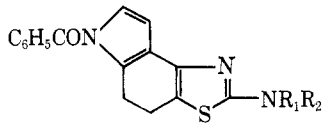
TABLE II

2-SUBSTITUTED-6-BENZOYL-4,5-DIHYDRO-6*H*-PYRROLO[3,2-*e*]BENZOTHIAZOLES



Compd	R_1R_2	Yield, %	Mp, °C	Formula	Analysis
2a	H, H	79	190–193	$C_{16}H_{13}N_3OS$	C, H, N, S
b	H, CH_3	92	171–174	$C_{17}H_{15}N_3OS$	C, H, N, S
c	H, $CH_2CH{=}CH_2$	95	138–141	$C_{19}H_{17}N_3OS$	C, H, N, S
d	CH_3, CH_3	75	117–120	$C_{18}H_{17}N_3OS$	C, H, S
e·HBr		68	255–257	$C_{21}H_{22}N_4OS \cdot HBr$	C, H, N, S, Br

filtered. The solids were extd with dil HCl, and the ext was brought to pH 7 with NaOH, whereupon a ppt formed. This ppt of **3d** (153 mg, 16%) was washed with H_2O and dried in air. It has an ir spectrum superimposable with that of the same product prepd from **3b**.

2-Methylamino-6*H*-pyrrolo[3,2-*e*]benzothiazole (3c) was prepd as described for **3d** from **3b**. From 454 mg of **3a** was obtd, after recrystn from MeOH, 158 mg (53%) of **3c** of yellow cryst, mp 195–196°. *Anal.* ($C_{10}H_9N_3S$) C, H, N, S.

5,6,7,8-Tetrahydropyrrolo[4,3,2-*de*]cinnolin-3-2*H*-one (7).—A mixt of 890 mg of 4-oxo-4,5,6,7-tetrahydroindole-3-carboxamide (**5**)[4] and 7 ml of hydrazine hydrate heated at reflux temp for 2 hr, cooled, and filtered. Recrystn of the product from MeOH gave 431 mg (65%) of **7** as white solid which did not melt at < 350°; uv max 233 mμ (ε 10,000), 267 (5700), 276 (6100), 298 (4700); ir 3.1–3.45 μ (NH), 6.15 (CONH); nmr (CF_3CO_2H) δ 11.6 (broad, pyrrole NH), 7.98 (d, J = 2.5 Hz, pyrrole, deshielded by CO), 2.7–2.4 (m, 6, $CH_2CH_2CH_2$) ppm. *Anal.* ($C_9H_9N_3O$) H, N; C: calcd, 61.70; found, 62.28.

(4) H. Stetter and R. Lauterbach, *Justus Liebigs Ann. Chem.*, **655**, 120 (1962).

2,7,8,9-Tetrahydro-3*H*-pyridazino[5,4,3-*de*]cinnolin-3-one (8).—A mixt of **6** (7.66 g) and hydrazine hydrate (20 ml) was stirred at room temp for 1 hr, cooled in ice, and filtered. The solids were extd with cold MeOH. The sol portion, after recryst from Me_2CO–hexane, gave 2.53 g (34%) of **8** as yellow needles: mp 251–255° dec; uv max 253 mμ (ε 4400), 261 (5000), 294–300 (4200); ir 3.1–3.4 μ (NH), no unconj CO, 6.15 (NCOC=C); nmr (CF_3CO_2H) δ 10.23 (s, proton in pyrazine ring deshielded by CO), 3.65 and 3.45 (each is t, 2, J = 6 Hz, $CH_2CH_2CH_2$), 2.51 (m, 2, $CH_2CH_2CH_2$) ppm. *Anal.* ($C_9H_8N_4O$) C, H, N.

The insol portion (1.31 g), after recryst from boiling MeOH, gave golden needles: mp 188–190°; uv max 256 mμ (ε 8500); ir 2.94–3.45 μ, no unconj CO, 6.15; nmr (DMSO-d_6) δ 12.0 (broad, s), 8.08 (s), 6.23 (broad, 2), 2.95–2.5 (m, 4, CH_2CH_2), 1.93 (m, 2, $CH_2CH_2CH_2$) ppm. *Anal.* ($C_9H_{12}N_4O_2$) C, H, N.

Acknowledgment.—We thank Mr. L. Brancone and staff for microanalyses, Mr. W. Fulmor and staff for spectra data, Dr. A. E. Sloboda for antiinflammatory assays, and Mr. A. C. Dornbush for antibacterial and antifungal assays.

Antimalarial Activity of Guanylhydrazone Salts of Aromatic Ketones. 2. Development of Active Polyhalo Derivatives[1a,b]

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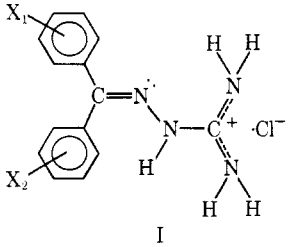
Twenty-four guanylhydrazones of polyhalo-substituted benzophenones were synthesized and tested in the primary antimalarial screen in mice infected with *Plasmodium berghei*. All compds but one bore halo or halogen-containing substituents on both rings. The minimum requirement for activity within this context is the presence of a CF_3 group in the 3 or 4 position or a F_3CO group in the 4 position on one ring and halo or CF_3 in the 3 or 4 positions on the second ring. Eighteen of these compds were active and 16 were at least partially curative at one or more dose levels. Twelve compds produced 100% cures at one or more dose levels. One compd (3,4-dichloro-4′-trifluoromethylbenzophenone guanylhydrazone·HCl) was outstanding and yielded 100% cures over the dose range 80–640 mg/kg. Replacement of H by Me in the guanidine moiety abolished antimalarial activity.

In the first paper in this series[2] the syntheses and antimalarial activities of 30 compds were presented. The generic type is represented by structure I. It became apparent that optimal activity resided in benzophenone guanylhydrazones wherein both rings bore halo or halo-



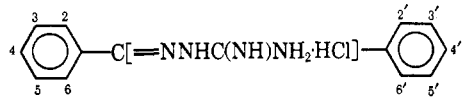
I

gen-containing substituents. It was found that the presence of a CF_3 group on one ring was essential for

(1) (a) This investigation was conducted under Contract DA-49-193-MD-3016 from the U. S. Army Research and Development Command. This is Contribution No. 885 to the Army Research Program on Malaria. (b) Presented in part at the 169th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstract MEDI-57. (c) Department of Psychiatry, Stanford University School of Medicine, Palo Alto, Calif.

(2) J. R. DoAmaral, E. J. Blanz, Jr., and F. A. French, *J. Med. Chem.*, **12**, 21 (1969).

TABLE I
GUANYLHYDRAZONE HYDROCHLORIDES OF SUBSTITUTED BENZOPHENONES

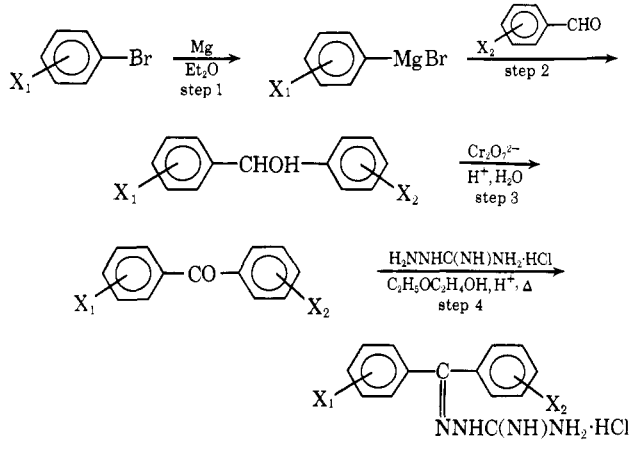


No.	Ring A	Ring B	Procedure[a]	Reaction solvent[b]	Crystn solvent[c]	Mp, °C dec	Formula	Analyses
1	4-F	4′-CF_3[d]	A	EG	I	208–209	$C_{17}H_{16}F_4N_4\cdot HCl$	C, H, Cl, F; N[e]
2	4-Cl	4′-CF_3	A	EG	II, III	294–295	$C_{15}H_{12}ClF_3N_4\cdot HCl$	C, H, Cl, N
3	3,4-Cl_2	4′-CF_3	A	DMAG	IV	310–311	$C_{15}H_{11}Cl_2F_3N_4\cdot HCl$	C, H, Cl, F, N
4	4-I	4′-CF_3	A	DMAG	II, V	309–310	$C_{15}H_{12}F_3IN_4\cdot HCl$	C, H, Cl, I, N
5	4-Br	4′-CF_3[f]	A	Cel	VI	260–263	$C_{16}H_{14}BrF_3N_4\cdot HCl$	C, H, Br, Cl, F, N
6	4-F	4′-CF_3[f]	A	DMAC	VII	222.5–223.5	$C_{16}H_{14}F_4N_4\cdot HCl$	C, H, Cl, F, N
7	4-Br	4′-CF_3[d]	A	Cel	VIII	257–258	$C_{17}H_{16}BrF_3N_4\cdot HCl$	H, F, N; C, Br, Cl[g]
8	4-I	3′-CF_3	A	Cel	IX	271–273	$C_{15}H_{12}F_3IN_4\cdot HCl$	H, F, N; C, Cl, I[h]
9	4-CH_3	4′-CF_3	B	Cel	III	289–289.5	$C_{16}H_{15}F_3N_4\cdot HCl$	C, H, Cl, F, N
10	2,4-Cl_2	4′-CF_3	B	Cel	IV, V	240[i]	$C_{15}H_{11}Cl_2F_3N_4\cdot HCl\cdot H_2O$	C, H, Cl, F, N
11	4-CF_3O	4′-Br	B	Cel	X	230.5–231.5	$C_{15}H_{12}BrF_3N_4O\cdot HCl$	C, H, Br, Cl, N; F[j]
12	3,4-Cl_2	3′,5′-$(CF_3)_2$	B	Cel	XI	60	$C_{17}H_{11}Cl_2F_6N_4\cdot HCl\cdot 0.25H_2O\cdot 0.167C_6H_6$	C, H, Cl, N; F[k]
13	4-CF_3O	4′-CF_3	B	Cel	V, XII	272–272.5	$C_{16}H_{12}F_6N_4O\cdot HCl$	C, H, Cl, F, N
14	4-CF_3	3′-CF_3, 4′-Cl	B	Cel	IX	287–288	$C_{16}H_{11}ClF_6N_4\cdot HCl$	C, H, Cl, F, N
15	4-CF_3	3′,5′-$(CF_3)_2$	B	Cel	XIII	158.5–159.5	$C_{17}H_{11}F_9N_4\cdot HCl$	C, H, Cl, F, N
16	3,4-Br_2	4′-CF_3	B	Cel	IX	306–307	$C_{15}H_{11}Br_2F_3N_4\cdot HCl$	C, H, F, N
17	3,4,5-Cl_3	4′-CF_3	B	Cel	IX	261–262.5	$C_{15}H_{10}Cl_3F_3N_4\cdot HCl$	C, H, Cl, F, N
18	3,4-Cl_2	3′-CF_3	B	Cel	IX	294–294.5	$C_{15}H_{11}Cl_2F_3N_4\cdot HCl$	C, H, Cl, F, N
19	3-Cl, 4-F	4′-CF_3	B	Cel	IX	258–259	$C_{15}H_{11}ClF_4N_4\cdot HCl$	C, H, F, N; Cl[l]
20	3,4-Cl_2	4′-CF_3O	B	Cel	V	235.5–236.5	$C_{15}H_{11}Cl_2F_3N_4O\cdot HCl$	C, H, Cl, F, N
21	4-CF_3	3′-CF_3, 4′-Br	B	Cel	IX	285–286	$C_{16}H_{11}BrCl_3N_4\cdot HCl$	C, H, Br, Cl, N; F[m]
22	4-CF_3O	3′-CF_3, 4′-Br	B	Cel	XIV	206–209	$C_{16}H_{11}BrF_6N_4O\cdot HCl$	C, H, Br, Cl, N; F[n]
23	3,5-Cl_2	4′-CF_3	B	Cel	IX	250–251	$C_{15}H_{11}Cl_2F_3N_4\cdot HCl$	C, H, Cl, F, N
24	3,5-Cl_2	4′-CF_3O	B	Cel	XIV	108–140	$C_{15}H_{11}Cl_2F_3N_4O\cdot HCl$	C, H, Cl, N; F[o]

[a] A: see procedure D, ref 2. B: see Chemistry. [b] EG = ethylene glycol, DMAC = dimethylacetamide, Cel = Cellosolve. [c] I = AcOEt; II = H_2O–EtOH; 4:1; III = H_2O–EtOH, 1:1; IV = H_2O–EtOH, 1:1, twice; V = C_6H_6–EtOH, 1:2; VI = *i*-PrOH–MeOH, 95:5; VII = *i*-PrOH–MeOH, 95:5, then Et_2O to turbidity; VIII = H_2O; IX = reaction product; X = $CHCl_3$; XI = Et_2O–C_6H_6, 95:5; XII = $CHCl_3$–EtOH, 5:1; XIII = Et_2O; XIV = partitioned between $CHCl_3$–H_2O, 1:1, product in $CHCl_3$ phase. [d] $NNHC(NH)NH_2$=$NNHC(NH)NHCH_3$. [e] N: calcd, 14.41; found, 14.85. [f] $NNHC(NH)NH_2$=$NNHC(NCH_3)NHCH_3$. [g] C: calcd, 45.40; found, 44.79. Br and Cl: calcd, 25.64; found, 26.33. [h] C: calcd, 38.44; found, 38.99. Cl: calcd, 7.56; found, 6.73. I: calcd, 27.07; found, 26.35. [i] Change at 124–127°, mp 147–165°, m again at 192° and at 240°. [j] F: calcd, 13.02; found, 12.15. [k] F: calcd, 22.93; found, 21.93. [l] Cl: calcd, 17.94; found, 17.47. [m] F: calcd, 23.28; found, 22.22. [n] F: calcd, 22.54; found, 23.65. [o] F: calcd, 13.22; found, 14.36.

high activity and sometimes a CF_3O group could play a similar role.

SCHEME I



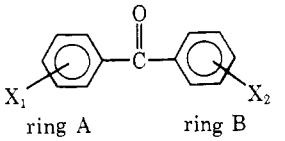
Chemistry.—In step 1 Grignard reagent formation was recalcitrant in many CF_3 and F_3CO derivatives. In these cases the reaction was initiated without solvent. Step 2 presented no problems but isolation and purification at the carbinol stage proved troublesome and wasteful. Hence the crude carbinols were oxidized (step 3) directly to the ketones which were carefully purified.

The difficulties encountered earlier with step 4[2] were largely resolved by using ethoxyethanol as a solvent and about 1 mole % excess of the ketone. The excess ketone could generally be removed by stirring with Et_2O, C_6H_6, or petr ether. Tlc studies indicated that a reaction time of 15 min at reflux temp was usually sufficient. Compds with CF_3 groups in the 3′ and 5′ positions were difficult to isolate and purify. For example, in the preparation of **20** and **21** (Table I) removal of the reaction solvents at reduced pressure yielded a gluish residue. Extensive manipulation of these residues with solvents was necessary.

It was observed previously[2] and during this study that when the guanylhydrazone salts were developed under the reported conditions (tlc) 2 spots appeared, the assumed cis and trans forms of the guanylhydrazone salt.[3] However, all of these salts had sharp melting points with 2 exceptions. Compd **10**, a monohydrate, has a transition temp of 124–127°, melts at 147–165°,

(3) Dr. T. R. Sweeney, Walter Reed Army Institute of Research, personal communication, 1969.

TABLE II
SUBSTITUTED BENZOPHENONES



No.	Ring A	Ring B	Procedure[a]	Crystn solvent[b]	Mp, °C	Formula	Analyses
25	4-CH_3	4′-CF_3	C	I	144.5–150	$C_{15}H_{11}F_3O$	C, H; F[c]
26	4-Cl	4′-CF_3	C	II	120–121	$C_{14}H_8ClF_3O$	C, H, Cl, F
27	4-I	4′-CF_3	C	III	156–157	$C_{14}H_8F_3IO$	C, H, F, I
28	4-I	3′-CF_3	D	IV	104–106	$C_{14}H_8F_3IO$	C, H, F, I
29	3,4-Cl_2	4′-CF_3	C	II, III, I	97–98	$C_{14}H_7Cl_2F_3O$	C, H, Cl
30	2,4-Cl_2	4′-CF_3	C[d]	II, III	63.5–65.5	$C_{14}H_7Cl_2F_3O$	C, H, Cl, F
31	3,4-Cl_2	3′-CF_3	C	VII	70–71	$C_{14}H_7Cl_2F_3O$	C, H, Cl, F
32	3-Cl, 4-F	4′-CF_3	C	VII	66.5–67.5	$C_{14}H_7ClF_4O$	C, H, Cl, F
33	3,4-Br_2	4′-CF_3	C	II	110.5–111	$C_{14}H_7Br_2F_3O$	Br, F; C, H[e]
34	3,4,5-Cl_3	4′-CF_3	C	II	118–118.5	$C_{14}H_6Cl_3F_3O$	C, H, Cl, F
35	4-CF_3	3′-CF_3, 4′-Cl	C	III, V	61.5–62	$C_{15}H_7ClF_6O$	C, H, Cl, F
36	4-CF_3	3′,5′-Cl_2	C	X	68–71	$C_{14}H_7Cl_2F_3O$	C, H, F; Cl[f]
37	4-CF_3	3′-CF_3, 4′-Br	C	V	88.5–89.5	$C_{15}H_7BrF_6O$	C, H, Br, F
38	3,4-Cl_2	3′,5′-$(CF_3)_2$	C	IV, III, V	99.5–100.5	$C_{15}H_6Cl_2F_6O$	C, H, Cl, F
39	4-CF_3	3′,5′-$(CF_3)_2$	C	VI	*g*	$C_{16}H_7F_9O$	C, H, F
40	4-CF_3O	4′-Br	C	II	95.5–96.5	$C_{14}H_8BrF_3O$	C, H, Br; F[h]
41	4-CF_3O	4′-CF_3	C[i]	VI, V	60–61	$C_{15}H_8F_6O_2$	C, H; F[j]
42	4-CF_3O	3′,4′-Cl_2	C	VII, III, V	52–52.5	$C_{14}H_7Cl_2F_3O_2$	C, H, Cl, F
43	4-CF_3O	3′-CF_3, 4′-Br	C	VI	*k*	$C_{15}H_7BrF_6O_2$	C, H, Br, F
44	4-CF_3O	3′,5′-Cl_2	C	VI	*l*	$C_{14}H_7Cl_2F_3O_2$	C, H, Cl; F[m]
45	3-CF_3, 4-Cl	H	*n*	VIII, IX	*o*	$C_8H_4ClF_3O$	C, H, Cl, F
46	3-CF_3, 4-Br	H	*n*	VIII, IX	52.5–53.5	$C_8H_4BrF_3O$	C, H, Br, F
47	3-Cl, 4-F	H	*n*	VIII, IX	*p*	C_7H_4ClFO	C, H, Cl, F

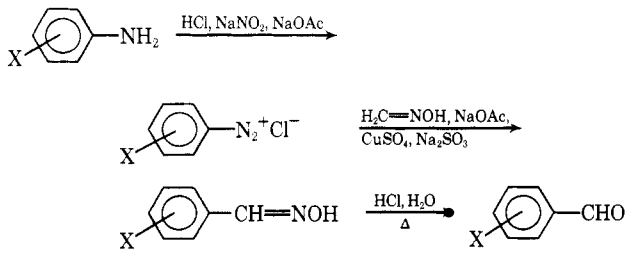
[a] Experimental Section. [b] I = petr ether, bp 60–110°; II = EtOH; III = sublimation under reduced pressure; IV = I, repeated 3 times; V = petr ether, bp 30–60°; VI = distn under reduced pressure; VII = MeOH; VIII = steam distn; IX = $NaHSO_3$ derivative; X = reaction product. [c] F: calcd, 21.57; found, 20.74. [d] Refluxing repeated for 15 min. [e] C: calcd, 41.20; found, 41.91. H: calcd, 1.73; found, 1.30. [f] Cl: calcd, 22.21; found, 21.65. [g] $n^{20}D$ 1.4663. [h] F: calcd, 16.51; found, 15.75. [i] For the syn of *p*-$CF_3C_6H_4CHO$ see Experimental Section. [j] F: calcd, 34.11; found, 30.39. The corresponding guanylhydrazone had the correct element anal. [k] $n^{25}D$ 1.5235. [l] $n^{28.5}D$ 1.5524. [m] F: calcd, 17.00; found, 17.42. [n] See ref 5 and 6. [o] $n^{18.5}D$ 1.4964. [p] $n^{25.5}D$ 1.5435.

and remelts at 240°. Compd **24** is not solvated but shows transition-melting behavior from 108 to 140°.

Compds bearing a F_3CO group (**11**, **13**, **20**, **22**, **24**) were isolated by partitioning between $CHCl_3$ and H_2O. Extraction into the $CHCl_3$ phase was complete in one step when the phase volumes were equal.

The aldehydes, **45–47** (Table II), were synthesized by the method of Beech[4] as modified by Jolad and Rajagopal[5] with the following change. To prevent excessive foaming during the addition of the diazonium salt soln to the formaldoxime soln the latter was covered by a toluene layer 3 cm deep.

SCHEME II



p-Trifluoromethylbenzaldehyde, used in the preparation of **15**, was synthesized by a modification of the method of Haas and Bender.[6] It is important in this method to allow adequate time for the formation of the aci-salt of 2-nitropropane and adequate solvent volume for complete soln before addition of the substituted benzyl bromide.

Typical procedures are given in the Experimental Section and in the previous article.[2] No attempt was made to optimize yields. The main objective was to obtain sufficient analytically pure material for biological testing.

Biological Data and Correlations.—The data in Table III, and previous data,[2] show that when there is a 4-CF_3 group on one ring the order of antimalarial activity for 4′ substituents on the other ring is: Br > I > Cl > F, while the order of toxicity is: F > Cl > Br > I. It has been noted earlier[2] that the 3-bromo-4′-trifluoromethyl derivative is less toxic than the 4,4′ isomer. The 4-iodo-3′-trifluoromethyl derivative **8** is slightly more active than the 4,4′ derivative **4**. When Me groups are substituted for H on the guanidine side chain, activity is abolished (**5–7**). A Me group in place of halogen (**9** *vs.* **2** and **4**) also yields inactive and toxic compds. A number of polysubstitution patterns involving CF_3 groups and halogens were studied. Compds **3**, **4**, **8**, **14–17**, and **20–24** give 100% cures at one or more dose levels and **3** (the 3,4-dichloro-4′-trifluoromethyl derivative) is outstanding in this regard, yielding 100% cures over the dose range 80–640 mg/kg with no signs of gross toxicity. The close analogs, **16–19**, are less active. Compd **3** has been selected for advanced studies by the Walter Reed Army Institute of Research.

(4) W. F. Beech, *J. Chem. Soc.*, 1297 (1954).
(5) S. D. Jolad and S. Rajagopal, *Org. Syn.*, **46**, 13 (1966).
(6) H. B. Haas and M. L. Bender, *J. Amer. Chem. Soc.*, **71**, 1767 (1949).

TABLE III

ANTIMALARIAL ACTIVITY OF GUANYLHYDRAZONE HYDROCHLORIDES OF SUBSTITUTED BENZOPHENONES

	Increase in mean survival time,[a] % cures (C),[b] (% toxic deaths) — Dose, mg/kg					
No.	20	40	80	160	320	640
c	0.2	0.2	0.8	2.0	3.4	6.2
		0.2		1.0		7.6
2	6.6	9.0	10.3, 40% C	23.6, 60% C (20%)	80% C (20%)	19.6, 40% C (20%)
		8.8		22.6, 80% C		20% C (80%)
3	2.2	2.8	100% C	100% C	100% C	100% C
		3.4		100% C		100% C
4	0.8	2.8	10.9, 20% C	8.6, 60% C	18.6, 80% C	8.6, 80% C
		3.0		13.6, 80% C		100% C
8	0.7	14.1, 20% C	15.0, 40% C	18.5, 40% C	100% C	100% C
		13.5, 20% C		15.7, 60% C		100% C
11	1.6	12.4	13.1, 20% C	27.1, 40% C		
		12.0		24.3, 60% C		
12	0.6	0.9	2.4	7.7	12.0	25.4, 60% C
		0.8		8.0		24.3, 60% C
14	0.2	1.5	19.3, 20% C	100% C	100% C	100% C
		1.6		100% C		100% C
15	0.4	0.5	0.8	4.1	14.3, 60% C	100% C
		0.6		4.2		100% C
16	0.2	0.6	5.2	13.4	22.1, 40% C	17.8, 60% C
	0.2	0.6	6.0	13.2	18.2	12.8, 80% C
		0.4		13.4		9.8, 80% C
		0.6		13.0		100% C
17	0.2	0.6	6.0	100% C	100% C	100% C
		0.8		100% C		100% C
18	0.3	0.3	0.5	5.9	6.9	10.1
	0.2	0.6	0.6	5.8	7.0	
19	0.3	1.3	3.9	17.4, 20% C	19.9, 60% C	26.9, 60% C
	0.4	1.6	4.0	19.7, 40% C	21.3, 60% C	
20	0.3	0.5	1.7	7.9, 60% C	100% C	100% C
	0.2	0.8	2.0	8.7, 80% C	100% C	
21	0.3	3.9	18.2, 40% C	29.9, 80% C	100% C	100% C
	0.4	4.0	18.5, 40% C	100% C	100% C	
22	0.3	0.3	2.7	21.7, 60% C	29.7, 80% C	100% C
	0.4	0.4	3.0	21.3, 60% C	100% C	
23	0.7	3.9	20.9, 40% C	100% C	100% C	100% C
	0.5	3.9	21.0, 40% C	100% C	100% C	
24	0.5	0.5	12.2, 20% C	100% C	100% C	100% C
	0.3	0.5	12.4, 20% C	100% C	100% C	

[a] Mean survival time of treated mice − mean survival time of controls in days. [b] Per cent of treated mice in a group of 5 surviving 60 days. [c] The syn of this compd (the 3,5-$(CF_3)_2$ deriv) was described in the first paper in this series (ref 2). No biol data were available at that time.

The 2,4-dichloro-4′-trifluoromethyl isomer (**10**) is inactive. In the entire study hydrophilic substituents led to a loss of activity.

The F_3CO derivatives (**11**, **20**, **22**, and **24**) are active, but **13** is toxic and inactive. The F_3CO derivatives are the only compds in the series that are highly lipophilic and are readily extracted from aq soln by $CHCl_3$. In spite of this large difference in partition coefficient the antimalarial activities of the analogous CF_3 and F_3CO compds are usually parallel.

The mechanism of antimalarial activity of these compds is not known. Both 4,4′-ditrifluoromethylbenzophenone guanylhydrazone and the corresponding 4-fluoro-4′-trifluoromethyl derivative are active inducers of the enzyme *O*-demethylase.[3] Compds **2–7**, **9**, and **11** were tested on L-1210 leukemia in BDF_1 mice and found inactive at maximum tolerated doses.[7]

Experimental Section

Biological Methods.—The antimalarial data presented in Table III were obtained from the Walter Reed Army Institute of Research. The methods were developed by Rane.[8]

Chemical Procedures.—The following synth procedures are representative for prepn of the compds in Tables I and II. The melting points are uncor and were detd with a Thomas-Hoover melting point apparatus. Unless otherwise reported, the tlc system for the ketones was silica gel 254,[9] C_6H_6–EtOH (95:5), 15 min, visualization with uv light, then I_2. For the guanylhydrazone salts it was AcOEt–*i*-PrOH–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, anal. results obtained for those elements are within ±0.4% of the theor values. Procedure A in this paper is procedure D in ref 2.

Procedure C (Scheme I). 4-Trifluoromethyl-4′-methylbenzophenone (25) was prepd according to procedure A.[2] $CHCl_3$ was used instead of PhH in the $Cr_2O_7^{2-}$ oxidn of the carbinol; the

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

(8) T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

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

reaction mixt was filtered through a Celite bed after addn of H_2O at the end of the oxidn stage.

Procedure D. 4-Iodo-3′-trifluoromethylbenzophenone (28).—The reaction flask was flushed with dry N_2 and cooled by an ice water bath. *n*-BuLi, 22.3 wt % in hexane (Alfa Inorganics; Inc., Beverly, Mass.), 36 ml (approx 0.077 mole), was added dropwise to *m*-bromobenzotrifluoride (15.7 g, 0.07 mole) in 50 ml of dry Et_2O during 20 min. The resultant soln was added dropwise to 13.0 g (0.056 mole) of *p*-iodobenzaldehyde dissolved in 120 ml of dry Et_2O. Refluxing was contd for 0.5 hr, and the mixt was added to 90 g of crushed ice and allowed to stand overnight. The resultant mixt was acidified with HCl, and the Et_2O layer was saved. The H_2O layer was extd 3 times with Et_2O. The combined Et_2O layer and Et_2O exts were dried ($MgSO_4$) and filtered, and the solvent was stripped off. The liquid residue (19.4 g) crystd on standing. A tlc plate showed 5 spots, 1 very large. The crude reaction product was oxidized as described in procedure C.

***p*-Trifluoromethylbenzaldehyde (Modified Procedure).**—This compd was prepd according to ref 6 with the following modifications. *p*-Trifluoromethylbenzyl bromide was prepared by adding 120 g (0.682 mole) of *p*-trifluoromethylbenzyl alcohol to 145 g (0.859 mole) of 48% HBr and 38 g of concd H_2SO_4. The reaction mixt was refluxed for 2 hr and left standing overnight. H_2O (60 ml) was then added to the reaction mixt. The halide layer was sepd, washed once with cold concd H_2SO_4, H_2O, dil $NaHCO_3$ soln, and H_2O, dried ($MgSO_4$), and filtered. The crude product weighed 138.1 g. Distn from a Vigreux-type column yielded 132.5 g of product (81%), mp 31.5° [ref 7 gives bp 65–66° (5 mm), $n^{20}D$ 1.4918]. The bromide had the correct elemental analysis and showed a single spot on tlc. It is a lacrimator and a skin irritant. In the last step a sufficient vol of EtOH was maintained in the EtONa soln so that on addition of 2-nitropropane pptn of the Na salt did not occur. A reaction time greater than 0.5 hr was allowed before the addition of p-$F_3CC_6H_4CH_2Br$. The pure aldehyde was obtained in a 40.7% yield.

Procedure B. 3-Trifluoromethyl-3′,4′-dichlorobenzophenone Guanylhydrazone·HCl (18).—3-Trifluoromethyl-3′,4′-dichlorobenzophenone (5 g, 0.0157 mole), aminoguanidine·HCl (1.7 g, 0.0155 mole), 7 ml of Cellosolve, and 6 drops of concd HCl were refluxed for 15 min. The reaction was monitored by tlc. The reaction mixt was cooled to room temp and some solid material sepd. The reaction material was added to 100 ml of H_2O and stirred for 0.5 hr. The solid material was filtered under suction, washed 3 times with PhH, 3 times with Et_2O, weighed 5.1 g (80%), had mp 294–294.5° dec, was clean in tlc (R_f 0.6), and had the correct elemental anal.

4-Trifluoromethoxy-3′,4′-dichlorobenzophenone Guanylhydrazone·HCl (20).—4-Trifluoromethoxy-3′,4′-dichlorobenzophenone (5.0 g, 0.0134 mole), aminoguanidine·HCl (1.47 g, 0.0133 mole), 7 ml of Cellosolve, and 5 drops of concd HCl were refluxed for 15 min. The reaction mixt was then cooled to room temp, and the solvent was removed under reduced pressure. The residue was partitioned between 200 ml of H_2O and 200 ml of $CHCl_3$. The $CHCl_3$ layer was saved, dried ($MgSO_4$), and filtered, and the solvent was removed under reduced pressure. The residue was stirred for 1 hr with 50 ml of pet ether (bp 30–60°), filtered, weighed 2.4 g, was clean in tlc (R_f 0.8), had mp 235.5–236.5° dec, and had the correct elemental anal.

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2,4-Diamino-6-arylethylpteridines as *Streptococcus faecium* Growth Inhibitors

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A synthesis is reported for 2,4-diamino-6-*p*-carboxyphenethylpteridine along with the 3,4,5-trimethoxy and 3,4-dichlorophenyl analogs. The compounds were moderately effective growth inhibitors of an amethopterin-resistant strain of *Streptococcus faecium*. The tetrahydro derivatives were inactive toward this organism.

In the preceding paper of this series[1] we reported the potent growth inhibitory activity of 10-deazapteroic acid (**1**) and its tetrahydro derivative against *Streptococcus faecium*, a folate-dependent organism. It was observed that the activity of the pteroic analog was greatly enhanced by reduction to the tetrahydro compound. Since 2,4-diamino pteridines should be more capable of cell penetration[2] it was of interest to extend the investigation to 2,4-diamino analogs of I. Accordingly 2,4-diamino-6-*p*-carboxy- (**8d**), 3,4-dichloro- (**8a**), and 3,4,5-trimethoxyphenethylpteridine (**8b**) (Table I) were synthesized and evaluated.

The synthesis of the compds is outlined in Scheme I and the general method has been well discussed previously.[1,3,4] 2,4-Diamino-5-nitro-6-chloropyrimidine was condensed with the appropriate α-amino ketone blocked as the ketal or semicarbazone. An improvement in the process was the use of CF_3COOH for hydrolysis of the blocking group. It was also of interest that the use of 5% NaOH in 2-$MeOC_2H_4OH$ permitted rapid hydrolysis (30 min) of the ester **8c** without concurrent hydroxylic displacement of the pteridine 4-amino group.

As shown in Table II the compds were good inhibitors of *S. faecium* growth, being of the same order of magnitude as aminopterin. Three were moderately active against an amethopterin-resistant strain of *S. faecium* and activity was noted also against *Lactobacillus casei*. Activity against *Pediococcus cerevisiae* was low. Reduction to the tetrahydropteridine derivatives markedly decreased activity against all of the organisms tested.

The carboxylic acid **8d** appeared to be the most active of these compds. However, when tested for antima-

(1) J. I. DeGraw, P. Tsakotellis, R. L. Kisliuk, and Y. Gaumont, *J. Heterocycl. Chem.*, **8**, 105 (1971).

(2) R. C. Wood and G. H. Hitchings, *J. Biol. Chem.*, **234**, 2377, 2381 (1959).

(3) J. I. DeGraw, V. H. Brown, M. Cory, P. Tsakotellis, R. L. Kisliuk, and Y. Gaumont, *J. Med. Chem.*, **14**, 206 (1971).

(4) J. I. DeGraw, J. P. Marsh, E. M. Acton, O. P. Crews, C. W. Mosher A. Fujiwara, and L. Goodman, *J. Org. Chem.*, **30**, 3404 (1965).