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Antimalarials. 1. Heterocyclic Analogs of N-Substituted Naphthalenebisoxazines

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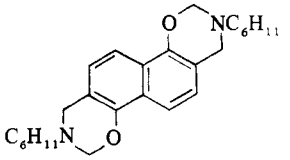
Several bisoxazines have been synthesized by a Mannich-type condensation involving substituted 4,7-, 4,8-, 5,8-, and 6,7-dihydroxyquinolines, 1,4- and 1,5-dihydroxynaphthalenes, and 5,8-dihydroxyquinoxalines. These compounds were evaluated for antimalarial activity against *Plasmodium berghei* in mice and against *Plasmodium gallinaceum* in chicks. The bisoxazines derived from 5,8-dihydroxy-2-(trifluromethyl)quinoline showed the highest antimalarial activity against *P. berghei.* The most active members of this series were 2,3,4,5,6,7-hexahydro-3,6-di(*p*-chlorobenzyl)-10-(trifluoromethyl)bis[1,3]oxazino[6,-5-*f*:5',6'-*h*]quinoline and 2,3,4,5,6,7-hexahydro-3,6-dipiperonyl-10-(trifluoromethyl)bis[1,3]oxazino[6,-5-*f*:5',6'-*h*]quinoline. The first compound was hydrolyzed to 5,8-dihydroxy-2-(trifluoromethyl)-6,7-bis(*p*-chlorobenzylaminomethyl)quinoline dihydrochloride which retained antimalarial activity comparable to that of the corresponding bisoxazine. None of the compounds were active against *P. gallinaceum.*

The principal aim of this investigation was the discovery of new antimalarials. Our approach involved the introduction of various structural changes in compounds which had previously displayed some antimalarial activity. In 1957, Duffin and Rollo synthesized a series of monohydroxy- and dihydroxy-substituted naphthalenes by the acid-catalyzed hydrolysis of the corresponding mono- or bisoxazines.[1] Among these compounds, 1,6-dihydroxy-2,5-bis(cyclohexylaminomethyl)naphthalene dihydrochloride showed promising antimalarial activity against *Plasmodium berghei* in mice, *Plasmodium gallinaceum* in chicks, and *Plasmodium cathemerium* in canaries. It was also shown in this investigation that some oxazines, such as the bisoxazine 2,8-cyclohexyl-1,2,3,4,7,8,9,10-octahydro-2,8-diaza-4,10-dioxachrysene (**1**), possessed activity

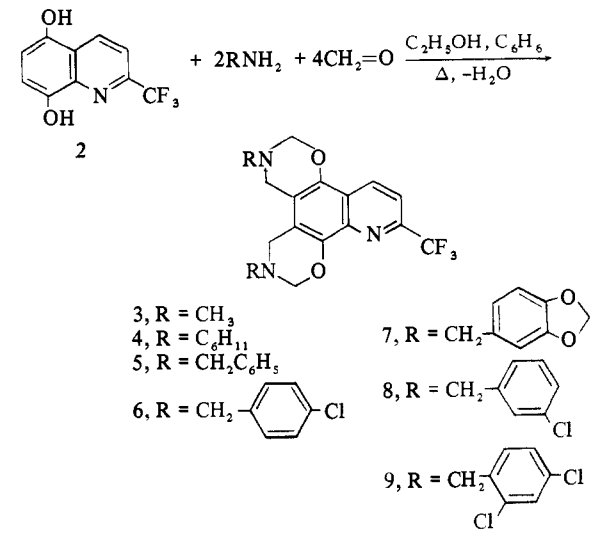


1

comparable to that of the corresponding aminomethylnaphthol, in this instance, 1,5-dihydroxy-2,6-bis(cyclohexylaminomethyl)naphthalene. This relationship suggested that aminomethylnaphthols might be *in vivo* degradation products of the oxazines. To extend this work we prepared several bisoxazine derivatives of substituted 1,4- and 1,5-dihydroxynaphthalenes, 5,8-dihydroxyquinoxaline, and 4,7-, 4,8-, 5,8-, and 6,7-dihydroxyquinolines. The replacement of the naphthalene ring by a quinoline ring in the last series of compounds was the most important structural change introduced in the basic bisoxazine nucleus since quinolines are known to possess superior antimalarial activity.[2]

Organic Syntheses. The 5,8-quinolinebisoxazines were synthesized by the condensation of 2-(trifluoromethyl)-5,8-dihydroxyquinoline (**2**) with paraformaldehyde and appropriate amines (Scheme I). The same procedure (Scheme I) was used to prepare 4,7-, 4,8-, and 6,7-quinolinebisoxazines, 1,4- and 1,5-naphthalenebisoxazines, and 5,8-quinoxalinebisoxazines. These compounds are shown in Scheme II. The 6,7-quinolinebisoxazines **11–13** were obtained from 6,7-dihydroxy-2-(trifluromethyl)quinoline (**10**). The 4,7- and 4,8-quinolinebisoxazines were synthesized from 4,7-dihydroxy-2-(trifluoromethyl)quinoline (**16**) and 4,8-dihydroxy-2-(trifluoromethyl)quinoline (**14**), respectively. The 5,8-quinoxalinebisoxazines **19–26** were prepared from 2,3-diphenyl-5,8-dihydroxyquinoxaline (**18**). The 1,4- and 1,5-naphthalenebisoxazines **27** and **28** were obtained from 1,4- and 1,5-dihydroxynaphthalene, respectively. Compounds **2**, **10**, **14**, and **16** were obtained by the route shown in Scheme III.

Scheme I



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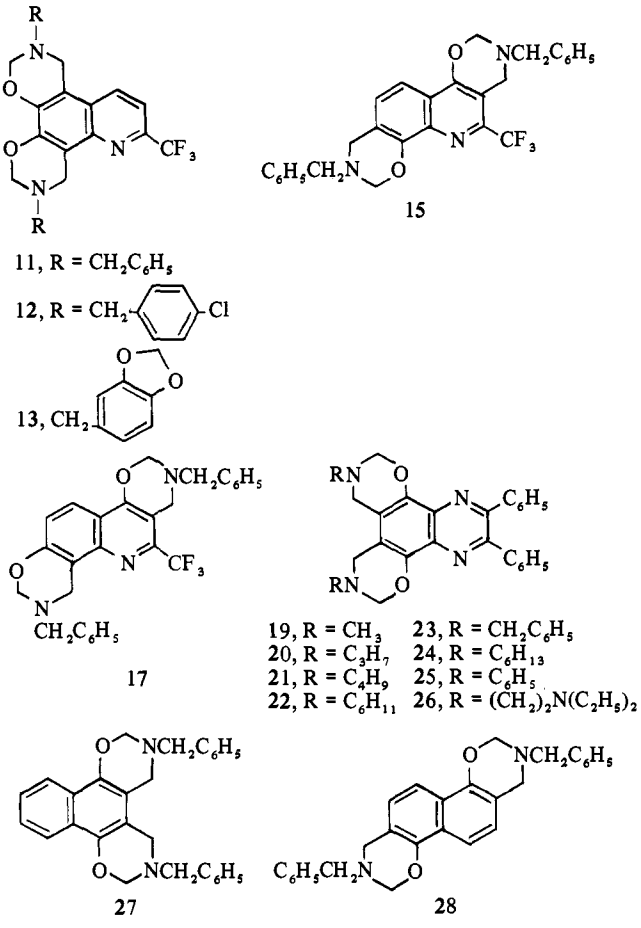
Methoxyanilines were condensed with ethyl trifluoroacetoacetate, in the presence of polyphosphoric acid, to give 4-hydroxyquinolines. 2,5- and 3,4-dimethoxyaniline yielded 5,8-dimethoxy-2-(trifluoromethyl)-4-hydroxyquinoline (**29**) and 6,7-dimethoxy-2-(trifluoromethyl)-4-hydroxyquinoline (**32**). *o*-Anisidine yielded 8-methoxy-2-

Scheme II



11, R = $CH_2C_6H_5$
12, R = CH_2-(p-Cl-C_6H_4)
13, CH_2-(3,4-methylenedioxy-C_6H_3)
15
17
19, R = CH_3 23, R = $CH_2C_6H_5$
20, R = C_3H_7 24, R = C_6H_{13}
21, R = C_4H_9 25, R = C_6H_5
22, R = C_6H_{11} 26, R = $(CH_2)_2N(C_2H_5)_2$
27
28

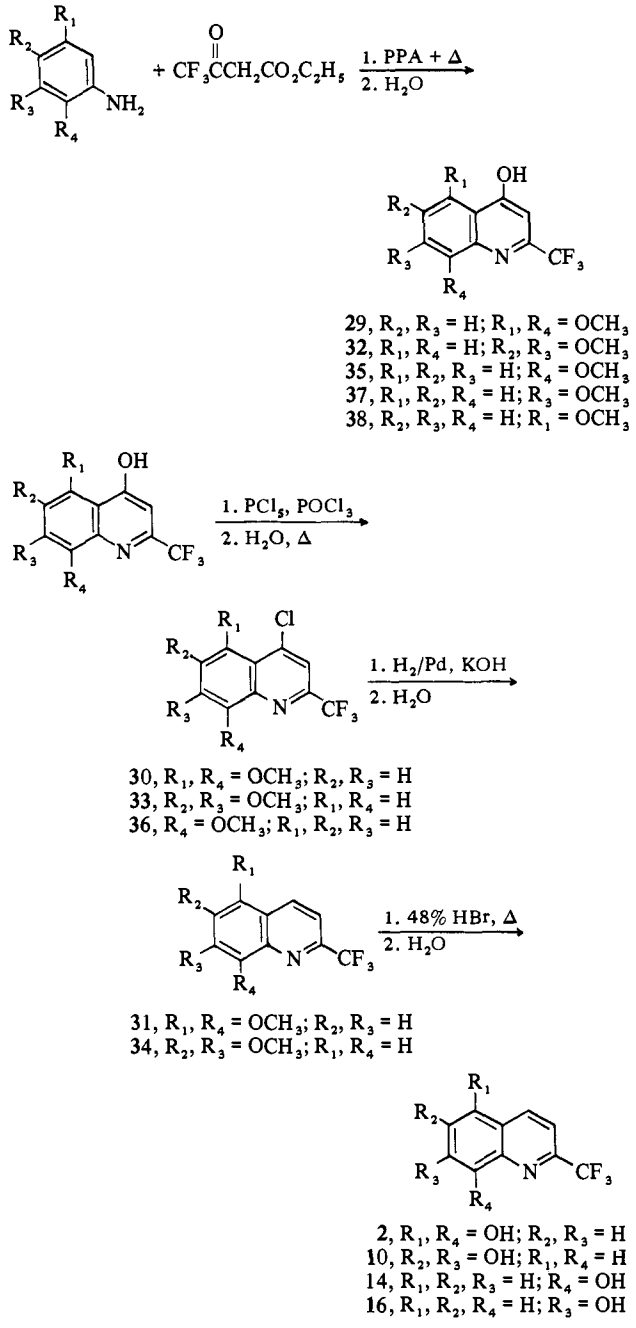
(trifluoromethyl)-4-hydroxyquinoline (**35**). The condensation of *m*-anisidine with ethyl trifluoroacetoacetate gave a mixture of 7-methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (**37**) and 5-methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (**38**).[3] These 4-hydroxyquinolines were treated with phosphorus pentachloride and phosphorus oxychloride to give the corresponding 4-chloroquinolines. Under these conditions, **29**, **32**, and **35** yielded 5,8-dimethoxy-2-(trifluoromethyl)-4-chloroquinoline (**30**), 6,7-dimethoxy-2-(trifluoromethyl)-4-chloroquinoline (**33**), and 8-methoxy-2-(trifluoromethyl)-4-chloroquinoline (**36**), respectively. The 4-chloro group was removed by reductive dehalogenation. On hydrogenolysis with 10% palladium-on-carbon catalyst, **30** and **33** afforded 2-(trifluoromethyl)-5,8-dimethoxyquinoline (**31**) and 2-(trifluoromethyl)-6,7-dimethoxyquinoline (**34**), respectively. The methoxyquinolines **31**, **34**, **35**, and **37** were hydrolyzed to the corresponding hydroxyquinolines **2**, **10**, **14**, and **16** with 48% hydrobromic acid and heat. Compound **14** was also obtained by the hydrolysis of compound **36**.

The starting material **18**, required for the synthesis of the quinoxalinebisoxazines **19-26**, was obtained as shown in Scheme IV.

The nitration of 1,4-dimethoxybenzene yielded a mixture of 2,3-dinitro- and 2,5-dinitro-1,4-dimethoxybenzenes. These compounds were reduced, without prior separation, to the corresponding 2,3- and 2,5-diamino-1,4-dimethoxybenzenes which were then heated with benzil. Only the 2,3 isomer reacted with benzil to give 5,8-dimethoxy-2,3-diphenylquinoxaline. This compound was hydrolyzed with 48% hydrobromic acid to give **18**.

The starting materials for the synthesis of the 1,4- and 1,5-naphthalenebisoxazines, 1,4- and 1,5-dihydroxynaphthalene, were commercially available.

Scheme III



29, R_2, R_3 = H; R_1, R_4 = OCH_3
32, R_1, R_4 = H; R_2, R_3 = OCH_3
35, R_1, R_2, R_3 = H; R_4 = OCH_3
37, R_1, R_2, R_4 = H; R_3 = OCH_3
38, R_2, R_3, R_4 = H; R_1 = OCH_3

30, R_1, R_4 = OCH_3; R_2, R_3 = H
33, R_2, R_3 = OCH_3; R_1, R_4 = H
36, R_4 = OCH_3; R_1, R_2, R_3 = H

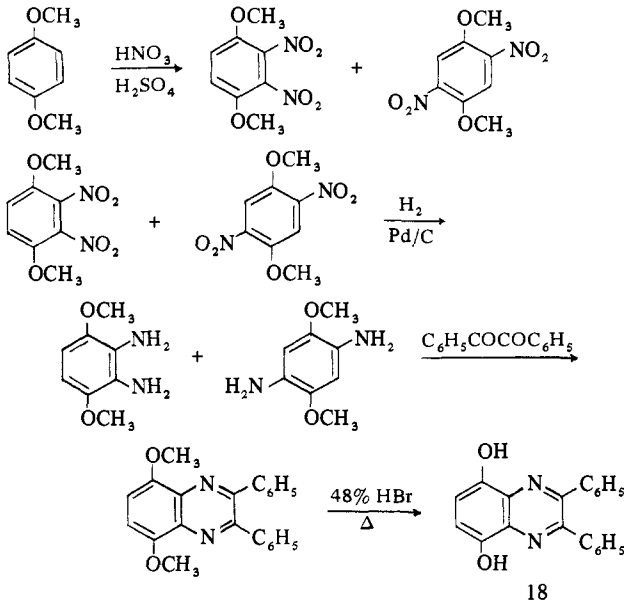
31, R_1, R_4 = OCH_3; R_2, R_3 = H
34, R_2, R_3 = OCH_3; R_1, R_4 = H

2, R_1, R_4 = OH; R_2, R_3 = H
10, R_2, R_3 = OH; R_1, R_4 = H
14, R_1, R_2, R_3 = H; R_4 = OH
16, R_1, R_2, R_4 = H; R_3 = OH

In order to compare the antimalarial activity of the bisoxazines with that of their open-chain derivatives, one of the more active quinolinebisoxazines, **6**, was hydrolyzed to the corresponding 5,8-dihydroxy-2-(trifluoromethyl)-6,7-bis(*p*-chlorobenzylaminomethyl)quinoline dihydrochloride (**39**) as shown in Scheme V.

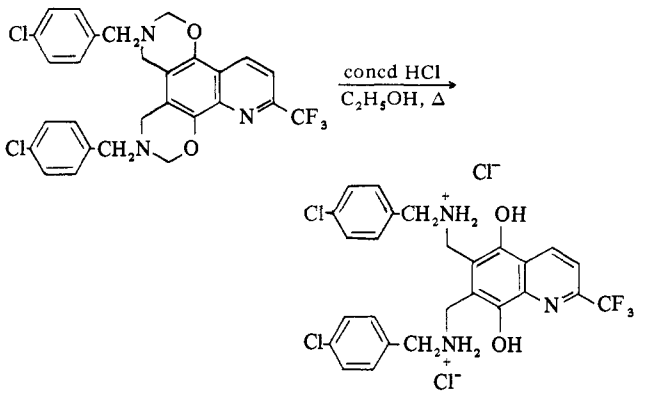
Antimalarial Test Results. The antimalarial test results were provided by the Walter Reed Army Institute of Research. The tests were based upon the relative response of *P. berghei* malaria in mice[4] to each of the submitted compounds as expressed by the mean survival time of treated animals (MSTT) and the mean survival time of controls (MSTC). A single dose of the test compound was given 72 hr after the mice were infected with *P. berghei*. Untreated animals died within 6-8 days and had a mean survival time (MSTC) of about 6.1 days. Treated animals were kept

Scheme IV



18

Scheme V



39

under observation for 60 days. The prolongation of life for 2.5 days was deemed statistically significant. A minimum mean survival time of 12 days was required for the compounds to be considered active. Animals which survived for 60 days and showed no parasitemia were considered cured. The antimalarial test results for the compounds prepared in this investigation are shown in Table I.

It may be seen from Table I that bisoxazines **3-9** possessed measurable antimalarial activity. Of these, **6** and **7** were the most active. The hydrolyzed product **39** also showed activity. No significant increase in mean survival time was observed with compounds **17**, **19**, **23**, **26**, **27**, and **28**.

Table I. Antimalarial Test Results

	Increase in mean survival time, days	
	Dose, mg/kg	
Compound	320	640
3[a]	3.0	
4	8.0	8.8
5	5.3	9.7
6	10.5	13.9
7[b]	11.5	13.7
8	3.9	4.9
9		5.9
39	4.1	9.1

[a] All five animals died on the fourth day. [b] 4.1 at 80 mg/kg.

Some of the compounds which served as intermediates in our syntheses, **2**, **10**, **14**, **16**, **29**, **30**, and **34-38**, were also tested for antimalarial activity. None of these, however, were found to be active. In addition, all of the compounds we prepared, **2-39**, were inactive against *P. gallinaceum* malaria in chicks.

Structure-Activity Relationships. Because of the potential usefulness of the substituted bisoxazines derived from 5,8-dihydroxyquinoline (**3-9**), we examined the effect of various structural modifications on their antimalarial activity. The nature of the R group on the oxazine ring (Scheme I) proved to be significant. When R was aromatic, the activity of the bisoxazine increased at high test dosages. In aromatic groups, the nature and position of the various ring substituents also affected activity. Ortho- and para-directing substituents, *e.g.*, -Cl or $-OCH_3$, that activate the ring by resonance but deactivate it by induction, increased the activity of the system when present at the para position. Thus, bisoxazines **6** and **7** showed the highest activity in the series. When a chloro substituent was present in the meta position, compound activity diminished. Thus, bisoxazine **8** was less active than **5**. The introduction of a second chloro substituent in the ring similarly decreased the activity of the system. Activity was also reduced when a cyclohexyl group or an aromatic ring was replaced by a methyl group. Bisoxazine **3** was less active than **4** and **5** and, furthermore, showed toxic properties at a dose rate of 640 mg/kg.

The orientation and number of the oxazine rings on the quinoline nucleus also influenced the activity of the system. Bisoxazines **11**, **12**, and **13** differ from **5**, **6**, and **7** only in the position of attachment of the oxazine rings. This difference, however, was sufficient to produce a complete loss of activity in **11**, **12**, and **13**. When one of the oxazines was moved to the hetero ring, the resulting compound was inactive. The isomeric bisoxazine **17** was also inactive. Two oxazine rings seem to be necessary for antimalarial activity. Although compounds **3-9** were active, the removal of one of the oxazine rings from **4**, **5**, or **6** produced inactive compounds. The synthesis of these substituted monooxazines will be reported in a subsequent publication.†

The introduction of a second nitrogen atom in the hetero ring destroyed the antimalarial activity of the system. Although bisoxazines **4** and **5** were active, their quinoxaline analogs **22** and **23** were both inactive. None of the quinoxalinebisoxazines showed antimalarial activity.

Bisoxazine **27**, which is the naphthalene analog of bisoxazine **5**, was also inactive, as was the other isomeric bisoxazine, **28**.

The hydrolysis of bisoxazine **6** yielded a product (**39**) which showed approximately the same antimalarial activity as the starting material. This observation supports the suggestion that bisoxazines break down *in vivo* to the corresponding aminomethylhydroxy derivatives.[1]

Experimental Section

General Procedures. Solids were recrystallized to constant melting point and dried *in vacuo* in an Abderhalden pistol containing sodium hydroxide. Melting points were determined in a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were carried out by Midwest Microlab, Ltd., Indianapolis, Ind. Melting points, recrystallization solvents, per cent yields, reflux times, and analytical data are given in Table II.

†L. C. March, W. A. Romanchick, G. S. Bajwa, and M. M. Joullié, unpublished results.

Table II. Chemical and Analytical Data

Compd no.	Formula	Mp, °C[a]	Recrystn solvent[b]	% yield	Reflux time[c]	Analyses[d]
2	$C_{10}H_6F_3NO_2$	159–160	A, B	63	6	C, H, N, F
3	$C_{16}H_{16}F_3N_3O_2$	180–182 dec	A	58	10	C, H, N, F
4	$C_{26}H_{32}F_3N_3O_2$	150–152 dec	A	45	10	C, H, N, F
5	$C_{28}H_{24}F_3N_3O_2$	154–156 dec	D	53	10	C, H, N, F
6	$C_{28}H_{22}Cl_2F_3N_3O_2$	110–112	G	49	21	C, H, N
7	$C_{30}H_{24}F_3N_3O_6$	142–144	D	51	21	C, H, N
8	$C_{28}H_{22}Cl_2F_3N_3O_2$	130–132	F	20	50	C, H, N
9	$C_{28}H_{20}Cl_4F_3N_3O_2$	167–170	B	22	22	C, H, N
10	$C_{10}H_6F_3NO_2$	238.5–241	G	84	6	C, H, N F
11	$C_{28}H_{24}F_3N_3O_2$	149–152	B	33	24	C, H, N, F
12	$C_{28}H_{22}Cl_2F_3N_3O_2$	165–169	B	34	19	C, H, N
13	$C_{30}H_{24}F_3N_3O_6$	182–185	B	20	19	C, H, N
14	$C_{10}H_6F_3NO_2$	261–263	G	27	6	C, H
15	$C_{28}H_{24}F_3N_3O_2$	184–189	B	28	17	C, H, N
16	$C_{10}H_6F_3NO_2$	322–324	B	94	6	C, H, N
17	$C_{26}H_{32}F_3N_3O_2$	109–111	E	34	23	C, H, N
18	$C_{20}H_{14}O_2N_2$	174–175[e]	H	63	4	
19	$C_{26}H_{24}N_4O_2$	222–223 dec	I	61	2	C, H, N
20	$C_{30}H_{32}N_4O_2$	160–161 dec	D	57	0.5	C, H, N
21	$C_{32}H_{36}N_4O_2$	168–169 dec	D	53	4	C, H, N
22	$C_{36}H_{40}N_4O_2$	190–192 dec	A	63	4	C, H, N
23	$C_{38}H_{32}N_4O_2$	200–202 dec	A	48	4	C, H, N
24	$C_{36}H_{44}N_4O_2$	156–158 dec	D	51	4	C, H, N
25	$C_{36}H_{28}N_4O_2$	216–218 dec	A	46	10	C, H, N
26	$C_{36}H_{46}N_6O_2$	147–148 dec	D	40	4	C, H, N
27	$C_{28}H_{26}N_2O_2$	129–131	E	47	17	C, H, N
28	$C_{28}H_{26}N_2O_2$	217–219	B	57	17	C, H, N
29	$C_{12}H_{10}F_3NO_3$	223–224	B	45	2	C, H, N, F
30	$C_{12}H_9ClF_3NO_2$	139–140.5	B	89	2	C, H, Cl, F
31	$C_{12}H_{10}F_3NO_2$	61–63	G	72		C, H, N, F
32	$C_{12}H_{10}F_3NO_3$	297–300	B	41	2	C, H, N, F
33	$C_{12}H_9ClF_3NO_2$	143–145	B	90	1	C, H, N, F
34	$C_{12}H_{10}F_3NO_2$	121–122.5	B	90		C, H, N, F
35	$C_{11}H_8F_3NO_2$	163–164	G	60	3	C, H, N, F
36	$C_{11}H_7ClF_3NO$	91–92	B	95	2	C, H, N, Cl, F
37	$C_{11}H_8F_3NO_2$	255–256	B	44	2.5	C, H, N
38	$C_{11}H_8F_3NO_2$	131–132	B	31	2.5	C, H, N
39	$C_{26}H_{24}Cl_4F_3N_3O_2$	202–204	B	50	1	C, H, N

[a]Decomposition points are indicated by dec. [b]A = benzene; B = 95% ethanol; C = chloroform; D = petroleum ether (bp 60–110°); E = absolute ethanol; F = ethanol and standing in refrigerator for 3 weeks; G = ethanol followed by addition of water; H = glacial acetic acid; I = pyridine. [c]Total reflux or heating time in hours. [d]Analytical results obtained for those elements were within 0.3% of the theoretical values. [e]Lit.[12] mp 176°.

Substituted 4-Hydroxyquinolines 29, 32, 35, 37, and 38 (Scheme III). The general procedure used for the preparation of these compounds was based upon a method developed by Staskun and Israelstam.[5,6] Polyphosphoric acid (150 ml) was heated, with stirring, in a 500-ml round-bottomed flask fitted with a condenser, addition funnel, and mechanical stirrer. The desired aromatic amine (0.16 mol) was added at 80–100°. An equimolar amount of ethyl trifluoroacetoacetate was then added to the flask over a period of 15–20 min. The reaction mixture was stirred vigorously at 100–120° for several hours. At the end of the heating period, the entire mixture was poured into 2500 ml of ice–water and stirred overnight. The solid that formed was removed by filtration, dried, and recrystallized from a suitable solvent (Table II).

Under these conditions the condensation of *m*-anisidine and ethyl trifluoroacetoacetate gave a mixture of **37** and **38**. These isomers were separated by "dry-column" chromatography.[3]

Substituted 4-Chloroquinolines 30, 33, and 36 (Scheme III). The synthesis of these compounds from the corresponding 4-hydroxyquinolines was based upon a procedure developed by Snyder, *et al.*[7] The substituted 4-hydroxyquinoline (0.072 mol) was placed in a 500-ml three-necked, round-bottomed flask fitted with a mechanical stirrer, water-condenser, and addition funnel. Phosphorus pentachloride (0.072 mol) and phosphorus oxychloride (0.260 mol) were alternately added to the 4-hydroxyquinoline, in small portions, over a period of 30 min. The mixture was stirred vigorously during this addition. It was then heated under reflux for an appropriate period of time. The reaction mixture was cooled, poured into 2500 ml of an ice–water mixture, and stirred overnight. The solid that formed was collected by filtration, dried, and recrystallized from a suitable solvent (Table II).

Reductive Dehalogenation. Preparation of 31 and 34 (Scheme III). The reductive dehalogenation of **30** and **33** to **31** and **34** was based upon a procedure used for the hydrogenolysis of 3-halo-6,8-dimethoxyisoquinolines.[8] The substitued 4-chloroquinoline (0.05 mol) and 2.0 g of 10% palladium-on-carbon catalyst were mixed in a hydrogenation bottle. Ethanolic potassium hydroxide (1 *N*, 130 ml) was added to the reaction mixture and it was shaken in a Parr hydrogenator until the theoretical amount of hydrogen was consumed (3–5 hr). The catalyst was removed by filtration and the filtrate was concentrated on a rotary evaporator. The residue was poured into 100 ml of an ice–water mixture and stirred overnight. The solid that formed was removed by filtration, dried, and recrystallized from a suitable solvent (Table II).

2,3-Diphenyl-5,8-dimethoxyquinoxaline (Scheme IV). This compound was prepared from 2,3-dinitro-1,4-dimethoxybenzene as shown in Scheme IV. The nitration of 1,4-dimethoxybenzene was based upon a procedure devised by Kawai[9] and Gregory.‡ 1,4-Dimethoxybenzene (138 g, 1.0 mol) was treated with a solution of nitric (438 ml, 7 mol) and glacial acetic (438 ml) acids. The yellow solid that formed [171 g, 75% yield, mp 154–170° (lit.[6] mp 155–178°)] was a mixture of the 2,3- and 2,5-dinitro-1,4-dimethoxybenzenes;[6] the 2,3 isomer was the major component.[10] This mixture (22 g, 0.010 mol) was reduced directly with 1 g of 10% palladium-on-carbon catalyst in a Parr hydrogenator. The product thus obtained [18.3 g, 76% yield, mp 250–252° dec (lit.[11] mp 251–252° dec)] was a mixture of the 2,3- and 2,5-diamino-1,4-dimethoxybenzene dihydrochlorides. These salts (137 g, 0.57 mol) were dissolved in ethanol and heated with benzil (120 g, 0.57 mol) for 5 min. The resulting solution was cooled to induce crystallization. The solid was collected and recrystallized from glacial acetic acid, affording 144 g (74% yield) of 2,3-diphenyl-5,8-dimethoxyquinoxaline as an orange solid, mp 223–226° (lit.[12] mp 226–227°).

‡M. Gregory, Ph.D. Dissertation, University of Pennsylvania, 1969.

Substituted Dihydroxyquinolines 2, 10, 14, and 16 (Scheme III) and Dihydroxyquinoxaline 18 (Scheme IV). These compounds were prepared by the hydrolysis of the corresponding dimethoxy derivatives. The procedure was based upon a method used for the cleavage of aryl alkyl ethers.[13]

(a) The dimethoxyquinoline or dimethoxyquinoxaline (0.18 mol) was heated under reflux with 450 ml of 48% hydrobromic acid for 6 hr. The solution was cooled, poured into 2500 ml of an ice–water mixture, and stirred overnight. The precipitate that formed was collected by filtration, dried, and recrystallized from a suitable solvent. Compounds **2**, **10**, and **14** were obtained from **31**, **34**, and **35** (or **36**) by this procedure. Compounds **10** and **14** were isolated from the solution by neutralization with 5% aqueous sodium bicarbonate.

(b) The synthesis of **16** from **37** (6 g, 0.0247 mol) required 600 ml of 48% hydrobromic acid. The reaction mixture was heated for 6 hr, cooled, and neutralized with ammonium hydroxide. The addition of dilute hydrochloric acid (1 ml) caused the immediate formation of a precipitate which was processed in the usual manner.

(c) The preparation of **18** from 2,3-diphenyl-5,8-dimethoxyquinoxaline (144 g, 0.42 mol) required 1000 ml of 48% hydrobromic acid and a heating period of 4 hr. The resulting solution was poured into 4000 ml of an ice–water mixture. The solid that formed was treated as described previously.

Preparation of Bisoxazines. The synthesis of these compounds was based upon a procedure used to prepare bisoxazines from hydroxybenzenes or hydroxynaphthalenes.[14,15]

(a) The quinolinebisoxazines, **4–9**, **11–13**, **15**, and **17**, and the naphthalenebisoxazines, **27** and **28**, were prepared by the following general procedure. Paraformaldehyde (0.52 g, 0.017 mol), the desired amine (0.0087 mol), and a solution of absolute ethanol (20 ml) and benzene (20 ml) were placed in a 250-ml, two-necked, round-bottomed flask fitted with a water condenser and addition funnel. The mixture was refluxed for 2 hr. The dihydroxyquinoline or dihydroxynaphthalene derivatives (0.0044 mol) were then dissolved in 20 ml of hot ethanol and added slowly to the refluxing mixture over a span of 15 min. After an additional reflux period, the reaction mixture was cooled and the solvent was removed *in vacuo*. The remaining mass was crystallized from a suitable solvent to afford the corresponding bisoxazine (Table II).

(b) The quinolinebisoxazine **3** was prepared as described in (a) with the following modifications. Paraformaldehyde (3.60 g, 0.12 mol) and 40% aqueous methylamine (4.65 g, 0.06 mol) were first mixed in 25 ml of ethanol and then heated under reflux until a clear solution was obtained. To this was added the dihydroxyquinoline (4.58 g, 0.02 mol) dissolved in 100 ml of benzene.

(c) The quinoxalinebisoxazines **19–26** were prepared as described in (a) with the following modifications. Paraformaldehyde (0.12 mol) and the amine (0.06 mol) were mixed in 25 ml of ethanol and heated under reflux until a solution was obtained. To this was added 2,3-diphenyl-5,8-dihydroxyquinoxaline (0.02 mol) dissolved in 100 ml of hot benzene. After an additional reflux period, the solvent was removed *in vacuo*. The remaining mass was washed with diethyl ether and recrystallized from an appropriate solvent.

5,8-Dihydroxy-2-(trifluoromethyl)-6,7-bis(*p*-chlorobenzylaminomethyl)quinoline Dihydrochloride (39, Scheme V). This compound was prepared by the hydrolysis of **6**. The reaction was based upon a procedure used to hydrolyze naphthalenebisoxazines.[1,16] Bisoxazine **6** (5.5 g) was dissolved in 50 ml of 95% ethanol. To this was added 5 ml of concentrated hydrochloric acid. The reaction mixture was heated under reflux for 1 hr. The hot solution was filtered and the filtrate was concentrated *in vacuo* to 20 ml. The solution was then cooled to induce crystallization. The solid was collected by filtration, washed with diethyl ether, and recrystallized from a suitable solvent (Table II).

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