added slowly, with stirring, to a Cu_2Cl_2 solution prepared from 62.6 g of $CuSO_4 \cdot 5H_2O$ by Fieser's procedure.[15] The crude product, which precipitated immediately with N_2 evolution, was purified by chromatography over Al_2O_3, using 5% Et_2O in 30–60° petroleum ether as eluent; yield 56.1 g, mp 68–75°. Recrystallization (MeOH–H_2O) gave material of mp 73–74°. Preparative glpc gave an analytical specimen (mp 75.5–76.5°). *Anal.* ($C_9H_8ClIO_2$) C, H.

Methyl 4′,5-Dichloro-6-methylbiphenyl-3-carboxylate (10).—Methyl 3-chloro-5-iodo-*p*-toluate (28.0 g, 0.09 mole), 4-chloroiodobenzene (47.0 g, 0.2 mole), and 100 g of Cu powder were heated together at 230° for 4 hr. The reaction mixture was cooled and the crude product was extracted from the inorganic material with hot C_6H_6. The extract was evaporated *in vacuo* to leave a partially crystalline residue. Extraction of the residue with boiling pentane left a solid that melted at 125–135°. The pentane extract was chromatographed over 800 g of silica gel, using pentane as the initial eluent. When elution of by-product 4,4′-dichlorobiphenyl ceased, 5% Et_2O in pentane was used to remove the product (8.2 g, 25%). Recrystallized from heptane, it melted at 71.5–73°. *Anal.* ($C_{15}H_{12}Cl_2O_2$) C, H, Cl.

The insoluble residue remaining from the pentane extraction consisted largely of 4,4′-dichlorobiphenyl, but a second component, dimethyl 5,5′-dichloro-6,6′-dimethyl-3,3′-biphenyldicarboxylate, could be isolated by silica gel chromatography. Pentane eluted the 4,4′-dichlorophenyl and Et_2O, the new product. Crystallization from CCl_4–pentane gave colorless crystals melting at 176–176.5°. *Anal.* ($C_{18}H_{16}Cl_2O_4$) C, H, Cl.

4′,5-Dichloro-6-methyl-3-biphenylcarboxylic Acid. Hydrolysis of the methyl ester (**10**) in 3 *N* NaOH in 50% aqueous EtOH (reflux, 2 hr) provided this acid after acidification of the reaction mixture: mp 204–206° (MeOH–H_2O). *Anal.* ($C_{14}H_{10}Cl_2O_2$) C, H, Cl.

4′,5-Dichloro-6-methyl-3-biphenylcarboxamide.—Treatment of the acid with $SOCl_2$ gave the acid chloride; this was treated with excess gaseous NH_3 in C_6H_6 solution to provide the amide, mp 180–180.7° (MeOH–H_2O), yield 82%. *Anal.* ($C_{14}H_{11}Cl_2NO$) C, H.

4′,5-Dichloro-6-methyl-3-biphenylamine (5).—To a solution of 6.72 g (24 mmoles) of 4′,5-dichloro-6-methyl-3-biphenylcarboxamide in 100 ml of MeOH was added consecutively, with stirring, a solution of 56 mmoles of NaOMe in 40 ml of MeOH and 3.84 g (24 mmoles) of Br_2. The mixture was refluxed for 15 min and cooled. AcOH was added (to pH 6) and the solvent was removed *in vacuo*. The solid residue was washed with H_2O and dried to give 7.17 g of crude methyl N-(4′,5-dichloro-6-methyl-3-biphenylyl)carbamate, mp 140–147°. The product contained some unreacted starting amide. The carbamate was hydrolyzed by refluxing for 1 hr in 100 ml of 3 *N* NaOH in 50% aqueous EtOH. The EtOH was removed *in vacuo* and the residue was extracted with Et_2O. The combined Et_2O extracts were dried over Na_2SO_4 and evaporated to dryness *in vacuo*. The residue was extracted with hot heptane to remove the product. The insoluble residue consisted of 1.9 g of crude sodium 4′,5-dichloro-6-methyl-3-biphenylcarboxylate. The heptane extracts gave 4.61 g (80%) of product, mp 81–82°, upon cooling in Dry Ice. *Anal.* ($C_{13}H_{11}Cl_2N$) C, H, N.

N-(2-Diethylaminoethyl)biphenylamines. General Procedure for 17, 20, 22, and 25.—The biphenylamines were refluxed overnight in 95% EtOH with 2 molar equiv of 2-chlorotriethylamine hydrochloride. The pH of the reaction mixture was adjusted to 8 with dilute NaOH. Excess $Na_2S_2O_3$ was added (to destroy excess alkylating agent) and refluxing was continued for 0.5 hr. The reaction mixture was cooled, diluted with H_2O, and extracted with Et_2O to isolate the crude products. For **17**, **20**, and **22**, chromatography over silica gel (Et_2O elution) provided the pure oily products. Vacuum distillation (bp 128–144°, 0.15 mm) was used to purify **25**. Oxalate salts were formed in high yield by mixing molar equivalents of the free bases and oxalic acid in Me_2CO solution. Recrystallization from Me_2CO served to purify the salts when necessary (**17** and **20**). Yields ranged from 32 to 58%.

A modification of this procedure, using equimolar amounts of biphenylamine and 2-chlorotriethylamine free base in aqueous DMF, gave similar results.

N-Biphenylylsuccinimides (11). General Procedure.—Equimolar amounts of the biphenylamine and succinic anhydride were heated together at 200–215° for 2 hr. Recrystallization of the dark melts, once or twice, provided products suitable for the next reaction with the exception of **33**, for which column chromatography over Al_2O_3 (Et_2O–petroleum ether elution) was necessary. Table IV summarizes pertinent data for these compounds.

N-Biphenylyl-N′,N′-tetramethylenesuccinamides (12). General Procedure.—Solutions (*ca.* 20%) of the N-biphenylylsuccinimides (11) in pyrrolidine were refluxed for 1–2 hr. After cooling, the solutions were treated with excess 3 *N* or 6 *N* HCl and the solid precipitated products were isolated by decantation or filtration. Compound **38** precipitated as an oil and was isolated by extraction with $CHCl_3$. It subsequently crystallized from CCl_4 to give material melting at *ca.* 70° when examined immedi-

(12) Melting points were taken in capillary tubes on a Mel-Temp apparatus and are corrected. Infrared and proton magnetic resonance spectra were obtained on Perkin-Elmer Model 137 and Varian HR100 or A60 instruments, respectively. Microanalyses were performed by the Stanford Research Institute Analytical Department. Where analyses are indicated only by symbols of the elements, analytical results were within ±0.4% of the theoretical values.

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TABLE IV
N-BIPHENYLYLSUCCINIMIDES (11)

No.	Biphenylamine used in prepn	Yield, %	Mp, °C	Crystn solvent	Formula[a]
31	3	62	125.5–127	MeOH	$C_{17}H_{15}NO_2$
32	4	36	165–166	MeOH	$C_{16}H_{12}ClNO_2$
33	5	38	114–115	CCl_4–pentane	$C_{17}H_{13}Cl_2NO_2$
34	2-Biphenylamine	80	132–133.5	Aq MeOH	$C_{16}H_{13}NO_2$

[a] All compounds were analyzed for C, H.

ately. The melting point rose spontaneously over several days to a maximum of 97.5–99°. This behavior was apparently due to a crystalline transition because low-melting material gave the same combustion analysis as older, high-melting samples. Characterization data for these compounds are given in Table V.

TABLE V
N-BIPHENYLYL-N′,N′-TETRAMETHYLENESUCCINAMIDES (12)

No.	Biphenylamine used in prepn	Yield, %	Mp, °C	Crystn solvent	Formula[a]
35	3	89	150–152	Aq MeOH	$C_{21}H_{24}N_2O_2$
36	4	92	160–162	Aq MeOH	$C_{20}H_{21}ClN_2O_2$
37	5	95	210–211	MeOH	$C_{21}H_{22}Cl_2N_2O_2$
38	2-Biphenylamine	70	97.5–99	CCl_4	$C_{20}H_{22}N_2O_2$

[a] All compounds were analyzed for C, H.

N-[4-(1-Pyrrolidino)butyl]biphenylamines. General Procedures for 18, 21, 23, and 26.—Solutions of the N-biphenylylsuccinamides in THF were added at 0° to four- to sevenfold molar equivalents of $LiAlH_4$ or BH_3 in THF[16] over a few minutes. After several hours of refluxing, the reaction mixtures were cooled and, in the case of $LiAlH_4$ reduction, H_2O was slowly and carefully added with stirring until the gray color of the salts changed to white. The filtrate, after removal of the inorganic salts, yielded crude products requiring chromatography over silica gel (Et_2O, Et_2O–MeOH elution) for purification.

The cooled BH_3 reaction mixtures were treated with 6 *N* HCl, the THF was boiled off, and refluxing was continued for 1 hr to hydrolyze the unusually stable amine–BH_3 complexes present. Neutralization with NaOH and Et_2O extraction provided essentially pure products as the free bases. Yields with both reducing agents were in the 70–80% range. Oxalic acid salts were formed in Me_2CO solutions.

N-(6-Bromohexanoyl)biphenylamines (14). General Procedure.—A solution of the biphenylamine in pyridine was treated over 5 min with a 10% molar excess of 6-bromohexanoyl chloride (from the acid and $SOCl_2$), with stirring at 0°. After stirring a few minutes at room temperature, a small piece of ice was added to hydrolyze excess acid chloride. The mixture was diluted with excess 3 *N* HCl and the crude product was isolated by Et_2O extraction. Back-extraction of the product solution with dilute $NaHCO_3$ removed 6-bromohexanoic acid. The product from amine **3**, N-(6-bromohexanoyl)-6-methyl-3-biphenylamine, melted at 85–87° (57%, MeOH–H_2O). *Anal.* ($C_{19}H_{22}BrNO$) C, H. The amide from amine **5**, N-(6-bromohexanoyl)-4′,5-dichloro-6-methyl-3-biphenylamine, melted at 120–122.5° (MeOH). *Anal.* ($C_{19}H_{20}BrCl_2NO$) C, H. The amide from 2-biphenylamine was oily and was not characterized.

N-(6-Diethylaminohexyl)biphenylamines. General Procedure for Compounds 19, 24, and 27.—A 5–10% solution of the N-(6-bromohexanoyl)biphenylamine in Et_2NH was refluxed for *ca.* 4 hr and most of the solvent was removed *in vacuo*. The residue was partitioned between H_2O and Et_2O. The ether-soluble N-(6-diethylaminohexanoyl)biphenylamines (15) were reduced to N-(6-diethylaminohexyl)biphenylamines and purified in essentially the same manner as the corresponding four-carbon chain analogs. Crystalline dioxalate salts formed upon mixing 1 molar equiv of amine with 2 molar equiv of oxalic acid in Me_2CO solution. Monooxalate salts failed to form.

1-(6-Methyl-3-biphenylyl)piperazine Dihydrochloride (6).—A solution of 6.6 g (19 mmoles) of 1-benzyl-4-(6-methyl-3-biphenylyl)piperazine (**7**) in 260 ml of absolute EtOH, after addition of 13.4 ml of 3 *N* HCl (40 mmoles), was hydrogenated at atmospheric pressure in the presence of 1.32 g of 10% Pd–C. H_2 uptake stopped at 95% of theoretical after 1 hr. The mixture was warmed to dissolve some crystalline precipitate of product and the filtered solution was concentrated to ~150 ml by boiling. After cooling, the crystalline product was collected, washed with Et_2O, and dried; yield 3.8 g (62%), mp 225–255° dec. A sample prepared in a similar previous experiment, mp 210–265° dec, was analyzed.

1-(*cis*-3-Carboxyacryloyl)-4-(6-methyl-3-biphenylyl)piperazine (29).—A solution of 862 mg (3.42 mmoles) of 1-(6-methyl-3-biphenylyl)piperazine in 3 ml of anhydrous THF was treated with 335 mg (3.42 mmoles) of maleic anhydride in 3 ml of THF. After very brief heating (~1 min) on the steam bath, the mixture was cooled and slowly diluted to 20 ml with Et_2O while stirring. The flask was seeded and cooled at −20° overnight to give 891 mg (74%) of product, mp 139.5–141.5°. It was recrystallized from THF for analysis.

1-[3-(*p*-*t*-Butylphenoxy)propyl]-4-(6-methyl-3-biphenylyl)piperazine Hydrochloride (30).—A C_6H_6 solution (10 ml) of 1.32 g (5.2 mmoles) of 1-(6-methyl-3-biphenylyl)piperazine (**6**) was treated with 1.0 ml of Et_3N and then with a C_6H_6 solution (5 ml) of 1.66 g (6.7 mmoles) of 3-(*p*-*t*-butylphenoxy)propionyl chloride. After 10 min, the mixture was diluted with 50 ml of Et_2O and was extracted four times with diluted NaOH. The crude 1-[3-(*p*-*t*-butylphenoxy)propionyl]-4-(6-methyl-3-biphenylyl)piperazine (2.52 g) was chromatographed over 50 g of Merck basic Al_2O_3 to give 1.89 g of pure product.

The pure propionylpiperazine was reduced with BH_3–THF[16] and worked up as in the reduction of the biphenylylsuccinamides (12). The crude product (HCl salt) was water insoluble; it was isolated by filtration, washed with H_2O, and recrystallized from 25 ml of 95% EtOH to give 1.38 g (67%) of product in two crops (mp 150–153°). Above the melting point, recrystallization occurred, with a final melting point of 220–230° dec. The first crop was analyzed after drying for 0.5 hr at 70° *in vacuo*.

3-(*p*-*t*-Butylphenoxy)propionitrile was prepared from *p*-*t*-butylphenol and acrylonitrile in 65% yield by the general method of Lichtenberger, *et al.*;[17] mp 52–55° (aqueous EtOH). *Anal.* ($C_{13}H_{17}NO$) C, H.

3-(*p*-*t*-Butylphenoxy)propionic Acid.—Hydrolysis of 10.0 g (49 mmoles) of the acid in a mixture of 25 ml of concentrated HCl and 30 ml of glacial AcOH produced 10.4 g of crude acid (mp 82–91°) after dilution of the reaction mixture with 170 ml of H_2O; mp 91–94° (aqueous MeOH). *Anal.* ($C_{13}H_{18}O_3$) C, H.

Schistosomiasis Drug-Testing Procedure.[10]—Groups of five mice 40–60 days of age were exposed by tail immersion to 2000–3000 cercariae of *Schistosoma mansoni*. A single dose (640, 1280, or 1920 mg/kg, peanut oil suspension) of the test chemical was administered subcutaneously 1–3 days postexposure. Control mice infected with these heavy cercarial inocula die between days 18 and 30, with a mean survival time of 25 days. Since a few control mice (~2%) survive the heavy cercarial exposure, a single survivor or a single mouse still alive after 30 days cannot be considered as evidence of drug activity. Early mortality (days 1–15) is excluded from the analysis of mean survival time. A mean survival time exceeding 30 days suggests antischistosomal activity in this test. Mice surviving to day 49 are sacrificed for total worm count. With niridazole, at 640 mg/kg, mortality in this test is only 20% and surviving mice do not harbor adult schistosomes at necropsy.

Acknowledgment.—The authors are very grateful to Dr. William T. Colwell and Mrs. Lynne Stietzel for their considerable efforts during the early phases of this project.

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