Antimalarials. 2. Dihydro-1,3-oxazinoquinolines and Dihydro-1,3-pyridobenzoxazines

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A number of dihydro-1,3-oxazinoquinolines and dihydro-1,3-pyridobenzoxazines have been synthesized by a Mannich-type reaction involving various hydroxyquinolines, paraformaldehyde, and amines. Some dihydro-1,3-oxazinoquinolinones were prepared by the cyclization of *o*-hydroxyquinolinecarboxylic acids with *N,N*-dialkylcarbodiimides. All of the compounds were evaluated for antimalarial activity against *Plasmodium berghei* in mice and against *Plasmodium gallinaceum* in birds. 9-Amino-3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-4*H*-1,3-oxazino[5,6-*c*]quinolin-4-one and 2-benzyl-8-chloro-2,3-dihydro-10-methyl-1*H*-pyrido[3,2-*f*]-1,3-benzoxazine produced statistically significant prolongation of life in mice infected with *P. berghei*. None of the remaining compounds exhibited appreciable antimalarial activity.

The mono- and bisoxazines derived from naphthalene have been reported to possess antimalarial activity.[1] Similar activity was found in some quinolinebisoxazines.[2] These results led us to prepare a number of monooxazines derived from substituted quinolines. The removal of one of the oxazine rings from various quinolinebisoxazines, however, caused an almost complete loss of activity. Although the compounds prepared in this investigation were not sufficiently active to be useful antimalarials, they could possess other types of physiological activity. Similar dihydro-1,3-oxazines have recently been reported to have a strong cytotoxic effect on tumor cells, especially in low concentrations.[3]

Chemistry. Substituted quinolines were obtained by the Pfitzinger synthesis which involves the condensation of isatin with an aldehyde or ketone in the presence of base.[4] 3-Methoxy-2-phenylquinoline-4-carboxylic acid (**1**) was decarboxylated thermally in diphenyl ether to give 3-methoxy-2-phenylquinoline (**2**). Compound **2** was demethylated in refluxing 48% hydrobromic acid, affording 2-phenyl-3-hydroxyquinoline (**3**, Scheme I). The latter compound was treated with paraformaldehyde and a series of amines in a Mannich-type condensation to yield 2-substituted 2,3-dihydro-5-phenyl-1*H*-1,3-oxazino[6,5-*c*]quinolines **5-11** (Table I).

When **1** was treated with 48% hydrobromic acid, both **3** and 2-phenyl-3-hydroxyquinoline-4-carboxylic acid (**4**) were obtained (Scheme I). Compound **4** was treated with *N,N*-dialkylcarbodiimides in pyridine solution to give 2- and 3-substituted 5-phenyl-1*H*-1,3-oxazino[6,5-*c*]quinolin-1-ones **12** and **13** (Table II), as shown in Scheme I.

Several commercially available 4-hydroxyquinoline-3-carboxylic acids were treated with *N,N*-dialkylcarbodiimides in pyridine solution to give 2- and 3-substituted 2,3-dihydro-4*H*-1,3-oxazino[5,6-*c*]quinolin-4-ones **14-19** (Table III), as shown in Scheme II.

Scheme I

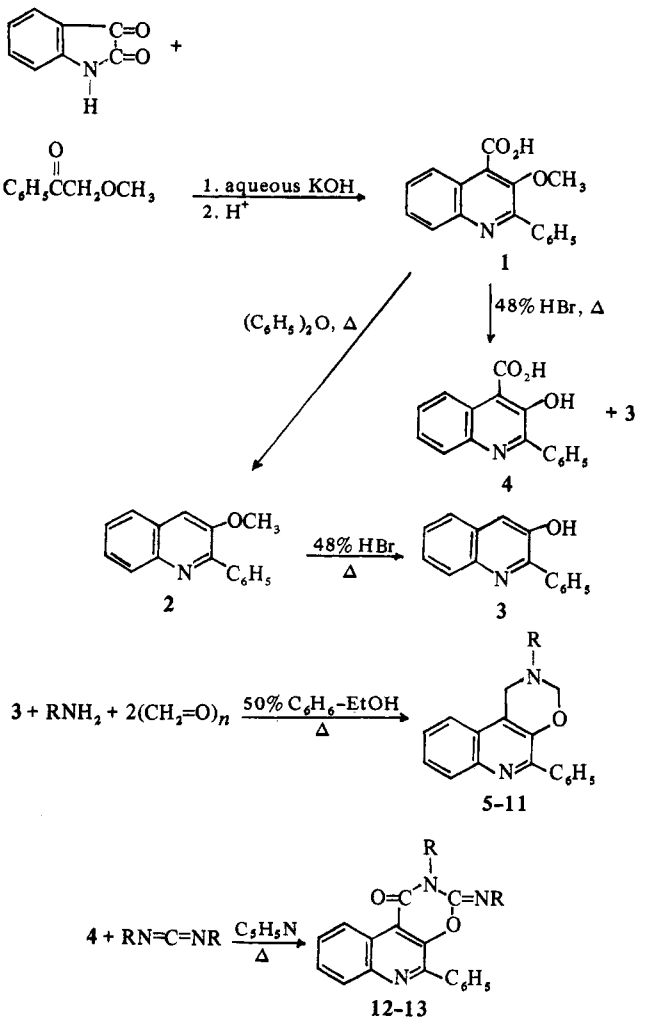
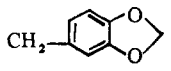
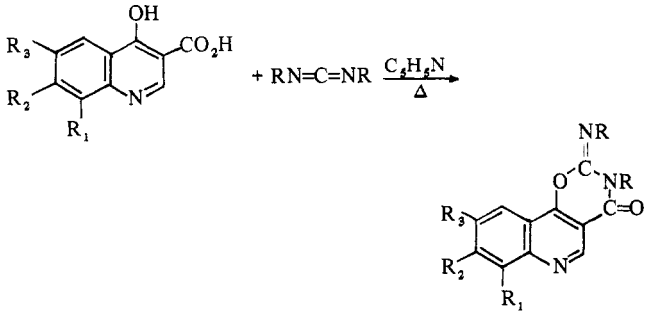


Table I. Chemical and Analytical Data for 2-Substituted 2,3-Dihydro-5-phenyl-1*H*-1,3-oxazino[6,5-*c*]quinolines

Compd no.	R	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
5	$CH_2C_6H_5$	47	131-132	EtOH	$C_{24}H_{20}N_2O$	C, H, N
6		27	153-155	EtOH	$C_{25}H_{20}N_2O_3$	C, H, N
7	$CH_2C_6H_4$-*m*-Cl	35	124-126	EtOH	$C_{24}H_{19}N_2OCl$	C, H, N, Cl
8	$CH_2C_6H_4$-*p*-Cl	55	198-199	$CHCl_3$-EtOH	$C_{24}H_{19}N_2OCl$	C, H, N
9	$CH_2C_6H_4$-*p*-CH_3	43	147-149	EtOH	$C_{25}H_{22}N_2O$	C, H, N
10	$CH_2C_6H_4$-*m*-CH_3	49	128-130	EtOH	$C_{25}H_{22}N_2O$	C, H, N
11	$-C_6H_2$-3,4,5-OCH_3	62	189-190.5	EtOAc	$C_{26}H_{24}N_2O_4$	C, H, N

[a] Analytical results were within 0.3% of the theoretical values.

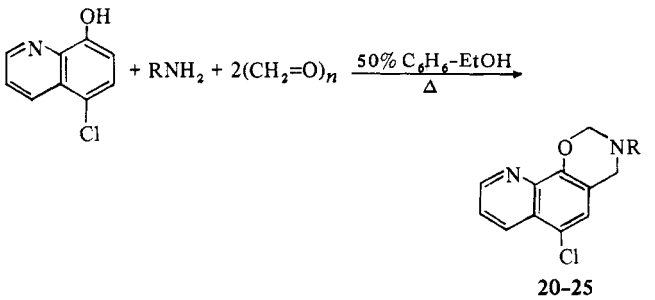
Scheme II



14-19

5-Chloro-8-hydroxyquinoline, which is commercially available, was treated with paraformaldehyde and various amines in refluxing 50% benzene-ethanol solution to yield 3-substituted 6-chloro-3,4-dihydro-2*H*-pyrido[3,2-*h*]-1,3-benzoxazines **20-25** (Table IV), as shown in Scheme III.

Scheme III

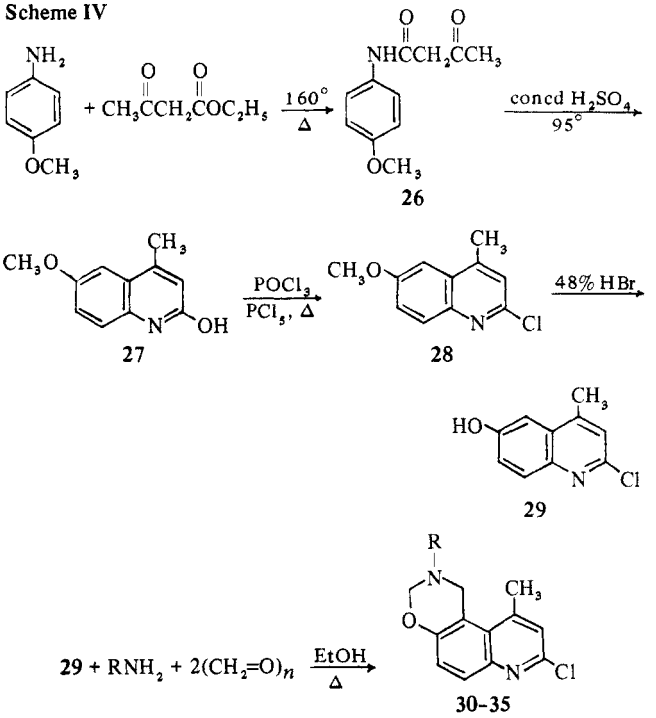


20-25

The reaction of ethyl acetoacetate with *p*-anisidine afforded *p*-acetoacetanisidine **(26)**. Ring closure in concentrated sulfuric acid gave 6-methoxy-4-methylquinolin-2-ol **(27)**. Compound **27** was treated with phosphorus oxychloride and phosphorus pentachloride to give 2-chloro-6-methoxy-4-methylquinoline **(28)** which was demethylated to 2-chloro-6-hydroxy-4-methylquinoline **(29)** with 48% hydrobromic acid. Compound **29** was treated with paraformaldehyde and various amines in refluxing ethanol to give 2-substituted 8-chloro-2,3-dihydro-10-methyl-1*H*-pyrido[3,2-*f*]-1,3-benzoxazines **30-35** (Table V), as shown in Scheme IV.

In this series of reactions, ring closure occurred only in

Scheme IV



30-35

Table II. Chemical and Analytical Data for 2- and 3-Substituted 2,3-Dihydro-5-phenyl-1*H*-1,3-oxazino[6,5-*c*]quinolin-1-ones

Compd no.	R	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
12	C_6H_{11}	53	173-174	CCl_4	$C_{29}H_{31}N_3O_2$	C, H, N
13	$(CH_3)_2CH$	20	94-95	Et_2O-petroleum ether[b]	$C_{23}H_{23}N_3O_2$	C, H, N

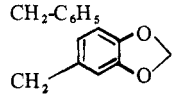
[a] Analytical results were within 0.3% of the theoretical values. [b] Bp 60-110°.

Table III. Chemical and Analytical Data for 2- and 3-Substituted 2,3-Dihydro-4*H*-1,3-oxazino[5,6-*c*]quinolin-4-ones

Compd no.	R	R_1	R_2	R_3	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
14	C_6H_{11}	CF_3	H	H	51	200-201	Et_2O	$C_{24}H_{26}N_3O_2F_3$	C, H, N, F
15	C_6H_{11}	H	OCH_3	H	81	205-206	Et_2O	$C_{24}H_{29}N_3O_3$	C, H, N
16	C_6H_{11}	H	H	Cl	43	235-235.5	1. Et_2O, 2. EtOH	$C_{23}H_{26}N_3O_2Cl \cdot H_2O$	C, H, N, Cl
17	C_6H_{11}	H	H	NO_2	67	240-241	1. Et_2O, 2. EtOH	$C_{23}H_{26}N_4O_4$	C, H, N
18	C_6H_{11}	H	H	NH_2	94	248-249	EtOH-H_2O	$C_{23}H_{28}N_4O_2$	C, H, N
19	$(CH_3)_2CH$	H	H	Cl	75	140-141	EtOH	$C_{17}H_{18}N_3O_2Cl$	C, H, N, Cl

[a] Analytical results were within 0.3% of the theoretical values.

Table IV. Chemical and Analytical Data for 3-Substituted 6-Chloro-3,4-dihydro-2*H*-pyrido[3,2-*h*]-1,3-benzoxazines

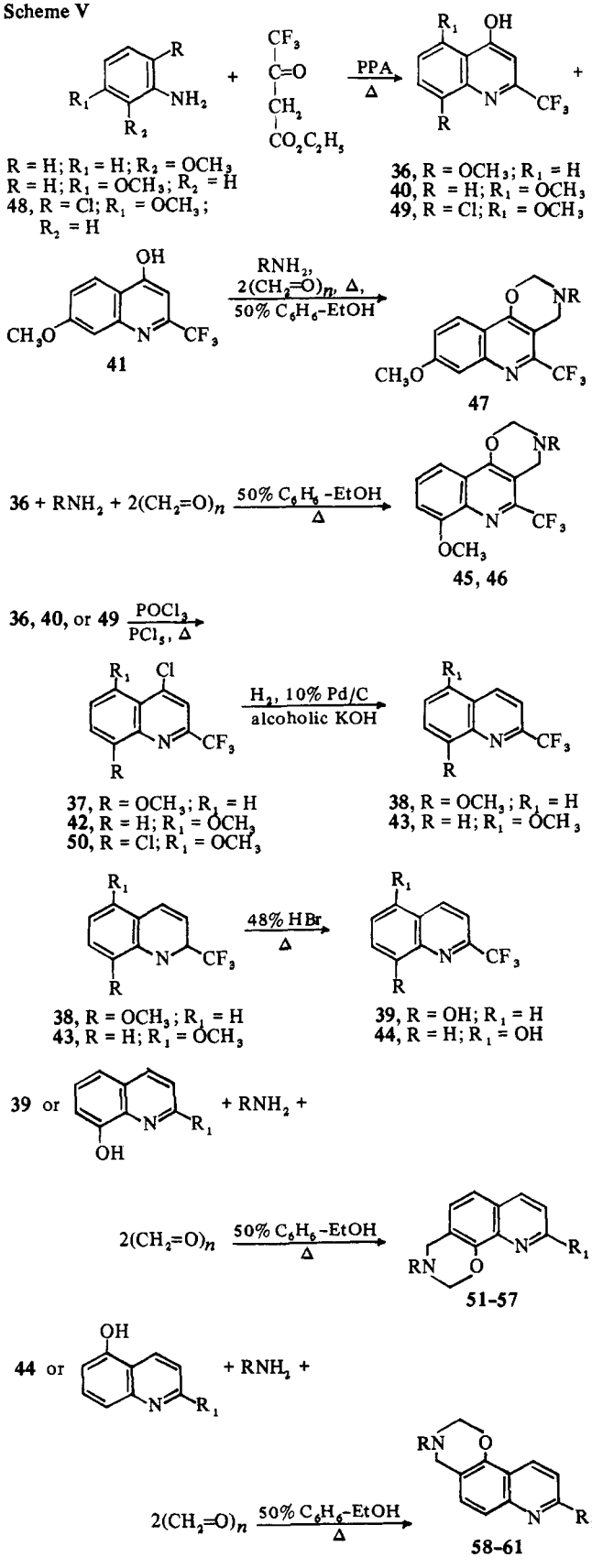
Compd no.	R	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
20	CH_2-C_6H_5	94	121-122	CCl_4-hexane	$C_{18}H_{15}N_2OCl$	C, H, N, Cl
21		97	153-155	EtOH	$C_{19}H_{15}N_2O_3Cl$	C, H, N, Cl
22	$CH_2C_6H_4$-*p*-Cl	52	149-151	Acetone	$C_{18}H_{14}N_2OCl_2$	C, H, N, Cl
23	$CH_2C_6H_4$-*m*-Cl	52	166-167	Acetone	$C_{18}H_{14}N_2OCl_2$	C, H, N, Cl
24	$CH_2C_6H_4$-*p*-CH_3	28	118-120	Acetone	$C_{19}H_{17}N_2OCl$	C, H, N, Cl
25	$CH_2C_6H_4$-*m*-CH_3	22	91-94	Et_2O	$C_{19}H_{17}N_2OCl$	C, H, N; Cl[b]

[a] Analytical results were within 0.3% of the theoretical values. [b] Cl: calcd, 10.91; found, 10.54.

the direction indicated; isomeric products were not detected. The structure assignments for compounds **30–35** were supported by their nmr spectra which showed an ortho coupling constant of ~9 cps for the protons in the 5 and 6 positions.

The condensation of ethyl trifluoroacetoacetate with *o*-anisidine in polyphosphoric acid yielded 8-methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (**36**). This compound was converted to 2-(trifluoromethyl)-8-hydroxyquinoline (**39**) by chlorination, reductive dehalogenation, and hydrolysis (Scheme V).

Scheme V



3-Substituted 3,4-dihydro-5-(trifluoromethyl)-7-methoxy-2*H*-1,3-oxazino[5,6-*c*]quinolines **45** and **46** were prepared from 8-methoxy-2-(trifluoromethyl)-4-hydroxyquinoline, paraformaldehyde, and amines (Table VI).

3-Substituted and 9-substituted 3,4-dihydro-2*H*-pyrido-[3,2-*h*]-1,3-benzoxazines **51–57** were synthesized from 2-(trifluoromethyl)-8-hydroxyquinoline (**39**) or 8-hydroxyquinoline, paraformaldehyde, and amines by a similar Mannich-type condensation (Table VII).

When *m*-anisidine was condensed with ethyl trifluoroacetoacetate under the same conditions as those used in the condensation of *o*-anisidine, both of the expected isomers, 7-methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (**41**) and 5-methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (**40**), were obtained in approximately equal amounts[4] (Scheme V). The reaction of compound **40** with phosphorus pentachloride and phosphorus oxychloride yielded 4-chloro-5-methoxy-2-(trifluoromethyl)quinoline (**42**). The reductive dehalogenation of **42** yielded 5-methoxy-2-(trifluoromethyl)quinoline (**43**) which was subsequently hydrolyzed to the corresponding hydroxy derivative **44**.

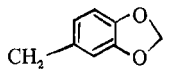
Compound **41** was treated with paraformaldehyde and *p*-chlorobenzylamine to give 3-(*p*-chlorobenzyl)-3,4-dihydro-5-(trifluoromethyl)-2*H*-1,3-oxazino[5,6-*c*]quinoline (**47**, Table VI).

Compound **44** underwent the usual Mannich-type reaction, affording 3- and 8-substituted 3,4-dihydro-2*H*-pyrido[2,3-*h*]-1,3-benzoxazines **58–61** (Table VIII). Compound **44** was also prepared from 2-chloro-5-methoxyaniline by using the same series of reactions. This scheme is discussed in detail in a previous paper.[4]

Biological Results. The antimalarial test results were provided by the Walter Reed Army Institute of Research. The tests were based upon the relative response of *Plasmodium berghei* malaria in mice[5] 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 6.1 days. Treated animals were kept 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. Compounds **1–3**, **5–12**, **14–25**, **30**, **32–34**, **36**, **40–44**, and **49–61** were so tested. All compounds were tested at a maximum dose of 640 mg/kg except for compounds **3**, **10**, **20**, and **25** (320 mg/kg) and compounds **60** and **61** (160 mg/kg). Compounds **18** and **30** increased the mean survival time of the test mice (IMST) by 2.9 (640 mg/kg) and 4.1 days (640 mg/kg), respectively. Their activities were approximately 20–30% of the activity of quinine sulfate which increases the mean survival time of the tested mice by 3.6 days at a dosage of 160 mg/kg. The IMST of all other compounds was less than 1 day with the exception of **17**, **33**, and **58**. At a dosage of 640 mg/kg, the IMST of these compounds was 1.3, 1.5, and 1.9 days, respectively. None of the compounds were toxic.

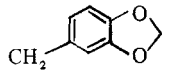
Compounds **11**, **15**, **30**, and **40** (100 mg/kg maximum dose); **1**, **7**, **18**, **21–23**, **33**, **37**, **38**, **45**, **46**, **51**, **52**, **56**, and

Table V. Chemical and Analytical Data for 2-Substituted 8-Chloro-2,3-dihydro-10-methyl-1*H*-pyrido[3,2-*f*]-1,3-benzoxazines

Compd no.	R	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
30	CH_2-C_6H_5	64	131–132	*b*	$C_{19}H_{17}N_2OCl \cdot H_2O$	C, H, N, Cl
31	CH_2-C_6H_4-*p*-Cl	27	172.5–173.5	EtOH	$C_{19}H_{16}N_2OCl_2 \cdot 0.5H_2O$	C, H, N
32	C_6H_{11}	53	123.5–124.5	EtOH[c]	$C_{18}H_{21}N_2OCl \cdot 0.5H_2O$	C, H, N, Cl
33	$(CH_2)_5CH_3$	25	80.5–81	EtOH	$C_{18}H_{23}N_2OCl \cdot 0.5H_2O$	C, H, N, Cl
34	$(CH_2)_2CH_3$	41	98–99.5	MeOH–H_2O[c]	$C_{15}H_{17}N_2OCl \cdot 0.5H_2O$	C, H, Cl; N[d]
35		28	215–216	EtOH–acetone	$C_{20}H_{17}N_2O_3Cl \cdot H_2O$	C, H, N, Cl

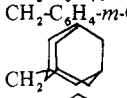
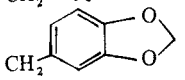
[a] Analytical results were within 0.3% of the theoretical values. [b] Purified by "dry-column" chromatography (silica gel, $CHCl_3$–hexane). [c] Purified by thin-layer chromatography (silica gel/$CHCl_3$) prior to recrystallization. [d] N: calcd, 9.80; found, 9.42.

Table VI. Chemical and Analytical Data for 3-Substituted 3,4-Dihydro-5-(trifluoromethyl)-2*H*-1,3-oxazino[5,6-*c*]quinolines

Compd no.	R	R_1	R_2	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
45	CH_2-C_6H_5	H	OCH_3	39	169–171	EtOH	$C_{20}H_{17}N_2O_2F_3$	C, H, N
46		H	OCH_3	41	187–188	EtOH	$C_{21}H_{17}N_2O_4F_3$	C, H, N
47	CH_2-C_6H_4-*p*-Cl	OCH_3	H	42	122–124	EtOH	$C_{20}H_{16}N_2O_2F_3Cl$	C, H, N

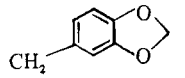
[a] Analytical results were within 0.3% of the theoretical values.

Table VII. Chemical and Analytical Data for 3-Substituted 3,4-Dihydro-9-(trifluoromethyl)-2*H*-pyrido[3,2-*h*]-1,3-benzoxazines

Compd no.	R	R_1	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
51	CH_2-C_6H_5	CF_3	50	129–131	EtOH	$C_{19}H_{15}N_2OF_3$	C, H, N
52	C_6H_{11}	CF_3	44	167–169	EtOH	$C_{18}H_{19}N_2OF_3$	C, H, N
53	CH_2-C_6H_4-*p*-Cl	CF_3	24	173–174	EtOH	$C_{19}H_{14}N_2OF_3Cl$	C, H, N
54	CH_2-C_6H_4-*m*-CH_3	CF_3	22	96–97	EtOH–H_2O	$C_{20}H_{17}N_2OF_3$	C, H, N
55		CF_3	47	152–155	EtOH–H_2O	$C_{23}H_{25}N_2OF_3$	C, H, N
56		CF_3	15	148–150	EtOH	$C_{20}H_{15}N_2O_3F_3$	C, H, N
57	CH_2-C_6H_5	H	18	104–105	EtOH–H_2O	$C_{18}H_{16}N_2O$	C, H, N

[a] Analytical results were within 0.3% of the theoretical values.

Table VIII. Chemical and Analytical Data for 3- and 8-Substituted 3,4-Dihydro-2*H*-pyrido[2,3-*h*]-1,3-benzoxazines

Compd no.	R	R_1	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses[a]
58	CH_2-C_6H_5	CF_3	43	83–85	EtOH–H_2O	$C_{19}H_{15}N_2OF_3$	C, H, N
59	CH_2-C_6H_4-*p*-Cl	CF_3	39	130–132	EtOH	$C_{19}H_{14}N_2OF_3Cl$	C, H, N
60		CF_3	33	87–90	EtOH	$C_{20}H_{15}N_2O_3F_3$	C, H, N
61	CH_2-C_6H_4-*p*-Cl	H	9	112–115	EtOH	$C_{18}H_{15}N_2OCl$	C, H, N

[a] Analytical results were within 0.3% of the theoretical values.

57 (120 mg/kg); **2**, **3**, **5**, **17**, **20**, **32**, **47**, **49**, **53**, **54**, and **59** (160 mg/kg); **25** and **58** (240 mg/kg); and **55** and **60** (320 mg/kg) were tested against *P. gallinaceum* parasite in birds but were found to be inactive. Only compound **5** was toxic.

Experimental Section

General Procedures. Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were carried out by Midwest Microlab, Ltd., Indianapolis, Ind. Analytical results (C, H, N, X) were within 0.3% of the theoretical values. Melting points, recrystallization solvents, percentage yields, and analytical data are given in Tables I–VIII. The structures assigned to all new compounds were supported by infrared spectra recorded on Perkin-Elmer 137 or 521 spectrophotometers and nuclear magnetic resonance spectra recorded on Varian A-60A or HA-100 spectrometers.

3-Methoxy-2-phenylquinoline-4-carboxylic Acid (1, Scheme I). Isatin (25 g, 0.17 mol) was added with stirring to a solution of potassium hydroxide (60 g, 0.93 mol) in 250 ml of water. When all of the solid dissolved, a solution of α-methoxyacetophenone (25.0 g, 0.17 mol) in 150 ml of absolute ethanol was added to it with stirring. The resulting mixture was heated under reflux for 4 hr. After the mixture cooled, the alcohol was removed *in vacuo*. The remaining suspension was diluted with 500 ml of water and acidified with glacial acetic acid. The solution thus obtained was cooled to induce crystallization of the product. The product was collected (44.8 g, 96.4% yield) and recrystallized from ethanol–water, affording colorless needles, mp 230.5–232°.

3-Methoxy-2-phenylquinoline (2, Scheme I). Compound **1** (10 g, 0.279 mol) was added slowly, in small portions, to 20 ml of diphenyl ether at 210°. Each addition produced vigorous carbon dioxide evolution. The diphenyl ether solution was cooled and treated with 300 ml of concentrated hydrochloric acid. The acid was added slowly with thorough mixing. The solid that formed was collected by filtration, washed with hexane, and dried to give 8.5 g of product (87.7% yield). The product was dissolved in 150 ml of water and 25 ml of acetic acid. The resulting solution was then treated with decolorizing carbon, heated on a steam bath for 1 hr, and filtered. Finally, the filtrate was made basic to litmus by the addition of 10% sodium hydroxide solution and cooled to induce crystallization (3.4 g, colorless solid, 40% yield, mp 73.5–75°).

3-Hydroxy-2-phenylquinoline (3, Scheme I). A mixture of **2** (1.0 g, 0.0043 mol) and 15 ml of 48% hydrobromic acid was heated under reflux for 7 hr. The resulting solution was poured onto 50 g of crushed ice causing the precipitation of a yellow solid. The suspension was first made basic with 10% sodium hydroxide solution to dissolve the solid and then was acidified with acetic acid to re-

precipitate it. The solid was collected by filtration and recrystallized from ethanol–water to afford the purified product (0.7 g, colorless crystals, mp 225–227°, 74% yield).

3-Hydroxy-2-phenylquinoline-4-carboxylic Acid (4, Scheme I). Compound **1** (32.7 g, 0.117 mol) was refluxed in 250 ml of 48% hydrobromic acid for 4 hr. The solution was allowed to stand overnight. The solid that formed was first dissolved in 10% sodium hydroxide solution and then reprecipitated with glacial acetic acid. This solid was a mixture of compounds **3** and **4**. The two products were separated by repeated fractional crystallization from ethanol. Compound **3** was obtained from the first fraction (8.12 g, 31% yield), R_f 0.92 (No. 1 Whatman paper, 1-butanol–water, 86:14); compound **4** was obtained from the second fraction (12.87 g, 41% yield), R_f 0.59 (No. 1 Whatman paper, 1-butanol–water, 86:14), yellow solid, mp 218–219°. When the sodium hydroxide treatment was omitted, the precipitate consisted exclusively of compound **4**. Evaporation of the hydrobromic acid filtrate yielded a mixture of **4** and 3-hydroxy-2-phenylquinoline hydrobromide, mp 292–294°, $C_{15}H_{11}NO \cdot HBr$. These compounds could be separated by fractional crystallization from ethanol to yield additional product.

2-Substituted 2,3-Dihydro-5-phenyl-1*H*-1,3-oxazino[6,5-*c*]quinolines 5–11 (Table I). These compounds were synthesized by the following general procedure described in detail for the preparation of 2,3-dihydro-5-phenyl-2-piperonyl-1*H*-1,3-oxazino[6,5-*c*]quinoline **(6)**. A mixture of paraformaldehyde (0.54 g, 0.018 mol), piperonylamine (1.37 g, 0.009 mol), absolute ethanol (40 ml), and benzene (40 ml) was heated under reflux for 2 hr. A solution containing compound **3** (2.0 g, 0.009 mol) in 80 ml of warm ethanol was then added to the refluxing mixture several milliliters at a time. The resulting solution was heated under reflux for an additional 17 hr. The solvent was then removed under reduced pressure. The tan solid residue was recrystallized from absolute ethanol, using decolorizing carbon, to afford the pure, colorless product.

2- and 3-Substituted 2,3-Dihydro-5-phenyl-1*H*-1,3-oxazino[6,5-*c*]quinolin-1-ones 12 and 13 (Table II). These compounds were synthesized by the following general procedure described in detail for the preparation of 2-cyclohexyl-3-(cyclohexylimino)-2,3-dihydro-5-phenyl-1*H*-1,3-oxazino[6,5-*c*]quinolin-1-one **(12)**. Compound **4** (2.653 g, 0.01 mol) was added to a solution of dicyclohexylcarbodiimide (8.25 g, 0.04 mol) in 50 ml of dry pyridine (distilled from calcium hydride). The reaction mixture was allowed to stand for 2 days. The precipitate of dicyclohexylurea was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was triturated with carbon tetrachloride. Insoluble material was removed by filtration. The filtrate was reduced in volume and treated with petroleum ether (bp 60–110°) to induce precipitation of the desired product.

2- and 3-Substituted 2,3-Dihydro-4*H*-1,3-oxazino[5,6-*c*]quinolin-4-ones 14–17 and 19 (Table III). These compounds were synthesized by the following general procedure described in detail for the preparation of 3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-9-nitro-4*H*-1,3-oxazino[5,6-*c*]quinolin-4-one **(17)**. 4-Hydroxy-6-nitroquinoline-3-carboxylic acid (4.68 g, 0.02 mol) was added to dicyclohexylcarbodiimide (12.36 g, 0.06 mol) in 200 ml of pyridine. The reaction mixture was heated under reflux for 0.5 hr. It was then allowed to stand at room temperature for 2 days. The pyridine was removed under reduced pressure and the residue was triturated with a large volume of diethyl ether. The insoluble dicyclohexylurea was removed by filtration. The filtrate was reduced in volume to induce crystallization of the product.

9-Amino-3-cyclohexyl-2-(cyclohexylimino)-2,3-dihydro-4*H*-1,3-oxazino[5,6-*c*]quinolin-4-one (18, Table III). Compound **17** (2.588 g, 0.00605 mol) was suspended in 100 ml of ethanol containing 0.65 g of 10% palladium-on-carbon catalyst. The mixture was shaken in a low-pressure Parr hydrogenator at room temperature for 16 hr. The catalyst was removed by filtration and the ethanolic filtrate was reduced in volume to induce crystallization of the product. The resulting yellow solid was collected by filtration. Additional product was obtained by diluting the filtrate with distilled water.

3-Substituted 6-Chloro-3,4-dihydro-2*H*-pyrido[3,2-*h*]-1,3-benzoxazines 20–25 (Table IV). These compounds were synthesized by the following general procedure described in detail for the preparation of 6-chloro-3-(*p*-chlorobenzyl)-3,4-dihydro-2*H*-pyrido[3,2-*h*]-1,3-benzoxazine **(22)**. Paraformaldehyde (0.66 g, 0.022 mol) and *p*-chlorobenzylamine (1.56 g, 0.011 mol) were heated under reflux for 2 hr with 30 ml of absolute ethanol and 30 ml of benzene. A solution containing 5-chloro-8-hydroxyquinoline (2.0 g, 0.011 mol) in 50 ml of hot ethanol was then added to the reaction mixture a few milliliters at a time. After an additional reflux period of 20 hr, the solvent was removed under reduced pressure. The green residue was dissolved in acetone and the solution was filtered to remove insoluble impurities. The filtrate was then cooled to induce crystallization of the product.

***p*-Acetoacetanisidine (26, Scheme IV).** Recrystallized *p*-anisidine (100 g, 0.81 mol) was added over a period of 30 min to ethyl acetoacetate (400 ml, 3.1 mol) at 160°. The mixture was held at this temperature for 30 min and then was cooled at 0° overnight. The crystals that formed were collected, washed with hexane, and dried to give 116 g of crude product (70% yield). A small portion of this solid was recrystallized from ethanol to afford a pure sample of product, mp 115–116° (lit.[6] mp 116–117°).

2-Methyl-6-methoxyquinolin-4-ol (27, Scheme IV). Compound **26** (116 g, 0.57 mol) was added to 80 ml of concentrated sulfuric acid over a period of 30 min. The temperature of the reaction mixture was maintained just below 35° with an ice–water bath. The mixture was then heated, with stirring, to approximately 90°, at which point vigorous gas evolution ensued. After the reaction subsided, the temperature of the mixture was held at 95° for 1 hr. It was then poured with stirring into 450 ml of ice water. The green crystals that formed were collected, washed with water, and then suspended in 200 ml of ice–water. The suspension was treated with ammonium hydroxide until the solution was neutral. The solid material was collected by filtration and dried to give 70 g of product, 70% yield. The product was purified by recrystallizing it from methanol, mp 273–274°, $C_{11}H_{11}NO_2$.

2-Chloro-6-methoxy-4-methylquinoline (28, Scheme IV). Compound **27** (5 g, 0.0265 mol), phosphorus pentachloride (4.3 g, 0.0206 mol), and phosphorus oxychloride (10 g, 0.0651 mol) were heated under reflux for 2 hr. The mixture was cooled and stirred with 215 ml of ice water. It was then allowed to stand overnight. The solid which formed was collected and recrystallized from ethanol to give 45.2 g of colorless product, 87% yield, mp 143.5–144.5°, $C_{11}H_{10}ClNO$.

2-Chloro-6-hydroxy-4-methylquinoline (29, Scheme IV). Compound **28** (4.18 g, 0.0201 mol) was heated under reflux for 4 hr with 40 ml of 48% hydrobromic acid. The reaction mixture was then allowed to stand overnight at room temperature. The precipitate that formed was collected by filtration and then suspended in water. The suspension was made basic with sodium carbonate and allowed to stand overnight. The remaining solid that formed was collected by filtration and recrystallized from ethanol–water to give 3.35 g (82%) of the colorless product, mp 194–196°, $C_{10}H_8NO \cdot 0.5H_2O$.

2-Substituted 8-Chloro-2,3-dihydro-10-methyl-1*H*-pyrido[3,2-*f*]-1,3-benzoxazines 30–35 (Table V). These compounds were synthesized by the following general procedure described in detail for the preparation of 2-benzyl-8-chloro-2,3-dihydro-10-methyl-1*H*-pyrido[3,2-*f*]-1,3-benzoxazine **(30)**. Benzylamine (1.440 g, 0.0134 mol) was added to a suspension of paraformaldehyde (0.801 g, 0.0267 mol) in 100 ml of ethanol. The mixture was heated under reflux for 2 hr. 2-Chloro-6-hydroxy-4-methylquinoline hemihydrate **(29,** 2.71 g, 0.0133 mol) was added to the mixture and it was refluxed for another 22 hr. The solution was concentrated and treated with diethyl ether. Crystals of unreacted starting material formed after 1 day and were removed by filtration. The filtrate was evaporated to dryness and the residue was then recrystallized from diethyl ether–petroleum ether (bp 60–110°) to give the desired product. An analytical sample was prepared by chromatographing the solid (dry-column chromatography, silica gel, chloroform–*n*-hexane, 50:50) and then treating it with diethyl ether.

8-Methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (36, Scheme V). The synthesis of this compound was based upon a method developed by Staskun and Israelstam.[7] Redistilled *o*-anisidine (20 g, 0.162 mol) and 150 ml of polyphosphoric acid were stirred at 100°. Ethyl trifluoroacetoacetate (31.9 g, 0.170 mol) was added dropwise to this mixture over a period of 15 min. After being stirred for 3 hr at room temperature, the entire mixture was poured into 2500 ml of ice–water. It was then stirred at room temperature overnight. The solid that formed was collected by filtration and dried to give 27 g of crude product (68% yield). This solid was purified by recrystallization from 95% ethanol and distilled water, mp 163–164°, $C_{11}H_8F_3NO_2$.

4-Chloro-8-methoxy-2-(trifluoromethyl)quinoline (37, Scheme V). The synthesis of this compound was based upon a procedure developed by Snyder, *et al.*[8] Phosphorus pentachloride (18.3 g, 0.88 mol) and phosphorus oxychloride (41 g, 0.27 mol) were added to compound **36** (20 g, 0.082 mol) in small portions over a period of 30 min. The mixture was stirred vigorously during this addition. It was then heated under reflux for 2 hr, cooled, and poured into 2500 ml of ice–water. The resulting solution was stirred overnight. The solid that formed was collected by filtration to give 19 g (89% yield) of product. It was further purified by recrystallization from 95% ethanol, mp 91–92°, $C_{11}H_7ClF_3NO$.

8-Methoxy-2-(trifluoromethyl)quinoline (38, Scheme V). The reductive dehalogenation of compound **37** was based upon a procedure used for the hydrogenolysis of 3-halo-6,8-dimethoxyisoquinolines.[9] Compound **37** (13 g, 0.049 mol) and 2 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 low-pressure Parr hydrogenator at room temperature until the theoretical amount of hydrogen was consumed. The catalyst was removed by filtration and the filtrate was concentrated on a rotary evaporator to give a yellow oil. The oil was dissolved in 40 ml of acetone and then poured into 2500 ml of ice–water. The solution was stirred overnight. The solid that formed was collected by filtration and purified by recrystallization from ethanol–water, 8 g, 71% yield, mp 90–92°, $C_{11}H_8F_3NO$.

2-(Trifluoromethyl)-8-hydroxyquinoline (39, Scheme V). Compound **38** (9 g, 0.039 mol) was refluxed in 90 ml of 48% hydrobromic acid for 6 hr. The reaction mixture was then poured into 1500 ml of ice–water and stirred overnight. The colorless solid that formed (6 g, 71% yield) was collected and recrystallized from ethanol–water, mp 48–49°.

5-Methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (40) and 7-Methoxy-2-(trifluoromethyl)-4-hydroxyquinoline (41, Scheme V). *m*-Anisidine (20 g, 0.16 mol) was added slowly to 150 ml of polyphosphoric acid. The resulting mixture was heated to 80°. Ethyl trifluoroacetoacetate (31.9 g, 0.170 mol) was then added to the mixture in small portions with vigorous stirring over a period of 20 min. After 2.5 hr at 100°, the flask was cooled and its contents were poured into 2500 ml of ice–water. The resulting mixture was stirred overnight. The precipitate that formed was collected by filtration, dried, and recrystallized from absolute ethanol to give 27 g of an isomeric mixture, mp 200–213°. The components of the mixture were separated by dry-column chromatography using a 2 × 24 in. column filled with 250 g of Woelm silica gel. The column was eluted with chloroform. The first fractions (3 × 500 ml) were collected and evaporated *in vacuo* to afford pure **40** (12.3 g, 31% yield), mp 131–132°. The column was next eluted with a 50:50 mixture of chloroform and absolute ethanol (4 × 400 ml). After the removal of solvent, these fractions afforded 17.2 g (43.5% yield) of **41**, mp 255–256°, $C_{11}H_8F_3NO_2$.

4-Chloro-5-methoxy-2-(trifluoromethyl)quinoline (42, Scheme V). Phosphorus pentachloride (5.49 g, 0.026 mol) and phosphorus oxychloride (12.3 g, 0.080 mol) were alternately added to compound **40** (6 g, 0.025 mol) in small portions over a period of 20 min. The reaction mixture was processed as described for compound **37** to give 5.8 g (91% yield) of the desired product, **42**, mp 92–94°, $C_{11}H_7ClF_3NO$.

5-Methoxy-2-(trifluoromethyl)quinoline (43, Scheme V). The reductive dehalogenation of compound **42** was carried out as described for compound **38.** The resulting solid was recrystallized from ethanol to give 2.5 g (52% yield) of product, mp 60–61°, $C_{11}H_8F_3NO$.

2-(Trifluoromethyl)-5-hydroxyquinoline (44, Scheme V). Compound **43** (15 g, 0.066 mol) and 150 ml of 48% hydrobromic acid were treated as described for compound **39.** The solid thus obtained was recrystallized from ethanol–water to give 12 g (85% yield) of product, **44**, mp 198–201°, $C_{10}H_6F_3NO$.

3-Substituted 3,4-Dihydro-5-(trifluoromethyl)-2*H*-1,3-oxazino[5,6-*c*]quinolines 45–47 (Table VI). These compounds were prepared from the corresponding substituted 4-hydroxyquinolines **36** and **41** using the general procedure described for the preparation of 2,3-dihydro-5-phenyl-2-piperonyl-1*H*-1,3-oxazino[6,5-*c*]quinoline **(6).**

3-Substituted 3,4-Dihydro-9-(trifluoromethyl)-2*H*-pyrido[3,2-*h*]-1,3-benzoxazines 51–57 (Table VII). These compounds were synthesized by the following general procedure described in detail for the preparation of 3-benzyl-3,4-dihydro-9-(trifluoromethyl)-2*H*-pyrido[3,2-*h*]-1,3-benzoxazine **(51).** Benzylamine (0.506 g, 0.004 mol), paraformaldehyde (0.282 g, 0.009 mol), and 60 ml of 50% benzene–ethanol were heated for 2 hr under reflux. To this was slowly added a solution of compound **39** (1 g, 0.004 mol) in 20 ml of absolute ethanol. The resulting mixture was heated under reflux for 9 hr. It was then cooled and evaporated *in vacuo* to afford a yellow oil. The oil was treated with decolorizing carbon and recrystallized from absolute ethanol.

3- and 8-Substituted 3,4-Dihydro-2*H*-pyrido[2,3-*h*]-1,3-benzoxazines 58–61 (Table VIII). These compounds were synthesized by the following general procedure described in detail for the preparation of 3-(*p*-chlorobenzyl)-3,4-dihydro-8-(trifluoromethyl)-2*H*-pyrido[2,3-*h*]-1,3-benzoxazine **(59).** Paraformaldehyde (0.28 g, 0.009 mol), *p*-chlorobenzylamine (0.66 g, 0.004 mol), and 40 ml of 50% ethanol–benzene were heated under reflux for 2 hr. Compound **44** (1 g, 0.004 mol) was added to the mixture and it was heated under reflux for an additional 26 hr. The solvent was removed *in vacuo* and the viscous material which remained was crystallized from ethanol to yield compound **59.**

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3,4-Dihydroisocarbostyril and 1,2,3,4-Tetrahydroisoquinoline Derivatives of Ephedrine

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3,4-Dihydroisocarbostyril and 1,2,3,4-tetrahydroisoquinoline derivatives of ephedrine were synthesized and screened for central nervous system activity in the mouse. Some of these compounds prevented reserpine ptosis, potentiated *d*-amphetamine toxicity, prolonged hexobarbital sleep time, and/or prevented hydrochloric acid writhing in mice.

Many heterocyclic derivatives of ephedrine and norephedrine have been synthesized and tested for biological activity. For example, morpholine, 2-oxazoline, oxazolidine, di- and tetrahydro-1,3,4-oxadiazines, 2-thiazoline, thiazolidine, dihydro-1,3,4-thiadiazine, tetrahydro-*as*-triazine, and imidazolidine derivatives have been reported.[1] Many of these compounds possess interesting biological activity.[1] For this

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