Table VII. Activity Data

No.	Anaesthetized cats[a] ED_{20},[c] mg/kg iv	Rel potency[d]	Renal hypertensive rats[b] ED_{20},[c] mg/kg po	Rel potency[d]	LD_{50}, mg/kg iv
39	0.01	10	2	5	50
40	0.02	5	1	10	150
41	0.03	3	3	3	100
42	0.01	10	0.5	20	80
43	0.02	5	2	5	150
44	0.02	5	1	10	600
45	0.03	3	1	10	600
46	0.1	1	20	0.5	1000
47	0.01	10	1.5	7	100
48	0.1	1	20	0.5	700
49	0.3	3	20	0.5	1000
50	0.1	1	5	2	100
51	0.04	2.5	5	2	100
52	0.05	2	5	2	150
53	0.05	2	5	2	100
54	0.1	1	5	2	700
55	0.1	1	5	2	700
56	0.07	0.7	5	2	80
57	0.1	1	1.5	7	150
Hydralazine	0.1	1	10.0	1	100

[a]Basal mean blood pressure, 130–150 mmHg. [b]Basal systolic blood pressure, 216 ± 2.9 (SD) mmHg (mean of 360 rats). [c]Dose producing a 20% pressure drop from basal value. The maximal effect was reached 20–30 min after administration in cats and 1–3 hr after administration in rats. [d]Ratio ED_{20} of hydralazine/ED_{20} of test compound.

dark solution was concentrated in vacuo. The residue was taken up with H_2O, made alkaline with 15% K_2CO_3, and extracted several times with $CHCl_3$. The combined extracts were washed with an aqueous solution of 5% HCl saturated with NaCl and then with a saturated NaCl solution and finally dried over Na_2SO_4. After evaporation, the solid residue was crystallized to give 9.5 g of **59**.

3-(*N*-Acetyl-*N*-isopropylamino)-6-benzylidenehydrazinopyridazine (VIIIb). Reaction of 3 g of **59** and 30 ml of 95% hydrazine at room temperature for 1 hr (method F) gave 1.55 g (37%) of VIIIb, mp 248–251° (from EtOH). Anal. ($C_{16}H_{19}N_5O$) C, H, N.

When the same reaction was performed at the reflux temperature for 2 hr, the *deacetyl* compound VIIIa was isolated in 15% yield: mp 202–204°. Anal. ($C_{14}H_{17}N_5$) C, H, N.

Reactions of compounds **58**, **60**, and **61** with 95% hydrazine under various conditions gave no condensation products and only the corresponding deacetylated derivatives **21**, **23**, and **24** were isolated from the reaction mixture.

3-Hydrazino-6-isopropylaminopyridazine dihydrochloride (57) was prepared by method G from VIIIb (10 g, 33.6 mmol) and 300 ml of 15% HCl and recrystallized from EtOH.

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Quinoxaline Studies. 23.[1a] Potential Antimalarials. Substituted 5,8-Dimethoxyquinoxalines[1b]

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Two series of 2,3-disubstituted 5,8-dimethoxy-6-[*N*-(ω-dimethylaminoalkyl)amino]quinoxalines were prepared: the first series with identical 2,3-substituents H, CH_3, C_6H_5, C_6H_4-4-Cl, and $CH_2C_6H_5$; and the second with identical styryl groups $CH{=}CHC_6H_5$, $CH{=}CHC_6H_4$-4-Cl, $CH{=}CHC_6H_3$-3,4-Cl_2, $CH{=}CHC_6H_4$-4-F, $CH{=}CHC_6H_4$-4-CF_3, and $CH{=}CHC_6H_4$-4-NO_2. None of the substances possessed antimalarial activity; several were toxic at highest dosage levels.

Previously reported[2] quinoxalinemethanols, unlike many quinolinemethanols, were without antimalarial capacity. It has been postulated[3–8] that the antimalarial activity of the quinoline compounds is due to quinoid materials formed in the host. It was hoped, therefore, that suitably substituted 5,8-dimethoxyquinoxalines would be especially easily transformed in vivo into the corresponding quinoxalinequinones, which might possess antimalarial qualities. And further, unpublished data related to earlier work[2] indicated that styryl derivatives of quinoxaline possessed some anti-

Table I. 2,3-Disubstituted 5,8-Dimethoxy-6-aminoquinoxalines[a,b]

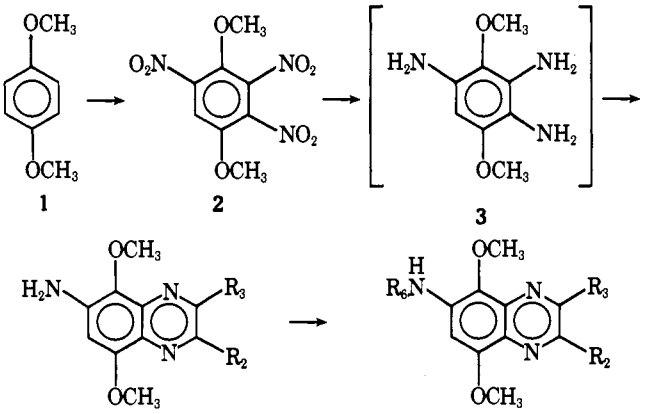
No.	R_2, R_3	Formula	Recrystn solvent (ml/g)	Mp, °C	% yield	Uv max, nm (ε)
4a	H	$C_{10}H_{11}N_3O_2$	C_6C_6 (25)	164.5–165	32	220 (17,100), 273 (46,200)
4b	CH_3	$C_{12}H_{15}N_3O_2$	C_6H_6 (10)	189–190	44	216 (27,300), 271 (50,700)
4c	C_6H_5	$C_{22}H_{19}N_3O_2$	CH_3OH (120)	209–210	66	272 (inf), 302 (47,500)
4d	4-ClC_6H_4	$C_{22}H_{17}Cl_2N_3O_2 \cdot 0.5CH_3OH$	CH_3OH (220)	220–221	87	220 (26,850), 277 (inf), 307 (46,100)
4e	$C_6H_5CH_2$	$C_{24}H_{23}N_2O_2$	C_6H_6 (5)	134–135	75	223 (34,300), 279 (84,900), 408 (5,960)
4f	4-$ClC_6H_4CH_2$	$C_{24}H_{21}N_3O_2Cl_2$	C_6H_6 (5)	172.5–173	94	213 (21,100), 228 (34,400), 415 (2,680)

[a] All compounds gave acceptable C, H, and N analyses. [b] NMR spectra were as expected.

malarial activity. The purpose of this paper is to report the syntheses for testing as antimalarials of two series of substituted 5,8-dimethoxyquinoxalines incorporating both above structural features.

Chemistry. The sequence by which the various quinoxaline derivatives were synthesized is outlined in Schemes I and II. As shown in Scheme II, 2,3-dimethyl-5,8-dimethoxy-6-[*N*-(ω-dimethylamino-*n*-propyl)amino]quinoxaline (**5**b-3) served as the portal compound for those styrylquinoxaline derivatives (**6**) prepared.

Scheme I

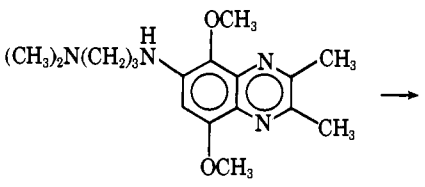


1 **2** **3**

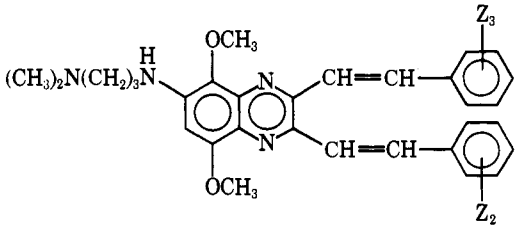
4a, $R_2 = R_3 = H$
b, $R_2 = R_3 = CH_3$
c, $R_2 = R_3 = C_6H_5$
d, $R_2 = R_3 = C_6H_4$-4-Cl
e, $R_2 = R_3 = CH_2C_6H_5$
f, $R_2 = R_3 = 4\text{-}ClC_6H_4CH_2$

5a, $R_2 = R_3 = H$
b, $R_2 = R_3 = CH_3$
c, $R_2 = R_3 = C_6H_5$
d, $R_2 = R_3 = C_6H_4$-4-Cl
e, $R_2 = R_3 = CH_2C_6H_5$
5x-2, $R_6 = CH_2CH_2N(CH_3)_2$
5x-3, $R_6 = CH_2CH_2CH_2N(CH_3)_2$

Scheme II



5b-3



6a, $Z_2 = Z_3 = H$
b, $Z_2 = Z_3 = 4\text{-}Cl$
c, $Z_2 = Z_3 = 3,4\text{-}Cl_2$
d, $Z_2 = Z_3 = 4\text{-}F$
e, $Z_2 = Z_3 = 4\text{-}CF_3$
f, $Z_2 = Z_3 = 4\text{-}NO_2$

Improvements were effected in the preparation of 2,3-dinitro-1,4-dimethoxybenzene and trinitro-1,4-dimethoxybenzene (**2**), both known compounds.[9-12] The nitration of *p*-dimethoxybenzene to 2,3-dinitro-1,4-dimethoxybenzene in almost quantitative yield was simplified by the use of concentrated (70%) nitric acid. Curiously, about 80–90% of the product was the 2,3-dinitro isomer rather than the 2,5-dinitro isomer, as evidenced from ^1H NMR and gas chromatographic analyses. Following isolation of the crude 2,3-dinitro-1,4-dimethoxybenzene, nitration in fuming (90%) nitric acid gave **2**.

Catalytic reduction of **2** to triamino-1,4-dimethoxybenzene (**3**) was executed over palladium/charcoal in dilute acetic acid–water solution. The reduction, strongly exothermic, was thereby slowed and the yield improved because of the heterogeneous character of the reduction mixture. As amino groups were formed by reduction of the nitro groups, the product dissolved in the dilute acid solution. Triamine **3**, extremely unstable, was used immediately by filtering the reduction solution into a solution of the appropriate dicarbonyl compound to form the various 2,3-disubstituted 5,8-dimethoxy-6-aminoquinoxalines. Data summarizing the properties of the 6-aminoquinoxaline derivatives are in Table I; parallel data for the acetyl derivatives are in Table II.

The 6-amino groups of 2,3-dimethyl-, 2,3-diphenyl- (in a limited fashion), and 2,3-dibenzyl-5,8-dimethoxy-6-aminoquinoxaline were nucleophilic enough for direct alkylation with the corresponding halide. However, the 6-amino group on related isomers, wherein the R_2 and R_3 groups were H, C_6H_5, *p*-ClC_6H_4, and *p*-$ClC_6H_4CH_2$, could not be directly alkylated. Therefore, except for the *p*-chlorobenzyl derivative (vide infra), the 6-amino groups of these latter compounds were tosylated and then transformed into the corresponding potassium salts. Data concerning these *p*-toluenesulfonamido derivatives are in Table III. The potassium tosyl salts were then alkylated, after which the tosyl groups were removed (Table IV).

Under no circumstances could the 6-amino group of 2,3-bis(*p*-chlorobenzyl)-5,8-dimethoxy-6-aminoquinoxaline be alkylated. A vain effort to prepare the desired 6-aminoalkyl derivative involved the transformation of 2,3-bis(*p*-chlorobenzyl)-5,8-dimethoxyquinoxaline into the corresponding 2,3-bis(*p*-chlorobenzyl)-5,8-quinoxalinequinone. All efforts to aminoalkylate the 6 position of the above quinone with 2-dimethylaminoethylamine failed.

The difficulty of alkylating the 6-amino group of several of the 2,3-disubstituted 5,8-dimethoxy-6-aminoquinoxalines instigated several other attempts to form the target compounds. Although all these alternate sequences failed, one is worthy of attention, because it terminated in an un-

Table II. 2,3-Disubstituted 5,8-Dimethoxy-6-acetamidoquinoxalines[a,b]

No.	R_2, R_3	Formula	Recrystn solvent (ml/g)	Mp, °C	% yield	Uv max, nm (ε)
4a-Ac	H	$C_{12}H_{13}N_3O_3$	C_6H_6 (10)	183–184	93	215 (15,200), 273 (58,200)
4b-Ac	CH_3	$C_{14}H_{17}N_3O_3$	C_6H_6 (15)	220.5–221.5	70	216 (inf), 273 (59,800)
4c-Ac	C_6H_5	$C_{24}H_{21}N_3O_3$	CH_3OH (35)	206.5–207.5	71	221 (32,600), 275 (31,300), 305 (53,400)
4d-Ac	4-C_6H_4Cl	$C_{24}H_{19}Cl_2N_3O_3$	CH_3OH (75)	220.1–220.5	92	203 (46,570), 224 (29,900), 277 (30,690), 307 (52,940)
4e-Ac	$C_6H_5CH_2$	$C_{26}H_{25}N_3O_3$	EtOH (10)	172–173	84	208 (52,700), 279 (83,700), 341 (4,910), 360 (4,590)
4f-Ac	4-$ClC_6H_4CH_2$	$C_{26}H_{23}Cl_2N_3O_3$·0.5EtOH	EtOH (40)	153.5–154.5	42	207 (inf), 219 (inf), 281 (53,100), 335 (7,000), 370 (5,600), 400 (3,800)

[a] All compounds gave acceptable C, H, and N analyses. [b] NMR spectra were as expected.

Table III. 2,3-Disubstituted 5,8-Dimethoxy-6-[*N*-(*p*-toluenesulfonamido)]quinoxalines[a,b]

No.	R_2, R_3	Formula	Recrystn solvent (ml/g)	Mp, °C	% yield	Uv max, nm (ε)
4a-Tos	H	$C_{17}H_{17}N_3O_4S$	MeOH (30)	213–214	86	215 (17,400), 271 (36,000)
4c-Tos	C_6H_5	$C_{29}H_{25}N_3O_4S$·0.5CH_3OH	MeOH or 95% EtOH (20)	222.5–223.5	97	220 (33,600), 272 (25,600), 305 (33,400)
4d-Tos	4-ClC_6H_4	$C_{29}H_{23}Cl_2N_3O_4S$	95% EtOH (50)	214–215	100	225 (42,000), 277 (30,600), 308 (48,900)

[a] All compounds gave acceptable C, H, and N analyses. [b] NMR spectra were as expected.

Table IV. 2,3-Disubstituted 5,8-Dimethoxy-6-[*N*-(ω-dimethylaminoalkyl)amino]quinoxalines (5)[a,b]

No.	R_2, R_3	Side chain $(CH_2)_n$	Formula	Recrystn, Ligroine ml/g	bp, °C	Mp, °C	% yield	Uv max, nm (ε)
5a-2	H	2	$C_{14}H_{20}N_4O_2$	10	60–75	64–65	36.8	208 (4,100), 225 (12,900), 282 (54,400), 312 (inf)
5a-3	H	3	$C_{15}H_{22}N_4O_2$	10	60–75	95–96	10.8	225 (inf), 282 (13,700), 312 (40,000)
5b-2	Me	2	$C_{16}H_{24}N_4O_2$	15	60–75	119–120.5	15	208 (inf), 225 (16,900), 279 (58,400), 310 (inf)
5b-3	Me	3	$C_{17}H_{26}N_4O_2$	20	60–75	106–107	24	207 (18,000), 224 (18,600), 279 (49,000)
5c-2	C_6H_5	2	$C_{26}H_{28}N_4O_2$	100	60–75	163.5–164.5	9	242 (20,300), 306 (51,300)
5c-3	C_6H_5	3	$C_{27}H_{30}N_4O_2$	30	100–115	141.5–143	18.3	250 (22,900), 309 (59,800)
5d-2	4-ClC_6H_4	2	$C_{26}H_{26}N_4O_2Cl_2$	50	100–115	191–193	14.7	207 (30,700), 223 (21,100), 260 (19,200), 314 (46,900)
5d-3	4-ClC_6H_4	3	$C_{27}H_{28}N_4O_2Cl_2$	50	100–115	160–160.5	10.0	204 (36,300), 223 (21,300), 258 (19,200), 315 (46,900)
5e-2	$C_6H_5CH_2$	2	$C_{28}H_{32}N_4O_2$	10	60–75	143–144	32	223 (inf), 279 (84,900), 408 (5,960)

[a] All compounds gave acceptable C, H, and N analyses. [b] NMR spectra were as expected, except that coupling between the amino proton and the two adjacent methylene protons of the alkyl side chain was observed.

usual deetherification cum oxidation during an attempted nitration, wherein 1,4-dimethoxy-2-(*p*-toluenesulfonamido)-5-acetamidobenzene gave good yields, on attempted nitration, of 2-(*p*-toluenesulfonamido)-5-acetamido-1,4-benzoquinone![13]

It was hoped that the 2,3-distyryl analogs of the above targets would be readily prepared via condensation of the active methyl groups of **5b**-3 with aromatic aldehydes by codistillation in a Dean-Stark apparatus. Initial experiments were positive, and 2,3-dimethyl-5,8-dimethoxy-6-aminoquinoxaline was successfully condensed with 2 equiv of benzaldehyde and *p*-chlorobenzaldehyde, respectively, in refluxing toluene.

However, substitution onto the 6-amino group of any function whatever, acyl or alkyl, interdicted this facile mode of styryl synthesis. Charles[14] has explained this curious circumstance as being due to the necessity of forming first an intermediate imine by reaction of the aromatic aldehyde with aromatic amine. Therefore, the modes of syntheses devised by Klicnar et al.[15] and Bennett and Willis,[16] who utilized boiling acetic anhydride to effect condensation of aromatic aldehydes with 2,3-dimethylquinoxalines, were

Table V. 2,3-Bis(substituted styryl)-5,8-dimethoxy-6-[*N*-(γ-dimethylamino-*n*-propyl)amino]quinoxalines (**6**)[a,b]

No.	Z_2, Z_3	Formula	Rxn time, hr	Recrystn ml/g	Recrystn Solvent[c]	Mp, °C	% yield	Uv max, nm (ε)
6a	H	$C_{31}H_{34}N_4O_2$	22	140	h	127–128	2.1	256 (26,640), 290 (inf), 327 (28,250), 357 (41,700), 483 (8,470)
6b	4-Cl	$C_{31}H_{32}Cl_2N_4O_2$	12	300	h	144–146	23	210 (20,860), 247 (inf), 260 (inf), 294 (inf), 330 (40,860), 357 (43,180), 484 (8,200)
6c	3,4-Cl_2	$C_{31}H_{30}Cl_4N_4O_2 \cdot 0.5H_2O$	12	135	m	77–79	33.8	209 (30,840), 260 (inf), 290 (inf), 331 (38,320), 358 (38,550), 486 (6,880)
6d	4-F	$C_{31}H_{32}F_2N_4O_2$	17	625	h	157.5–158.5	17.5	290 (inf), 329 (38,090), 355 (41,390), 485 (8,610)
6e	4-CF_3	$C_{33}H_{32}F_6N_4O_2$	6	160	h	151.5–152	41.4	216 (15,770), 244 (inf), 254 (inf), 319 (35,220), 361 (37,840), 420 (inf), 490 (7,880)
6f	4-NO_2	$C_{31}H_{32}N_6O_2$	4	400	e	243–245	65	211 (inf), 315 (inf), 372 (40,380), 460 (14,720)

[a] All compounds gave acceptable C, H, and N analyses. [b] NMR spectra were as expected. [c] h, hexane; m, methanol; e, ethanol.

resorted to. Excellent yields of the corresponding 6-acetamido-2,3-distyrylquinoxaline derivatives were obtained, but unfortunately no usual means succeeded in afterward removing the 6-(*N*-acetyl) group which the reaction environment injected onto the 6-amino group. The difficulty may be due to an acceptor–donor relationship between acetyl group and γ-nitrogen atom of the alkyl side chain which negates the requisite electrophilic character of acyl carbon and, hence, interdicts its hydrolysis.

This barrier was hurdled by *first* introducing a trifluoroacetyl group onto the 6-*N*-alkylated amino group *prior* to styrylization of the 2,3-dimethyl groups of quinoxaline. The Klicnar procedure was then applied (during which reactions very evidently the acetic anhydride medium did *not* displace the trifluoroacetyl group), and the very sensitive trifluoroacetyl group was removed afterward with dilute base. Table V summarizes the properties of these targets.

Biological Results. All compounds were tested by the Rane Laboratory, University of Miami, in *Plasmodium berghei* blood infected mice[17] and/or *Plasmodium gallinaceum* sporozoite infected chicks[18] at 10–640 mg/kg. The mean survival time of control mice was 6.2 days and of control chicks 8.5 days. Data for target compounds are in Table VI. All compounds were inactive; **5a**-2, **5b**-2, **5b**-3, **5c**-3, **5d**-2, and **5e**-2 were toxic at dose levels of 320 and/or 640 mg/kg of body weight of test animal, as listed in the footnotes, Table VI. In addition, intermediates **4a**-Ac and **4b** were toxic at dosage levels of 640 mg/kg, with 5/5 of the test mice killed.

Experimental Section

Chemical Methods and Materials. Melting points, uncorrected, were determined on a Thomas-Hoover apparatus. Spectra were recorded as follows: uv, Jasco ORD/UV in 95% EtOH in 1-cm quartz cells; ^{1}H NMR, Hitachi Perkin-Elmer R-20, 60 MHz, 34°, δ in parts per million from internal Me_4Si; ir, Beckman IR-10. Elemental analyses were performed by PCR, Inc., Gainesville, Fla. Tosyl chloride was recrystallized from THF; C_5H_5N was distilled from CaH_2 and stored over NaOH pellets.

2,3-Dinitro-1,4-dimethoxybenzene. 1,4-Dimethoxybenzene (69.1 g, 0.5 mol) was added portionwise over 1 hr to 280 ml of cold (0–5°), stirred, concentrated HNO_3. The suspension was further stirred for 1 hr at 24° and then for 1 hr on a steam bath.

The reaction mixture was drowned in ice and water, filtered, rinsed ($NaHCO_3$, aqueous), and dried to give 104.5 g (91.6%) of yellow powder, mp 160–185° (lit.[10] mp 155–178°; lit.[11] mp 186°).

A combination of ^{1}H NMR and gas chromatography demonstrated the product to be about 88% of 2,3-dinitro-1,4-dimethoxybenzene and about 12% of 2,5-dinitro-1,4-dimethoxybenzene (pure 2,5-dinitro-1,4-dimethoxybenzene,[10] mp 202°; pure 2,3-dinitro-1,4-dimethoxybenzene,[11] mp 186°).

Trinitro-1,4-dimethoxybenzene (2). Over a 1-hr period all above crude dry dinitro compound was slowly added to 420 ml of stirred, cold (0–5°) fuming HNO_3. After addition was completed, stirring was continued at 0° for at least 4 hr, at 24° for at least 4 hr (when convenient, the mixture can be stirred at either temperature for 12 hr, overnight; no difference in yield resulted), for 2 hr at 50°, and 1-hr periods each at 70°, 80°, and on a steam bath.

The reaction solution was drowned in ice and water, filtered, rinsed ($NaHCO_3$, aqueous), and dried to give 65.8 g (48.5%) of **2**, mp 97–99°.

Recrystallization of the crude **2** from MeOH (4 ml/g) gave 57.2 g (41.9%), mp 98–100° (lit.[12] mp 100–101°; lit.[19] mp 98–99°). Recovery and recrystallization of second-crop material afforded 6.2 g (4.5%), a total yield of 63.4 g (46.4%) of **2**.

Triamino-1,4-dimethoxybenzene (3). A suspension of 13.7 g (0.05 mol) of **2**, 0.5 g of 10% Pd/C, 120 ml of H_2O, and 17.3 ml of HOAc was reduced in a Parr reduction bottle at 24° and ~80 psi. About 4 hr were required to absorb ~40 psi (~0.49 mol, ~110%) of H_2. The material was extremely sensitive to air oxidation and was not isolated, but condensed in situ with the appropriate α-dicarbonyl compounds.

2,3-Disubstituted 5,8-Dimethoxy-6-aminoquinoxalines (4). Directly to the Parr reduction flask containing the solution of **3** was added a solution of 50 ml of water and 11.4 g (0.11 mol) of $NaHSO_3$ (except in the instance of the use of sodium glyoxal bisulfite monohydrate). The spent catalyst was removed by suction filtration, and to the filtrate was added 0.04–0.05 mol of the appropriate dicarbonyl compound.[20] The crude product was filtered from the reaction mixture after standing 24 hr at 24° [extracted with $CHCl_3$ in the instance of the $(CHO)_2$ condensation product] and recrystallized to a constant melting point. Data are given in Table I.

2,3-Disubstituted 5,8-Dimethoxy-6-acetamidoquinoxalines (4-Ac). The crude yields were recrystallized from appropriate solvents (Table II) to give 70–93% yields of pure material.

2,3-Disubstituted 5,8-Dimethoxy-6-(*p*-toluenesulfonamido)quinoxalines (4-Tos). A suspension of 1.0 mol of **4**, 1.1 mol of TsCl, and 1.2 l. of C_5H_5N was stirred at 24° for 48 hr and then heated on a steam bath for 10 min. Data are given in Table III.

2,3-Disubstituted 5,8-Dimethoxy-6-[*N*-(ω-dimethylaminoalkyl)amino]quinoxalines (5). Method A. By Direct Alkylation. A suspension of 0.02 mol of **4**, 0.02 mol of ω-(dimethylaminoalkyl) chloride hydrochloride, and 0.02 mol of $KHCO_3$ in 10–30 ml of redistilled diethylene glycol was stirred and heated at a con-

Table VI. Antimalarial Activity and Toxicity of Target Compounds in *Plasmodium berghei* Infested Mice and/or *Plasmodium gallinaceum* Infested Chicks

No.	Test animal	Antimalarial act., life-span increase, days, mg/kg of body wt[a]						
		10	20	40	80	160	320	640
5a-2	Chick				0.4	0.4	1.9[b]	
	Mouse		0.1	0.1	0.3	0.3	0.5	0.5
5a-3	Chick					0.0		
	Mouse		0.1	0.1	0.1	0.1	0.1	0.1
5b-2	Chick							
	Mouse		0.1	0.1	0.3	0.3	0.9[c]	0.0[d]
5b-3	Chick							
	Mouse		0.1	0.1	0.3	0.3	0.9[e]	1.9[f]
5c-2	Chick	0.0	0.0	0.0	0.0	0.0	0.0	
	Mouse	0.1	0.1	0.1	0.1	0.3	0.3	
5c-3	Chick				−0.1[g]	−0.9[h]	−0.4[i]	
	Mouse		0.1	0.1	0.1	0.1	0.3	0.3
5d-2	Chick	1.8	0.8	−0.4	0.0	3.6	1.4[j]	
	Mouse	0.1	0.1	0.1	0.1	0.1		
5d-3	Chick	1.4	1.4	0.6	−1.0	0.6	0.8	
	Mouse	0.1	0.1	0.1	0.1	0.1		
5e-2	Chick	−0.2	−0.2	−0.2	−0.2	−0.2[k]	0.0[l]	
	Mouse		0.1	0.1	0.1	0.3	0.1	0.3
6a	Chick	Insufficient sample, not tested						
	Mouse	Insufficient sample, not tested						
6b	Chick	0.2	0.2	0.2	0.2	0.2	0.4	
	Mouse			0.1		0.1		0.1
6c	Chick							
	Mouse			0.1		0.3		0.3
6d	Chick							
	Mouse							0.0
6e	Chick							
	Mouse			0.5		0.5		0.7
6f	Chick							
	Mouse			0.1		0.1		0.1

[a]Mean survival time: mice, 6.2 days; chicks, 8.5 days. [b]Toxic, 2/5. [c]Toxic, 3/5. [d]Toxic, 5/5. [e]Toxic, 2/5. [f]Toxic, 3/5. [g]Toxic, 2/5. [h]Toxic, 3/5. [i]Toxic, 4/5. [j]Toxic, 1/5. [k]Toxic, 3/5. [l]Toxic, 5/5.

stant temperature of 160° (±5°) for a total time of 2 hr. At intervals of 0.5 hr two further additions of 0.02 mol each of amine HCl and $KHCO_3$ were made to the reaction flask.

After cooling, 0.1 mol of KOH was added with stirring to the reaction paste. The product was then extracted from the reaction mixture with C_6H_6 (5 × 30 ml), each time stirring for about 10 min before decanting off the upper layer of C_6H_6.

The C_6H_6 layer was dried ($MgSO_4$), treated with Norite and Celite, and filtered. Solvent was removed at reduced pressure to yield a viscous brown oil.

The crude **5** was dissolved in 200 ml of 1 *N* HCl, and the solution was treated with Norite and Celite and then filtered. The filtrate was basified with KOH, and the solution was extracted with C_6H_6 (6 × 50 ml). After drying ($MgSO_4$), solvent was removed to give a yellow oil or solid which was dissolved in Et_2O (150 ml/g) and an Et_2O solution of resorcylic acid (60 ml/g) was added in the proportion of 3 mol of acid to 1 mol of **5**. The yellow precipitate which formed was stirred for 15 min, filtered, and rinsed with Et_2O. The solid residue, usually hygroscopic, was dissolved or suspended in H_2O (50 ml/g of crude amine product); the H_2O solution was basified with 10% NaOH and extracted with C_6H_6 (6 × 50 ml) or filtered if a solid precipitate was present. After drying ($MgSO_4$), the C_6H_6 was removed to give a light yellow oil or solid. The product was recrystallized from petroleum ether (bp 60–75°) with treatment with Norite and Celite. Recrystallizations were repeated (usually twice) until a constant melting point of **5** had been confirmed. Data are listed in Table IV.

Method B. By Alkylation of the Tosyl Intermediates, Followed by Detosylation. A 6 *N* solution of KOH was prepared in absolute EtOH or PrOH. A 1 molar equiv of 4-Tos was slowly added to this solution, and after stirring for 30 min, a 30% excess of ω-(dimethylaminoalkyl) chloride (liberated from its hydrochloride salt just before use by treatment with 50% NaOH solution) was added.

The mixture or solution was stirred and refluxed for 24–72 hr; then the solvent was removed under reduced pressure at 70° to yield an oily residue. The oily residue was dissolved in dilute (1–6 *N*) HCl (except **4d**-Tos which was insoluble in concentrated HCl and, hence, was directly detosylated) and filtered to remove starting material. The filtrate was treated with Norite and Celite and again filtered. The filtrate was basified with KOH and the insoluble oil was extracted with $CHCl_3$. After removal of the solvent, the crude tosyl derivative of the alkylated target was obtained as a golden oil.

The crude oil was dissolved in concentrated H_2SO_4 (5 ml/g) and stirred at 24° for 72 hr and then heated on a steam bath for 10 min. After cooling, the solution was slowly poured into ice and water (40 ml/ml of H_2SO_4), then basified with 50% aqueous NaOH, and extracted with $CHCl_3$. After drying ($MgSO_4$), removal of the solvent yielded crude **5**. The crude **5** was repeatedly extracted with 100-ml portions of boiling ligroine until extracts were colorless. The combined extracts were treated with Norite and Celite and filtered, and the volume was reduced to incipient crystallization. After cooling at 0° for 12 hr, the product was filtered, rinsed, and dried.

Recrystallization from ligroine was repeated, usually twice, until a constant melting point had been confirmed. Data are listed in Table IV.

2,3-Bis(*p*-chlorobenzyl)-5,8-dimethoxyquinoxaline. A solution of 11.9 g (0.05 mol) of 2,3-dinitro-1,4-dimethoxybenzene, 0.5 g of Pd/C, 50 ml of H_2O, and 15 ml of HOAc was hydrogenated at 60 psi for 4 hr; the Parr flask was evacuated and cooled (ice bath), and its contents were filtered directly into a stirred solution of 12.5 g (0.045 mol) of *s*-(*p*-chlorobenzyl)glyoxal[20] in 45 ml of THF. After

stirring for 1 hr, the mixture was filtered to give 18.96 g (96%) of yellow solid, mp 179–181°. Recrystallization from $CHCl_3$–ligroine (10 ml/g, 2:1) and concentration to 0.5 vol gave yellow solid of constant mp 181–182°. Anal. ($C_{24}H_{20}Cl_2N_2O_2$) C, H, N.

2,3-Bis(*p*-chlorobenzyl)-5,8-dihydroxyquinoxaline. A mixture of 4.90 g (0.011 mol) of 2,3-bis(*p*-chlorobenzyl)-5,8-dimethoxyquinoxaline and 13.3 g (0.1 mol) of $AlCl_3$ in 100 ml of C_6H_6 was refluxed for 6 hr. After cooling, the solution was poured into 250 ml of ice–H_2O. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (4 × 150 ml). The combined organic solvents were dried ($MgSO_4$) and evaporated under vacuum (40°) to give 4.30 g (93.7%) of yellow solid, mp 183–185°. Recrystallization from $CHCl_3$ (10 ml/g) with concentration to 0.5 vol gave yellow solid of constant mp 184.5–185.5°. Anal. ($C_{22}H_{16}Cl_2N_2O_2$) C, H, N.

2,3-Bis(*p*-chlorobenzyl)-5,8-quinoxalinequinone. A solution of 4.95 g (0.012 mol) of 2,3-bis(*p*-chlorobenzyl)-5,8-dihydroxyquinoxaline, 125 ml of H_2O, 6.0 ml of concentrated H_2SO_4, and 14.9 g (0.05 mol) of $Na_2Cr_2O_7$ was heated at 70 ± 5° for 3 hr; the cooled mixture was filtered to give 5.28 g (107%) of tan solid, mp 160–170°. Two recrystallizations from $CHCl_3$–ligroine (15 ml/g, 2:1) gave 2.93 g (59.7%) of yellow solid, mp 171–172°. Anal. ($C_{22}H_{14}Cl_2N_2O_2$) C, H, N.

***N*-(*p*-Toluenesulfonyl)-2,5-dimethoxyaniline.** A cold (5°) suspension of 14.3 g (0.1 mol) of 2,5-dimethoxyaniline, 12 ml (0.2 mol) of AcOH, 50 ml of THF, 16.4 g (0.12 mol) of $NaOAc·3H_2O$, 20.9 g (0.11 mol) of TsCl, and 150 ml of H_2O was stirred at 5° for 4 hr and at 24° for 20 hr. The reaction mixture was diluted with 500 ml of H_2O and filtered. The filter cake was dissolved in 200 ml of 0.5 *N* NaOH, treated with Norite and Celite, filtered, and then poured with stirring into 50 ml of 2 *N* HCl. Filtration gave 30 g (97.8%), mp 106.5–108.5°. Recrystallization from MeOH (2 ml/g) gave 27.6 g (90%), mp 108–108.5°. Anal. ($C_{15}H_{17}NO_4S$) C, H, N.

2,5-Dimethoxy-4-(*p*-toluenesulfonamido)nitrobenzene. To a cold (5°) mixture of 6.14 g (0.02 mol) of *N*-(*p*-toluenesulfonyl)-2,5-dimethoxyaniline in 20 ml of HOAc and 1 ml of H_2O was added dropwise over 30 min a cold solution of 6 ml each of HNO_3 (68–71%) and HOAc. Stirring was continued for 30 min at 5° and for 30 min at 24°. The reaction mixture was drowned in ice and water and the crude product was dissolved in 0.1 *N* NaOH which was treated with Norite and Celite and filtered. The solution was poured with stirring into 5 ml of 12 *N* HCl to precipitate 6.7 g (95%) of solid, mp 193–199°. Recrystallization from MeOH (100 ml/g) gave 5.0 g (0.0142 mol, 71%), mp 201–201.5°. Anal. ($C_{17}H_{16}N_2O_6S$) C, H, N.

2,5-Dimethoxy-4-(*p*-toluenesulfonamido)acetanilide. Method A. A solution of 3.52 g (0.01 mol) of 2,5-dimethoxy-4-(*p*-toluenesulfonamido)nitrobenzene in 10 ml of THF was reduced in a Parr pressure flask over 0.3 g of 10% Pd/C to take up 3.6 psi at 24° at about 40 psi. The flask was cooled in ice and opened, and its content was filtered into 2 ml of cold Ac_2O. After standing 8 hr at 24°, the colorless solid was filtered to give 3.6 g (100%), mp 188.5–190°. Recrystallization of the material from MeOH (18 ml/g) gave 3.3 g (91.6%), mp 189–189.5°. Anal. ($C_{17}H_{20}N_2O_5S$) C, H, N.

Method B. 2,5-Dimethoxy-4-nitroacetanilide[21] was prepared (87.5%) by nitrating 2,5-dimethoxyacetanilide using the same procedure outlined above for the nitration of the analogous *N*-(*p*-toluenesulfonyl)-2,5-dimethoxyaniline. Catalytic reduction of 2,5-dimethoxy-4-nitroacetanilide over Pd/C in H_2O, followed immediately by tosylation of the reduced material, gave product identical (melting point, mixture melting point, and ^1H NMR) with 2,5-dimethoxy-4-(*p*-toluenesulfonamido)acetanilide.

2-Acetamido-5-(*p*-toluenesulfonamido)-*p*-benzoquinone. To a cold (5°), stirred solution of 9.35 g (0.025 mol) of 2,5-dimethoxy-4-(*p*-toluenesulfonamido)acetanilide in 25 ml of HOAc and 2.5 ml of H_2O was added over 15 min a cold solution of 7.5 ml each of HNO_3 (69–71%) and HOAc. Stirring was continued for 15 min at 5° and for 30 min at 24°. After drowning the reaction mixture in water, 8.4 g (97.6%) of yellow powder, mp 216–218°, was obtained. Recrystallization from EtOH (125 ml/g) gave 6.76 g (78.8%), mp 218–218.5°. Anal. ($C_{15}H_{14}N_2O_5S$) C, H, N.

2-Amino-5-*p*-(toluenesulfonamido)-*p*-benzoquinone. A solution of 4 g (0.012 mol) of 2-acetamido-5-(*p*-toluenesulfonamido)-*p*-benzoquinone, 1.6 g of 85% KOH pellets, and 40 ml of EtOH–H_2O (1:1) was heated on a steam bath for 40 min. Upon cooling, the reaction mixture was brought to pH 4 with 7 ml of HOAc, drowned in H_2O, and filtered to give 3.55 g (101%) of crimson powder, mp 236–238° dec. Recrystallization from EtOH (100 ml/g) gave 3.36 g (96%) of large purple-colored crystals, mp 237–238° dec. Anal. ($C_{13}H_{12}N_2O_4S$) C, H, N.

2,3-Distyryl- and 2,3-Di(*p*-chlorostyryl)-5,8-dimethoxy-6-aminoquinoxalines. A solution of 2.33 g (0.01 mol) of **4b**, 4.28 g (0.04 mol) of C_6H_5CHO, 1 ml of HOAc, and 1.3 ml of diisopropylethylamine in 10 ml of $C_6H_5CH_3$ was refluxed for 24 hr in an apparatus equipped with a Dean-Stark water separator. The distilled water layer reached constant volume (2.2 ml) in 18 hr.

The reaction solution was steam distilled to remove $C_6H_5CH_3$ and excess C_6H_5CHO, and the residue was recovered to yield 4.97 g (122%) of crude product, mp 176–186° dec. Three recrystallizations from C_6H_6–ligroine (bp 68–70°) (1:3.4, 17 ml/g) gave 2.1 g (0.00513 mol, 51.3%) of maroon-colored crystals, mp 191.3–192.2° dec. Anal. ($C_{26}H_{23}N_3O_2$) C, H, N.

The acetyl derivative, by the general method cited above, was a hemihydrate, mp 238–239° (from EtOH, 150 ml/g). Anal. ($C_{28}H_{25}N_3O_3·0.5H_2O$) C, H, N.

In a similar fashion 48 hr of reaction time gave 81% of the 2,3-di(*p*-chlorostyryl) analog: mp 230–232° [from C_6H_6–ligroine (1:1), 160 ml/g]. Anal. ($C_{26}H_{21}Cl_2N_3O_2$) C, H, N.

2,3-Dimethyl-5,8-dimethoxy-6-[*N*-(ω-dimethylamino-*n*-propyl)]-6-trifluoroacetamidoquinoxaline. To a cold stirred solution of **5b-3** (4.77 g, 0.015 mol) in 30 ml of $CHCl_3$ (no H_2O and EtOH) was added dropwise 4.10 g (0.0195 mol) of redistilled trifluoroacetic anhydride. The reaction mixture, protected from H_2O with a drying tube, was stirred at 0° for 1 hr. The solution was rinsed (2 × 45 ml, 5% $NaHCO_3$; 1 × 15 ml, 10% K_2CO_3; 2 × 4 ml, H_2O). The organic layer was dried (Na_2SO_4), decolorized with Norite, and filtered, and the solvent was removed with reduced pressure to give 5.97 g of tacky yellow solid. This material was triturated with 15 ml of ligroine (bp 63–75°), cooled at −10° for 18 hr, and then filtered to give 5.68 g (91.5%) of yellow solid, mp 96–100°. Three recrystallizations from C_6H_{14} (17 ml/g) gave 4.0 g (70%) of light yellow product, mp 101–102°. Anal. ($C_{19}H_{25}F_3N_4O_3$) C, H, N.

2,3-Bis(substituted styryl)-5,8-dimethoxy-6-[*N*-(ω-dimethylamino-*n*-propyl)amino]quinoxalines (6). General Procedure. A solution of 4.14 g (0.01 mol) of 2,3-dimethyl-5,8-dimethoxy-6-[*N*-(ω-dimethylamino-*n*-propyl)]-6-trifluoroacetamidoquinoxaline, 0.90 g (0.013 mol) of HOAc, and 0.04 mol of the appropriate aldehyde in 5 ml of Ac_2O was refluxed for *x* hr in an apparatus protected from H_2O with a drying tube. At the end of the reaction period the solution was stirred in 100 ml of H_2O for 1 hr at 24°, after which time the solution was basified to pH of 8 with $KHCO_3$. A water-insoluble material formed, which was either extracted with CH_2Cl_2 (4 × 100 ml) or the H_2O was decanted from the resultant tar. This tar was then dissolved in 200 ml of CH_2Cl_2. The organic solution was dried (Na_2SO_4), clarified with Norite, and filtered, and the solvent was evaporated at reduced pressure to give a tar. The tar was dissolved in 30 ml of 0.9 *N* MeOH–KOH and stirred for 30 min at 24°. Evaporating the solvent at reduced pressure, dissolving the residue in 300 ml of CH_2Cl_2, drying (Na_2SO_4), clarifying with Norite, filtering, and removing the solvent at reduced pressure gave a maroon-colored glass. This glass was dissolved in Et_2O, clarified with Norite, and filtered, and the solvent was evaporated to give a tar. After dissolving in anhydrous Et_2O (20 ml/g), the solution was treated with Norite and filtered. The solution was poured into an ethereal solution of β-resorcylic acid (12 ml/g) in the proportion of 3 mol of acid to 1 mol of crude amine. The solid precipitate, which was very hygroscopic, was filtered, rinsed with Et_2O, and dried in vacuo to give a yellow solid. Suspension of the resorcylate salt in 100 ml of 1.8 *N* NaOH, stirring for 30 min, and filtration gave a red solid. Usually four recrystallizations with treatment with Norite and Celite were needed to give a constant melting point of final product. The data are listed in Table V.

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References and Notes

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Synthesis and Antibacterial Activities of Some Chloro Analogs of 3-Amino-3,4-dihydro-1-hydroxycarbostyril

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The effects of a chloro substituent upon the microbiological activities of 3-amino-3,4-dihydro-1-hydroxycarbostyril were determined. The 5-, 6-, and 7-chloro analogs were synthesized by reductive cyclizations of the appropriately chloro-substituted o-nitrophenylalanines, while the 8-chloro analog was obtained from the *N*-trifluoroacetyl-3-chloro-2-nitrophenylalanine ethyl ester. All of these compounds were observed to inhibit the growth of *Escherichia coli* 9723, *Leuconostoc dextranicum* 8086, and *Lactobacillus plantarum* 8014. The relative inhibitory activities of the chloro analogs were 7-Cl > 6-Cl > 8-Cl > 5-Cl in *E. coli* and 7-Cl > 6-Cl > 8-Cl = 5-Cl in *L. dextranicum* and *L. plantarum*. In each of the three microorganisms, the 7-Cl analog was a more effective growth inhibitor than the parent unsubstituted compound. The growth inhibitory activities of this class of compounds were demonstrated to be much more effective than those of the four corresponding lactams, the 5-, 6-, 7-, and 8-chloro analogs of 3-amino-3,4-dihydrocarbostyril.

Since our earliest report on the synthesis and potent antibacterial activity of the cyclic hydroxamic acid, 3-amino-3,4-dihydro-1-hydroxycarbostyril,[1] we have studied the structure–activity relationships of its 7-hydroxy and 7-methoxy derivatives,[2] its optically active forms,[3] and its lower condensed-ring homolog, 3-amino-1-hydroxy-2-indolinone.[4] The purpose of this paper was to further these studies by determining the effects upon microbiological activity of a chloro substituent at each of the benzenoid positions of the cyclic hydroxamic acid. Accordingly, the four isomeric chloro-substituted 3-amino-3,4-dihydro-1-hydroxycarbostyrils **12–15** were synthesized and their relative growth inhibitory activities were determined and compared with those of the unsubstituted parent compound in *Escherichia coli* 9723, *Lactobacillus plantarum* 8014, and *Leuconostoc dextranicum* 8086. The corresponding four chloro-substituted lactams were also studied for their activities in these microorganisms.

Chemistry. The desired chloro-substituted cyclic hydroxamic acids **12–15** and lactams **19–21** were synthesized either directly or indirectly by reductive cyclization of the appropriately chloro-substituted *o*-nitrophenylalanines **7–9**. A major portion of the synthetic work in this study involved the preparation of the requisite chloro-2-nitrophenylalanines (**7–9**) by the usual acetamidomalonic ester method as previously described for the synthesis of 5-chloro-2-nitrophenylalanine.[5]

The 5-Cl (**12**), 6-Cl (**13**), and 7-Cl (**14**) analogs of 3-amino-3,4-dihydroxy-1-hydroxycarbostyril were obtained in good yield by reductive cyclization of the hydrochloride salts of the respective chloro-2-nitrophenylalanines under acidic conditions of catalytic hydrogenation. In order to prevent hydrogenolysis of the chloro groups, platinum on