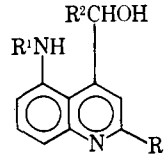
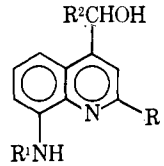
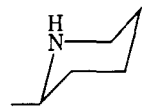
phenyl in the 2 position to block metabolic attack, and (3) an NH moiety in the 5 or 8 position to give a low $E_{HOMO} + E_{LEMO}$ or low phototoxicity. Derivatives which might be worthy of synthesis and evaluation include those of type XXII and XXIII where R^1 and R^2 are the commonly employed moieties in antimalarial drug design such as



XXII



XXIII



, $-(CH_2)_nN(C_2H_5)_2$, etc.

Such syntheses are in progress.

Acknowledgment.—The authors thank Dr. David P. Jacobus for fruitful and interesting discussions and for providing data relevant to these studies.

Antimalarial Activity of Guanylhydrazone Salts of Aromatic Ketones. I. Primary Search for Active Substituent Patterns[1]

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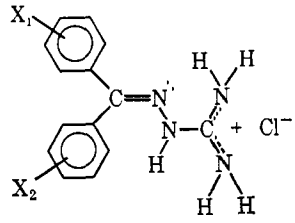
Thirty two guanylhydrazones of aromatic ketones were synthesized and tested in the primary antimalarial screen in mice infected with *Plasmodium berghei*. Biological data have been received on 30 compounds. Nine compounds showed significant activity and seven of these gave a high percentage of cures. The biological results and structure–activity correlation are discussed as well as drug design and the synthetic problems involved. Activity of some of these compounds on L1210 leukemia in mice is described.

In 1962 a small group of substituted benzophenone guanylhydrazones (I) was synthesized specifically to study their action on L1210 leukemia in mice.[2,3] Several of these compounds displayed significant activity.



I

However, the dose–response relations and therapeutic indices were so poor that the project was abandoned. In 1965 and 1966 we sent 17 of these compounds (Table I) to the Walter Reed Army Institute of Research for testing in the primary antimalarial screen (*Plasmodium berghei* in mice). One compound, 4-fluoro-4′-trifluoromethylbenzophenone guanylhydrazone hydrochloride (**15**), was quite active and caused some cures. As a consequence a contract was activated to pursue this lead.

Referring to structure I, one can introduce one or more substituents in either or both rings and insert various substituents in place of hydrogen on the aminoguanidine moiety. Considering the limited biological data available (Table III) a simple series was generated wherein the guanidine group was unchanged, a 4-CF_3 group was maintained on one ring, and a variety of substituents were placed on the 4′ position. These groups were chosen with the usual considerations. A range of electronic effects and influences on solubility-distribution behavior could be studied relatively easily. While this work was in progress information was received on the moderate activity of **7** and the high activity of **17**. Consequently, attention was focused on bromo, iodo, and additional trifluoromethyl substituents. The resultant series of compounds is shown in Table II.

Biological Data and Correlations.—An inspection of the data in Table III and a consideration of ancillary toxicity data make it apparent that there are two correlations involved in the structure–activity relationships: a toxicity correlation and an antimalarial activity correlation. Any activity which might conceivably have been displayed by compounds substituted only in one ring with fluoro, chloro, or trifluoromethyl is masked by high host toxicity. The same limitation applies when both rings bear fluoro or chloro substituents. For monosubstitution the toxicity decreased in the order: $CF_3 > I > F > Br$. When bromo and/or trifluoromethyl substituents are present in both rings toxicity is quite low.

The only monosubstituted compounds showing antimalarial activity in the primary screen were the 4-bromo and particularly the 4-iodo derivatives. In the new series of 4-trifluoromethyl-4′-halo derivatives the order of activity cannot be stated precisely at this time. However, incomplete advance biological data show that both the 4′-chloro and 4′-iodo derivatives are active. Curiously enough, the 4,4′-dibromo derivative is inactive but it has the expected low toxicity. In contrast, both the 4,4′-ditrifluoromethyl and the 4-bromo-

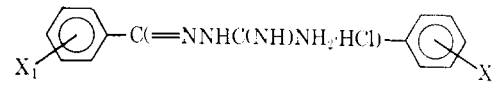
(1) This investigation was conducted under Contract DA-49-193-MD-3016 from the U. S. Army Research and Development Command. This is Contribution No. 313 to the Army Research Program on Malaria.

(2) F. A. French, E. J. Blanz, Jr., and C. C. Cheng, *Proc. Am. Assoc. Cancer Res.*, **4**, 20 (1963).

(3) This work was supported by Grant CA-03287 from the National Cancer Institute.

Table I

Guanylhydrazones of Benzophenones. First Group. Prepared by Procedure C at Reflux Temperature

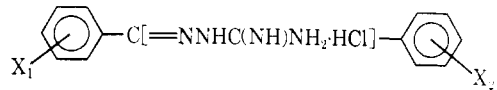


No.	X_1	X_2	Molar ratio AG·HCl[a]/ketone	Reaction solvents[b] (ml)	Reaction time, hr	Crystn solvent[c]	Mp, °C dec	Formula	Analyses
1	H	H	1.79	IV (25)	64.0	A, B	293–294	$C_{14}H_{14}N_4 \cdot HCl$	C, H, Cl, N
2	4-CH_3	H	2.08	I (100)	4.0	A	282–284	$C_{15}H_{16}N_4 \cdot HCl$	C, H, Cl, N
3	4-$N(CH_3)_2$	H	2.04	II (25)	0.5	C	269–271	$C_{16}H_{19}N_5 \cdot HCl$	C, H, Cl, N
4	4-CH_3	4′-CH_3	2.73	II (25)	1.0	D, B	219	$C_{16}H_{18}N_4 \cdot HCl$	C, H, Cl, N
5	4-F	H	1.06	I (100)	48.0	E	263–266	$C_{14}H_{13}FN_4 \cdot HCl$	C, H, Cl, F, N
6	4-Cl	H	1.09	I (100)	48.0	F	280–282	$C_{14}H_{13}ClN_4 \cdot HCl$	C, H, Cl, N
7	4-Br	H	1.35	III (50)	8.0	F	284.5–285.5	$C_{14}H_{13}BrN_4 \cdot HCl$	C, H, Br, Cl, N
8	2-F	H	2.00	II (25)	1.0	E, B	270–272	$C_{14}H_{13}FN_4 \cdot HCl$	C, H, Cl; F,[d] N[d]
9	4-F	4′-F	1.56	II (50)	1.5	E	273.5–274.5	$C_{14}H_{12}F_2N_4 \cdot HCl$	H, Cl, F; C,[e] N[e]
10	4-F	3′-F	2.00	II (25)	0.5	E, B	241.5–242.5	$C_{14}H_{12}F_2N_4 \cdot HCl$	H, Cl, F, N; C[f]
11	4-F	2′-F	2.00	II (25)	0.5	E, B[g]	244–245	$C_{14}H_{12}F_2N_4 \cdot HCl \cdot 0.5H_2O$	C, H, Cl, F; N[h]
12	3-F	3′-F	2.81	II (25)	1.0	E, B[g]	232–232.5	$C_{14}H_{12}F_2N_4 \cdot HCl$[i]	C, H, Cl, F, N
13	4-Cl	4′-Cl	1.36	II (50)	1.5	E	305–306	$C_{14}H_{12}Cl_2N_4 \cdot HCl$	C, H, Cl; N[j]
14	4-CF_3	H	3.45	II (50)	0.5	G	280–281	$C_{15}H_{13}F_3N_4 \cdot HCl$	C, H, Cl, F, N
15	4-CF_3	4′-F	3.57	II (50)	2.0	H	263–265	$C_{16}H_{12}F_4N_4 \cdot HCl$	C, H, Cl, F, N
16	3-CF_3	2′-F	3.57	II (25)	1.0	E, B	253.5–254[k]	$C_{15}H_{12}F_4N_4 \cdot HCl$	C, H, Cl, F, N
17	4-CF_3	3′-CF_3	3.94	II (25)	1.0	E	284–285	$C_{16}H_{12}F_6N_4 \cdot HCl$	C, H, Cl, F, N

[a] AG = aminoguanidine. [b] I = H_2O–EtOH (1:1), II = ethylene glycol, III = methyl Cellosolve, IV = AcOH. [c] A = EtOH, B = H_2O–EtOH (4:1), C = EtOH–H_2O (95:5), D = H_2O–EtOH (1:1), E = H_2O, F = H_2O–EtOH (5:1), G = H_2O–EtOH (8:1), H = H_2O–EtOH (98:2). [d] F: calcd, 6.94; found, 6.29. N: calcd, 19.14; found, 19.59. [e] C: calcd, 54.11; found, 54.81. N: calcd, 18.03; found, 17.47. [f] C: calcd, 54.11; found, 53.50. [g] Twice. [h] N: calcd, 17.52; found, 16.48. [i] Hygroscopic. [j] N: calcd, 16.30; found, 17.90. [k] Change at 219°.

Table II

Guanylhydrazones of Benzophenones. Second Group. Prepared by Procedure D



No.	X_1	X_2	Reaction solvent[a]	Crystn solvent[b]	Mp, °C	Formula	Analyses
18	4-I	H	EG	I	284–284.5	$C_{14}H_{13}IN_4 \cdot HCl$	C, H, Cl, I, N
19	4-Br	4′-Br	DMAC	II	308–309 dec	$C_{14}H_{12}Br_2N_4 \cdot HCl$	C, H, Br, N
20	4-Br	4′-CF_3	DMAC	III	300–301 dec	$C_{15}H_{12}BrF_3N_4 \cdot HCl$	C, H, Cl, N
21	4-Br	4′-CF_3	DMAC	II	123–124 dec	$C_{15}H_{12}BrF_3N_4 \cdot TsOH$[c]	C, H, Br, N, S
22	4-Br	3′,5′-$(CF_3)_2$	DMAC	IV, V	199–201 dec	$C_{16}H_{11}BrF_6N_4 \cdot HCl$	C, H, F, N
23	3-Br	4′-CF_3	EG	III[d]	258–259 dec	$C_{15}H_{12}BrF_3N_4 \cdot HCl$	C, H, Br, Cl, N
24	4-CF_3	4′-OC_2H_5	EG	II	253–255 dec	$C_{17}H_{17}F_3N_4O \cdot HCl$	C, H, Cl, F, N
25	4-CF_3	4′-OH	EG	VI, II	286–288 dec	$C_{15}H_{13}F_3N_4O \cdot HCl \cdot 0.5H_2O$	H, N; C,[e] Cl,[e] F[e]
26	4-CF_3	3′-OC_2H_5	EG	II	277 dec	$C_{17}H_{17}F_3N_4O \cdot HCl$	C, H, Cl, N
27	4-CF_3	3′-OH	EG	VI	245 dec	$C_{15}H_{13}F_3N_4O \cdot HCl$	C, H; Cl,[f] F,[f] N[f]
28	4-CF_3	*g*	EG	VII	294–294.5	$C_{13}H_{11}F_3N_4S \cdot HCl$	C, H, Cl, N, S
29	2-CF_3	4′-$N(CH_3)_2$	EG	VIII, II	259–261 dec	$C_{17}H_{18}F_3N_5 \cdot HCl$	C, H, Cl, N; F[h]
30	4-CF_3	*i*	DMAC	IX	282–282.5	$C_{14}H_{12}F_3N_5 \cdot HCl$	C, H, Cl, F; N[j]
31	4-CF_3	4′-CF_3	EG	II	306–308 dec	$C_{16}H_{12}F_6N_4 \cdot HCl$	C, H, N; Cl[k]
32	3,5-$(CF_3)_2$	H	EG[l]	X[m]	224–226.5	$C_{16}H_{12}F_6N_4 \cdot HCl$	C, H, Cl, N; F[n]

[a] EG = ethylene glycol, DMAC = dimethylacetamide. [b] I = EtOH–H_2O (95:5), II = H_2O, III = H_2O–EtOH (4:1), IV = C_6H_5-CH_3, V = $CHCl_3$–$C_6H_5CH_3$ (1:1), VI = H_2O–EtOH (5:1), VII = H_2O–EtOH (2:1), VIII = EtOH, IX = *i*-PrOH–H_2O (1:1), X = *i*-PrOH–MeOH (95:5). [c] *p*-Toluenesulfonate salt. [d] Twice. [e] C: calcd, 49.11; found, 49.77. Cl: calcd, 9.66; found, 8.84. F: calcd, 15.54; found, 15.07. [f] Cl: calcd, 9.88; found, 8.52. F: calcd, 15.89; found, 15.28. N: calcd, 15.62; found, 15.00. [g] $C_6H_4X_2$ = 2-thienyl. [h] F: calcd, 14.17; found, 13.50. [i] $C_6H_4X_2$ = 3-pyridyl. [j] N: calcd, 20.49; found, 20.97. [k] Cl: calcd, 8.63; found, 7.16. [l] or DMAC. [m] AcOEt added to the solution. [n] F: calcd, 27.75; found, 26.48.

4′-trifluoromethyl derivatives are very active and have a low toxicity.

When there is a 4-trifluoromethyl group and a 3′-bromo- or 3′-trifluoromethyl group present, curative activity is retained, but in the case of the 3,4′-ditrifluoromethyl derivative more toxicity is apparent. It is notable also that the 4-bromo-3′,5′-ditrifluoromethyl derivative is quite active. Compounds with hydrophilic hydrogen bonding groups such as OH, OC_2H_5, and $N(CH_3)_2$ have so far proven inactive; however, compounds bearing these groups (**24**–**27** and **29**) are nontoxic at the maximum dose of 640 mg/kg. *ortho* substituents have been avoided initially because of the possibility of neighboring-group effects.

It is apparent that the study of compounds with additional substituents and more complex substitution patterns should be interesting. There is a hint in the data that there may be an optimum range of Hammet's

TABLE III
ANTIMALARIAL ACTIVITY OF GUANYLHYDRAZONES OF BENZOPHENONES[a]

Compd no.	Dose, mg/kg	Increase in mean survival time[b] or no. of cures[c] (toxic deaths)
7	320	6.9
	640	(5)
15	20	8.1
	40	9.6, 9.7
	80	14.9, 3C
	160	3C (2)
17	80	1C
	160	4C (1)
	320	4C (1)
	640	(5)
18	40	6.4
	80	8.8 (2), 7.0
	160	9.8 (3), 1C (2)
20	40	6.8
	80	4C
	160	5C, 5C
	320	5C, 5C
	640	4C (1), 3C (2)
21	160	2C, 2C
	320	5C
	640	5C
22	160	1C, 1C
	320	5C
	640	5C
23	160	3C, 3C, 1C
	320	3C, 4C
	640	4C, 5C
31	160	5C, 5C
	320	5C
	640	5C, 5C

[a] The antimalarial test methods are those of Rane.[6] No data have been received on **30** and **32**. All other compounds are inactive. [b] Mean survival time of treated mice minus mean survival time of controls in days. [c] Number of treated mice in a group of five surviving 60 days (number followed by C).

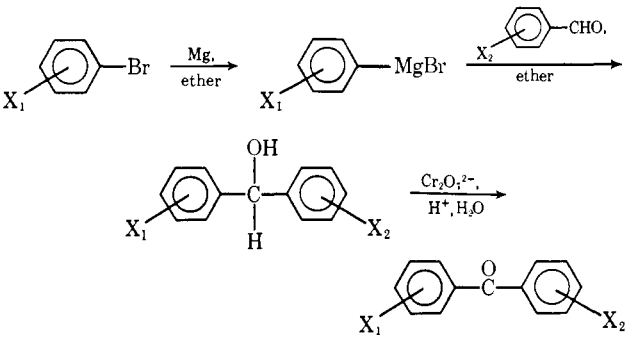
σ and Hansch's π constants.[4] A study has been initiated to examine this type of correlative approach.

The mechanism of antimalarial action of these compounds is unknown. Referring to structure I, one notes that these molecules can be divided into two regions: a very polar, hydrophilic, ionic hydrogen-bonding iminoguanidine group and a pair of polar hydrophobic tails. In the diphenylketimine region, while there is a relatively free rotation about the C-ring bonds, planar or quasi-planar conformations are somewhat preferred because of the π-orbital overlap. A similar situation, involving strong resonance energy, is apparent in the guanidine region. Whether or not there is intersystem coupling is not obvious. More data are required before this question can be discussed.

Compounds **5**, **6**, **9**, **15**, and **16** (Table I) are active in L1210 leukemia in mice and the others are not significantly active at maximum tolerated doses. The dose–response relationships are so steep and active doses are so nearly lethal that it was only possible to detect these activities by using extremely close dose-screening intervals (dose B = 1.2 × dose A, etc.). Compounds **18**, **20–24**, **26–30**, and **32** (Table II) were subjected to limited testing on L1210 and no activities were found. The antitumor and antimalarial activities are essentially independent except for one crossover point, the 4-fluoro-4′-trifluoromethyl derivative (**15**).

Chemistry.—Procedure A was generally used for the synthesis of the ketones (Scheme I). Other routes are

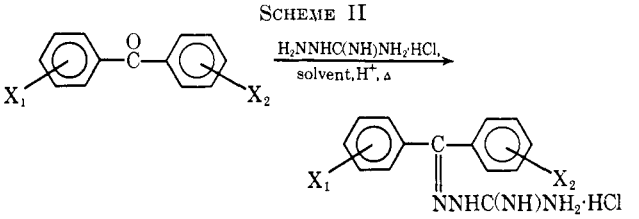
SCHEME I
PROCEDURE A



grouped as procedure B. A few of the aromatic ketones were commercially available. Others were synthesized for this study. The new compounds are reported in Table IV. Typical cases for each procedure are described in the Experimental Section.

The reaction in Scheme II was used in the synthesis of the guanylhydrazone salts. The guanylhydrazones

SCHEME II



in Table I were synthesized under various conditions (procedure C). Solvents used were H_2O–EtOH (1:1), EtOH, AcOH, and $HOCH_2CH_2OH$. Concentrations varied from 0.1 to 1 (w/v). The molar ratio of aminoguanidine hydrochloride/ketone varied from 1.06 to 3.94. The reaction mixture was generally maintained at reflux temperature. The reaction time ranged from 0.5 to 64 hr.

Before starting the syntheses of the guanylhydrazones in Table II, a study of reaction conditions was undertaken. Previous information[5] and our experience seem to indicate that the mechanism of condensation of amines with ketones generally agrees with the mechanism of oxime and semicarbazone formation (Scheme III). Either step may be rate determining depending

SCHEME III

$$R^1R^2CO + H_2N- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R^1R^2C(OH)NH- \underset{k_2}{\overset{k_1}{\rightleftharpoons}} R^1R^2C{=}N- + H_2O$$

on reaction conditions, the nature of R^1 and R^2, the catalyst, and the particular aminoguanidine and ketone involved.

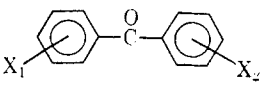
Dilute systems and mild conditions seemed unsatisfactory for the formation of the guanylhydrazone salts in short reaction times. The reaction medium was either dimethylacetamide or ethylene glycol. The choice of solvent was based on maximum ketone solubility. The optimal reaction conditions were (1)

(4) C. Hansch, R. M. Muir, T. Fujita, P. P. Maloney, C. F. Geiger, and M. J. Streich, *J. Am. Chem. Soc.*, **85**, 2817 (1963).

(5) R. L. Reeves in "The Chemistry of the Carbonyl Group," S. Patai, Ed., Interscience Publishers, Inc., New York, N. Y., 1966, p 611.

Table IV

Substituted Benzophenones



No.	X_1	X_2	Procedure	Crystn solvent[a]	Mp, °C	Formula	Analyses
33	4-CF_3	4′-F	A	I[b]	99.5–100.5	$C_{14}H_8F_4O$	H, F; C[c]
34	3-CF_3	2′-F	A	*d*	*e*	$C_{14}H_8F_4O$	H, F; C[c]
35	4-CF_3	3′-CF_3	A	I	97–98	$C_{15}H_8F_6O$	H; C,[g] F[g]
36	4-Br	4′-CF_3	A	I[b]	132.5–133.5	$C_{14}H_8BrF_3O$	C, H, Br, F
37	4-Br	3′,5′-$(CF_3)_2$	A	*h*	55–57	$C_{15}H_7BrF_6O$	C, H, Br, F
38	3-Br	4′-CF_3	A	*h*	96.5–98	$C_{14}H_8BrF_3O$	C, H; Br,[i] F[i]
39	4-CF_3	4′-OC_2H_5	A	I[b]	127–128	$C_{16}H_{13}F_3O_2$	C, H, F
40	4-CF_3	4′-OH	B	*h*	144–145	$C_{14}H_9F_3O_2$	C, H, F
41	4-CF_3	3′-OC_2H_5	A	I[b]	73–74.5	$C_{16}H_{13}F_3O_2$	C, H, F
42	4-CF_3	3′-OH	B	*h*	127–128	$C_{14}H_9F_3O_2$	C, H, F
43	4-CF_3	*j*	A	I[b]	112–113	$C_{12}H_8F_3OS$	C, H, S
44	4-CF_3	4′-$N(CH_3)_2$	B	I[b]	154–155	$C_{16}H_{14}F_3NO$	C, H, F
45	4-CF_3	4′-CF_3	A	II	66–72	$C_{15}H_8F_6O$	C, H, F
46	4-CF_3	*k*	A	III	52.5–54	$C_{13}H_8F_3NO$	C, H, F, N
47	3,5-$(CF_3)_2$	H	A	*l*	*l*	$C_{15}H_8F_6O$	C, H, F

[a] I = EtOH, II = MeOH, III = petroleum ether (bp 30–60°). [b] Sublimed under reduced pressure. [c] C: calcd, 62.69; found, 62.63. [d] Purified in the guanylhydrazone step (see Table I, **16**). [e] Bp 103–104° (1 mm), $n^{24.5}$D 1.5192. [f] C: calcd, 62.69; found, 57.73. The guanylhydrazone hydrochloride had the correct elemental analysis. [g] C: calcd, 56.61; found, 57.16. F: calcd, 35.82; found, 34.02. The guanylhydrazone hydrochloride had the correct elemental analysis. [h] Bp 122.5–123° (1.4 mm), n^{23}D 1.5274. [i] Br: calcd, 24.28; found, 23.74. F: calcd, 17.32; found, 16.29. [j] $C_6H_4X_2$ = 2-thienyl. [k] $C_6H_4X_2$ = 3-pyridyl. [l] Bp 112–113° (0.2 mm), n^{22}D 1.4935.

approximately 1 ml of solvent:1 g of reactants, (2) 1 g of aminoguanidine hydrochloride:1 g of ketone, (3) acid catalyst, (4) reflux conditions, and (5) an optimum reaction time usually of 30 min (procedure D). Product separation and purification was usually difficult. The presence of by-products and the broad variations in product solubility necessitated individual studies for each compound. The formation of hydrates and of addition compounds with alcohols led to additional complications. Some typical cases will be discussed in the Experimental Section. No attempt was made to optimize these reactions for high yields. The sole object was to obtain sufficient analytically pure material for biological testing.

Experimental Section

Biological Methods.—The antimalarial data presented were obtained from the Walter Reed Army Institute of Research. The methods were developed by Rane.[6] The antileukemic tests used in this laboratory have been described previously.[7]

Chemical Procedures.—The following synthetic procedures are representative for preparation of the compounds in Tables I, II, and IV. The melting points are uncorrected and were determined with a Thomas–Hoover capillary melting point apparatus. Unless otherwise reported the tlc system for the ketones was silica gel 254,[8] C_6H_6–EtOH (98:2), 20 min, visualization with uv light, then I_2. For the guanylhydrazone salts it was AcOEt–$(CH_3)_2CHOH$–H_2O (2:2:1), 40 min, visualization as above. Analyses were performed by Berkeley Analytical Laboratory, Berkeley, Calif., and Micro-Analysis, Inc., Wilmington, Del. Where analyses are indicated only by symbols of the elements, results obtained do not deviate more than ±0.4% from the calculated values.

Procedure A (Scheme I). 4-Bromo-4′-trifluoromethylbenzophenone (36).—The Grignard reagent was prepared from *p*-bromobenzotrifluoride (90 g, 0.4 mole) and Mg (10.6 g, 0.44 g-atom). The Grignard solution was added dropwise to *p*-bromobenzaldehyde (75 g, 0.4 mole) in 300 ml of dry Et_2O at a rate that maintained reflux. After addition was completed the solution was refluxed for 1 hr. It was then cooled and added to 170 ml of concentrated HCl in 800 g of ice–water and stirred for 1 hr, after which the ether layer was separated and saved and the H_2O layer was extracted three times (Et_2O). The ether layer and the combined Et_2O extracts were dried ($MgSO_4$) and filtered, and the ether was distilled, yielding 39.6 g (29.5%) of a viscous liquid which immediately solidified on standing. This solid (39.6 g, 0.119 mole, calculated as the benzhydrol) was dissolved in PhH (400 ml) and added dropwise, at room temperature during 2 hr, to a well-stirred oxidizing solution of $Na_2Cr_2O_7 \cdot 2H_2O$ (14.9 g, 0.05 mole) in H_2O, concentrated H_2SO_4, and AcOH. The layers were separated and the PhH layer was saved. H_2O (45 ml) was added to the aqueous layer and this was extracted three times (PhH). The benzene layer and the PhH extracts were combined, washed (H_2O, saturated $NaHCO_3$ solution, H_2O), dried ($MgSO_4$), and filtered. PhH was removed under reduced pressure, yield 29.3 g of solid (74.8%), mp 115–120°. The crude material was sublimed under reduced pressure. Recrystallization (EtOH) gave a chromatographically pure material, mp 132.5–133.5°.

Procedure B. 4-Trifluoromethyl-4′-hydroxybenzophenone (40).—4-Trifluoromethyl-4′-ethoxybenzophenone (prepared according to procedure A) (16.7 g, 0.057 mole) and pyridine hydrobromide (80 g, 0.5 mole) were heated with stirring at 210° for 0.5 hr. The reaction mixture was cooled, treated with 200 ml of H_2O, and filtered. The solid residue was washed (H_2O), dissolved in KOH solution, treated with Norit, filtered through a Celite bed, and acidified with 40% AcOH. The precipitate was filtered, washed several times with H_2O, and dried. The crude product weighed 13.4 g, mp 141.5–143°. It was sublimed under reduced pressure, yielding 11.0 g (77.1%) of crystalline solid, mp 144–145°, chromatographically pure (tlc).

4-Trifluoromethyl-3′-hydroxybenzophenone (42) was prepared following the above procedure from 4-trifluoromethyl-3′-ethoxybenzophenone (synthesized according to procedure A). For physical data see Table IV.

4-Trifluoromethyl-4′-N,N-dimethylaminobenzophenone (44).—*p*-Trifluoromethylbenzoyl chloride, bp 48–49° (0.4 mm), was prepared in 92.5% yield from *p*-trifluoromethylbenzoic acid (50 g, 0.263 mole) and $SOCl_2$ (113 g, 0.95 mole). The anilide, mp 205–206°, single spot in tlc (C_6H_6–EtOH (95:5), 25 min), was prepared in 98% yield from *p*-trifluoromethylbenzoyl chloride (50.6 g, 0.243 mole) and $PhNH_2$ (46 g, 0.49 mole). The procedure of Hurd and Webb[9] was adapted for the preparation of the ketone.

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(8) E. Merck, AG, Darmstadt, Germany.

(9) C. D. Hurd and C. N. Webb, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1944, p 217.

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.* ($C_3H_{14}N_4O_3S$) C, H, N, S.

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N-Dialkylaminoalkylbiphenylamines as Antimalarial and Antischistosomal Agents[1]

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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

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