# Studies with Antiinflammatory Oxindolecarboxanilides

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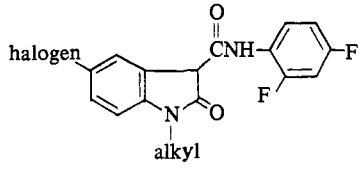
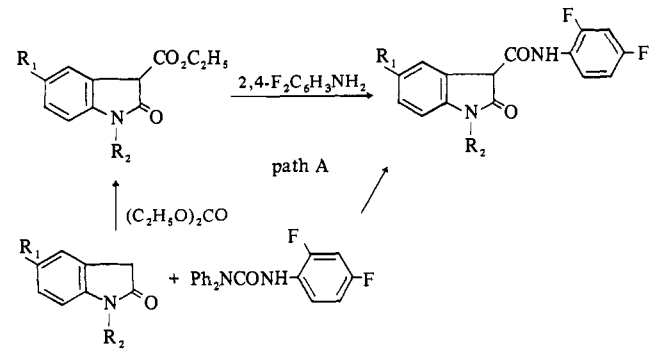
Two procedures for preparing 3-oxindolecarboxanilides are described. 2',4'-Difluorocarboxanilides of this series have potent antiinflammatory activity in the carrageenan-induced rat foot edema test. Physiochemical properties are reported and discussed in terms of relationship to antiinflammatory activity (rats) and plasma half-life (dogs).

Introduction of a carboxanilide moiety into various heterocyclic ring systems has been shown to lead to compounds with potent antiinflammatory activity in laboratory animals. Previous publications have described the antiinflammatory properties of carboxanilides of 1,3(2*H*,4*H*)-dioxoisoquinoline,[1] 3-oxo-2*H*-1,2-benzothiazine 1,1-dioxide,[2] and 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide.[3,4] Preparation of some carboxanilides of the oxindole ring system and description of their antiinflammatory activities and plasma half-lives form the basis of this report. In the earlier studied ring systems, hydroxylation at the 4 position of the carboxanilide substituent was shown to be the major route of metabolism, both in animals and man.[5,6] It has been reported[7] that *N*-alkyloxindoles are metabolized both by N-dealkylation and by hydroxylation at the 5 position of the oxindole ring system. The studies to be reported, therefore, examined the importance of N-alkylation and 5-halogenation in a series of 2',4'-difluorooxindole-3-carboxanilides (I), with respect to antiinflammatory potency and plasma half-life.




I

**Chemistry.** Two synthesis methods were employed in the preparation of the 3-oxindolecarboxanilides shown in Table I. The first, path A, comprised condensation of the appropriate 5-substituted 1-alkyloxindole with diethyl carbonate, followed by aminolysis of the intermediate ester with 2,4-difluoroaniline in xylene. The second preparative

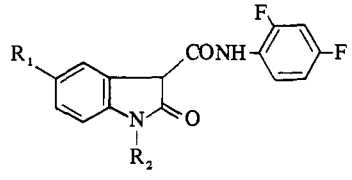



route, path B, utilized the reaction of the requisite oxindole with *N*,*N*-diphenyl-*N'*-(2,4-difluorophenyl)urea and sodium hydride in hexamethylphosphoramide and is a modification of a reaction employed in the synthesis of sulfonylureas.[8]

While several 1-alkyl-5-substituted oxindoles were commercially available or their preparation was reported in the chemical literature, a few (Table II) were synthesized from known para-substituted *N*-alkylanilines *via* acylation with chloroacetyl chloride or bromoacetyl bromide followed by cyclization of the intermediate *N*-alkylhaloacetanilide with aluminum chloride. Since purification and characterization of the *N*-alkylhaloacetanilide offered little overall advantage, these intermediates were subjected to Friedel-Crafts cyclization as they were isolated from the acylation reaction.

**Pharmacology.** Antiinflammatory activity was assessed by inhibition of edema formation in the hind paw of the rat (Charles River CD strain, average wt 170 g, 6 rats/group) in response to a subplantar injection of carrageenan. The experimental procedure followed that of Winter, *et al.*[9] Edema formation was measured 3 hr after oral administration of test drug (in aqueous solution), indomethacin (in pH

Table I. *N*-Alkyl-2',4'-oxindole-3-carboxanilides




| No. | $R_1$ | $R_2$ | Path | Mp, °C | Crystn solvent | Formula[g] |
|---|---|---|---|---|---|---|
| 1 | H | $CH_3$ | A | 170-171 | *a* | $C_{16}H_{12}F_2N_2O_2$ |
| 2 | H | $C_2H_5$ | A | 148.5-149.5 | *a* | $C_{17}H_{14}F_2N_2O_2$ |
| 3 | H | *n*-$C_3H_7$ | A | 162-165 | *b* | $C_{18}H_{16}F_2N_2O_2$ |
| 4 | F | $CH_3$ | B | 163-164 | *b* | $C_{16}H_{11}F_3N_2O_2$ |
| 5 | F | $C_2H_5$ | B | 167-168 | *c* | $C_{17}H_{13}F_3N_2O_2$ |
| 6 | Cl | $CH_3$ | B | 204-205 | *d* | $C_{16}H_{11}ClF_2N_2O_2$ |
| 7 | Cl | $C_2H_5$ | B | 161-162 | *e* | $C_{17}H_{13}ClF_2N_2O_2$ |
| 8 | Cl | *n*-$C_3H_7$ | B | 122-123 | *f* | $C_{16}H_{11}ClF_2N_2O_2$ |
| 9 | Br | $CH_3$ | B | 211.5-213 | *d* | $C_{16}H_{11}BrF_2N_2O_2$ |
| 10 | Br | $C_2H_5$ | B | 155-156 | *b* | $C_{17}H_{13}BrF_2N_2O_2$ |

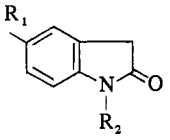
[a]Toluene–isopropyl ether. [b]Cyclohexane. [c]Ethanol–water. [d]Toluene. [e]Isopropyl ether. [f]Pentane. [g]All compounds were analyzed for C, H, and N.

9 buffer solution), or vehicle control. Each compound was compared with indomethacin at 3 or 4 dose levels, ranging between 1 and 33 mg/kg. Relative potencies were determined by comparison of the slopes of the least-squares fitted dose-response curves which did not deviate significantly from parallelism.

During determination of drug plasma half-lives, dogs were maintained in cages with free access to water. Drugs were administered intravenously (10 mg/kg) in aqueous solution. Blood samples were drawn (at hourly intervals for a period of 8 hr and after 24 hr) from the jugular vein into heparinized tubes; plasma was separated by centrifugation and stored at 4° until analyzed as follows: samples (2 ml) were acidified iwth 1 *N* NCl (0.5 ml) and extracted by shaking with *n*-heptane containing 1.5% isoamyl alcohol (5 ml). The layers were separated by centrifugation, and an aliquot (4 ml) of the organic layer was extracted with 0.1 *N* NaOH (5 ml). The optical density of the aqueous layer was determined at 250 and 310 mμ using a Beckman Model DU spectrophotometer. The ratio of the absorbances at 250 and 310 mμ for each of the oxindolecarboxanilides is essentially constant (0.7 ± 0.1), providing authentication of the material present in the sample. Samples of the organic extracts, when examined by paper chromatography [papers impregnated with $Me_2CO$-$HCONH_2$-AcOH (65:30:5) were run using PhH saturated with $HCONH_2$ as the mobile phase; compounds were visualized by examination of the dried papers under uv light], showed the presence only of the oxindolecarboxanilide administered. N-Dealkylated compounds were not extracted under the assay conditions. All assays were calibrated by carrying appropriate samples of known concentration (5-80 μg/ml) through the entire procedure. Lines were fitted (least-squares method) to the plasma concentrations. Extrapolation to zero time permitted calculation of the theoretical plasma concentration ($C_0$). For the oxindolecarboxanilides, $C_0$ fell between 56 and 83 μg/ml, equivalent to a volume of distribution of 120-180 ml/kg body weight, about that of plasma water.

Lipid/water partition ratios ($P_c$) were determined by equilibrating a solution of drug (100 μg/ml) in pH 7.4 buffer with an equal volume of octanol. After 30 min shaking at room temperature, the layers were separated and assayed as above. Potentiometric titrations were carried out in 2:1 dioxane-$H_2O$ (v/v) solvent using a Beckman Model G pH meter and standard 0.5 *N* NaOH; the apparent $pK_a$ values ($pK_a$*) correspond to the pH values at the half-neutralization point in these titrations.

Table II. *N*-Alkyloxindoles



| No. | $R_1$ | $R_2$ | Mp, °C | Crystn solvent | Formula[f] |
|---|---|---|---|---|---|
| 11 | H | $CH_3$ | 84.5-86 | *b* | $C_9H_9NO$[g] |
| 12 | H | $C_2H_5$ | *a* | | |
| 13 | H | $n$-$C_3H_7$ | 68-68.5 | *b* | $C_{11}H_{13}NO$ |
| 14 | F | $CH_3$ | 128-130 | *c* | $C_9H_8FNO$ |
| 15 | F | $C_2H_5$ | 110-113 | *c* | $C_{10}H_{10}FNO$ |
| 16 | Cl | $CH_3$ | 107-109 | *c* | $C_9H_8ClNO$[h] |
| 17 | Cl | $C_2H_5$ | 119-120 | *b* | $C_{10}H_{10}ClNO$ |
| 18 | Cl | $n$-$C_3H_7$ | 120-121 | *c* | $C_{11}H_{12}ClNO$ |
| 19 | Br | $CH_3$ | 133.5-135 | *d* | $C_9H_8BrNO$[i] |
| 20 | Br | $C_2H_5$ | 108-110 | *e* | $C_{10}H_{10}BrNO$[j] |

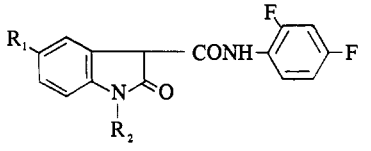
[a]Commercial material. [b]Hexane. [c]Cyclohexane. [d]Chloroform. [e]Isopropyl ether. [f]All new compounds were analyzed for C, H, and N. [g]Stollé, German Patent 355,673 [*Chem. Zentralbl.*, 2, 1065 (1921)]. [h]R. Huisgen, H. König, and A. Lepley, *Chem. Ber.*, 93, 1496 (1960). [i]M. Kisteneva, *Zh. Obshch. Khim.*, 26, 2019 (1956). [j]R. Stollé, R. Bergdoll, M. Luther, A. Auerhahn, and W. Wacker, *J. Prakt. Chem.*, 128, 1 (1930).

## Discussion

Table III shows the antiinflammatory activity and plasma half-lives of the oxindolecarboxanilides studied. No correlation exists between absolute antiinflammatory and lipophilicity; however, within three of the subseries, antiinflammatory activity tends to decrease with increasing lipophilicity.

Assuming that in this series of oxindolecarboxanilides, the routes of metabolism described[5-7] in analogous series are applicable, then N-dealkylation is the major variable contributing to determination of plasma half-life. In compounds **1-3**, alteration of the *N*-alkyl group ($CH_3$, $C_2H_5$, and $C_3H_7$, respectively) did not markedly change plasma half-life. By analogy with the studies of Beckett and

Table III. *N*-Alkyl-2',4'-difluoro-5-halooxindole-3-carboxanilides



| No. | $R_1$ | $R_2$ | $pK_a$* | $P_c$ (octanol/buffer) | Dog plasma half-life, hr[a] | Antiedema potency (indomethacin = 1) |
|---|---|---|---|---|---|---|
| 1 | H | $CH_3$ | 6.2 | 12.9 | 0.9, 1.6 | 0.9 |
| 2 | H | $C_2H_5$ | 6.3 | 24.6 | 1.0, 1.1 | 0.3 |
| 3 | H | $C_3H_7$ | 6.4 | 39.7 | 0.9, 1.2 | 0.3 |
| 4 | F | $CH_3$ | 5.2 | 21.5 | 1.5, 2.0 | 0.2 |
| 5 | F | $C_2H_5$ | 5.1 | 40.6 | | 0.1 |
| 6 | Cl | $CH_3$ | 5.0 | 42.3 | 3.3, 3.7 | 0.7 |
| 7 | Cl | $C_2H_5$ | 5.1 | 77.8 | 7.0, 8.0 | 0.5 |
| 8 | Cl | $C_3H_7$ | 4.7 | 97.9 | 10.6, 11.2 | 0.1 |
| 9 | Br | $CH_3$ | 4.7 | 60.3 | | 0.1 |
| 10 | Br | $C_2H_5$ | 4.9 | 128 | 11.0, 15.0 | 0.3 |
| | Indomethacin | | 7.0 | 0.3 | 0.3[b] | 1.0 |

[a]Determinations in two animals. [b]H. B. Hucker, A. G. Zacchei, S. V. Cox, D. A. Brodie, and N. H. R. Cantwell, *J. Pharm. Exp. Ther.*, 153, 237 (1966).

Morton,[7] this would indicate that either 5-hydroxylation is an important metabolic route or other elimination processes (urine and/or bile) are important. When the 5 position is blocked however, for example, by chlorine (compounds **6–8**), plasma half-life increases with the size of the *N*-alkyl group. While this is consistent with the observation of increasing difficulty in metabolic N-delkylation as size of the alkyl group increases,[10] it is also possible that the increasing partition ratio, noted as the alkyl group enlarged, contributed to facilitated renal reabsorption.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Analyses were carried out by the Physical Measurements Laboratory of Pfizer, Inc. Where analyses are indicated only by samples of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

1-Methyl-2',4'-difluorooxindole-3-carboxanilide (1, Path A). A mixture of 1.25 g (5.7 mmol) of ethyl 1-methyloxindole-3-carboxylate and 810 mg (6.27 mmol) of 2,4-difluoroaniline in 70 ml of xylene was heated to boiling in a distillation apparatus. After 60 ml of xylene had slowly been distilled, 20-ml portions of the solvent were added and distilled, and the addition and distillation procedure was repeated until three 20-ml portions had been collected. The product which crystallized on cooling was filtered, washed with $i$-$Pr_2O$, and dried: 1.27 g; mp 169–170°. The analytical sample was recrystallized from toluene-$i$-$Pr_2O$.

1-Methyl-2',4',5-trifluorooxindole-3-carboxanilide (4, Path B). To a slurry of 480 mg (10 mmol) of a 50% sodium hydride oil suspension in 40 ml of hexamethylphosphoramide was added 1.65 g (10 mmol) of 1-methyl-5-fluorooxindole. When the evolution of $H_2$ ceased, 3.57 g (11 mmol) of *N,N*-diphenyl-*N'*-(2,4-difluorophenyl)-urea was added and the mixture allowed to stir at room temperature overnight. The mixture was poured into $H_2O$ and rendered acid with dilute HCl, and the resulting precipitate was filtered, dried, and triturated with $i$-$Pr_2O$: 1.65 g; mp 148–152°. Recrystallization from cyclohexane provided the pure product, 1.0 g.

*N,N*-Diphenyl-*N'*-(2,4-difluorophenyl)urea. A mixture of 15.48 g (0.12 mol) of 2,4-difluoroaniline, 27.8 g (0.12 mol) of diphenylcarbamoyl chloride, and 24.28 g (0.24 mol) of TEA in 80 ml of EtOH was heated to reflux overnight. Most of the solvent was evaporated *in vacuo* and the residue partitioned between 400 ml of $H_2O$ and 250 ml of PhH. Following the extraction of the aqueous layer with additional PhH, the PhH layers were combined, successively washed with $H_2O$, dilute HCl, and saturated NaCl solution, and dried ($Na_2SO_4$). Removal of the solvent and recrystallization of the residue from $i$-$Pr_2O$ provided 18.5 g of product, mp 118–119°. *Anal.* ($C_{19}H_{14}F_2N_2O$) C, H, N.

Ethyl 1-Methyloxindole-3-carboxylate. To 150 ml of EtOH to which had been gradually added 2.28 g (0.099 g-atom) of Na metal was added 13.2 g (0.09 mol) of 1-methyloxindole followed by 13.8 g (0.117 mol) of $(EtO)_2CO$, and the mixture was heated to reflux overnight. The resulting precipitate was filtered and partitioned between 350 ml of 3 *N* HCl and 350 ml of $Et_2O$. The aqueous phase was extracted several times with $Et_2O$ and the organic extracts were combined and dried ($Na_2SO_4$). Removal of the solvent *in vacuo* provided 12.8 g of the desired compound as a tan solid, mp 107–108.5°. Recrystallization from 1:2 EtOH-$H_2O$ affords pure product, mp 107.5–108.5°. *Anal.* ($C_{12}H_{13}NO_3$) C, H, N.

Ethyl 1-Ethyloxindole-3-carboxylate. In a similar manner 27.4 g (0.17 mol) of 1-ethyloxindole and 26 g (0.22 mol) of $(EtO)_2CO$ were added separately to 250 ml of EtOH which had been reacted with 4.37 g (0.19 g-atom) of Na metal. The resulting solution, after refluxing overnight, was added to 1 l. of $H_2O$ containing 20 ml of 12 *N* HCl. The oily product, which crystallized on standing, was filtered and dried: 35.7 g; mp 48–51°. The product was used in subsequent reactions without further purification.

Ethyl 1-*n*-Propyloxindole-3-carboxylate. By an analogous procedure 58 g (0.33 mol) of 1-*n*-propyloxindole, 49.6 g (0.42 mol) of $(EtO)_2CO$, and 8.4 g (0.364 g-atom) of Na metal in 500 ml of EtOH were refluxed for 72 hr. The solution was poured into 3 l. of $H_2O$ containing 36 ml of 12 *N* HCl and the separated oil extracted with $Et_2O$. The $Et_2O$ was dried ($Na_2SO_4$) and concentrated to a dark oil (67 g), which was used without further purification.

1-Methyl-5-fluorooxindole. (a) *N*-Methyl-4-fluoroaniline. To a stirred solution of 111 g (1 mol) of 4-fluoroaniline in 500 ml of $Et_2O$ was added dropwise over *ca.* 1 hr 63 g (0.5 mol) of $Me_2SO_4$. The mixture was refluxed for 1.5 hr and cooled and the precipitate filtered. Following the addition of 300 ml of $Et_2O$ to the filtrate, the organic phase was washed with $H_2O$ and dried ($Na_2SO_4$). Evaporation of the $Et_2O$ *in vacuo* provided a dark, semisolid oil which on distillation gave 49.5 g of product, bp 71–75° (8 mm). *Anal.* ($C_7H_8FN$) C, H, N. This product was previously reported,[11] bp 79–80° (10 mm).

(b) *N*-Methyl-4-fluoro-α-bromoacetanilide. The above aniline, 49.5 g (0.395 mol), was added dropwise over 30 min to 40 g (0.198 mol) of bromoacetyl bromide in 250 ml of PhH, and the mixture was allowed to stir overnight. The precipitate was filtered and the PhH layer washed with dilute HCl, dried ($Na_2SO_4$), and concentrated *in vacuo*. The residue was triturated with toluene, the solids were filtered, and the filtrate was concentrated to an oil which on distillation gave 14.4 g of product, bp 163–167° (8 mm). *Anal.* ($C_9H_9BrFNO$) C, H, N.

(c) 1-Methyl-5-fluorooxindole. A mixture of 19.5 g (0.146 mol) of $AlCl_3$ and 14.4 g (0.058 mol) of the above acetanilide was heated to 220–225° in an oil bath and maintained at this temperature for 30 min. The mixture, while still hot, was poured onto 600 g of ice, and the resulting precipitate was filtered: 8.6 g; mp 116–126°. The analytical sample was recrystallized several times.

1-Ethyl-5-fluorooxindole. (a) *N*-Ethyl-4-fluoro-α-bromoacetanilide. *N*-Ethyl-4-fluoroaniline,[12] 88 g (0.63 mol), was added dropwise over 30 min to 63.5 g (0.315 mol) of bromoacetyl bromide in 500 ml of PhH. The mixture, after stirring overnight at room temperature, was washed with dilute HCl. The PhH phase was dried ($Na_2SO_4$) and concentrated to an oil, 64.7 g, which was used in subsequent reactions without further purification.

(b) 1-Ethyl-5-fluorooxindole. A mixture of 62.1 g (0.24 mol) of the above acetanilide and 56 g (0.42 mol) of $AlCl_3$ was heated to 220–225° for 30 min. The hot mixture was poured into 500 ml of ice and $H_2O$, and the resulting precipitate was filtered and dried: 40.3 g; mp 107–109°. The analytical sample was recrystallized twice.

1-Ethyl-5-chlorooxindole. (a) *N*-Ethyl-α,4-dichloroacetanilide. In a similar manner *N*-ethyl-4-chloroaniline,[12] 35.6 g (0.228 mol), was allowed to react with 12.9 g (0.114 mol) of chloroacetyl chloride in 350 ml of PhH. The crude product, 25.2 g, mp 68–70°, was cyclized without further purification.

(b) 1-Ethyl-5-chlorooxindole. In a manner analogous to those above, 15.9 g (0.69 mol) of the requisite acetanilide and 15.9 g (0.12 mol) of $AlCl_3$ were heated together at 180° for 2 hr. The precipitate which formed when the hot mixture was added to 250 ml of ice-$H_2O$ was filtered and dried: 13.7 g; mp 114–117°.

1-*n*-Propyl-5-chlorooxindole. A mixture of 26.2 g (0.1 mol) of *N*-*n*-propyl-α,4-dichloroacetanilide[13] and 26.6 g (0.2 mol) of $AlCl_3$ was heated at 200–210° in an oil bath for 2 hr. The hot reaction mixture was added to 500 g of ice, and the resulting semisolid precipitate was filtered and recrystallized from cyclohexane: 18.5 g; mp 119–121°.

1-*n*-Propyloxindole. (a) *N*-*n*-Propyl-α-bromoacetanilide. In a manner similar to analogous reactions, 100 g (0.5 mol) of bromoacetyl bromide and 135 g (1.0 mol) of *N*-*n*-propylaniline reacted in 1 l. of PhH provided, after work up, 125 g of the product as a yellow oil which was employed in subsequent reactions without further purification.

(b) 1-*n*-Propyloxindole. In a manner similar to previous procedures, a mixture of 100 g (0.39 mol) of the above acetanilide and 77 g (0.58 mol) of $AlCl_3$ when heated to 150° for 1 hr and 180° for 1 hr provided, after work up, 58 g of the crude product, mp 60–66°. The analytical sample was recrystallized twice.

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# Antimalarials. 1. Heterocyclic Analogs of N-Substituted Naphthalenebisoxazines

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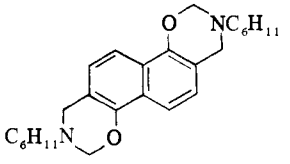
Several bisoxazines have been synthesized by a Mannich-type condensation involving substituted 4,7-, 4,8-, 5,8-, and 6,7-dihydroxyquinolines, 1,4- and 1,5-dihydroxynaphthalenes, and 5,8-dihydroxyquinoxalines. These compounds were evaluated for antimalarial activity against *Plasmodium berghei* in mice 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



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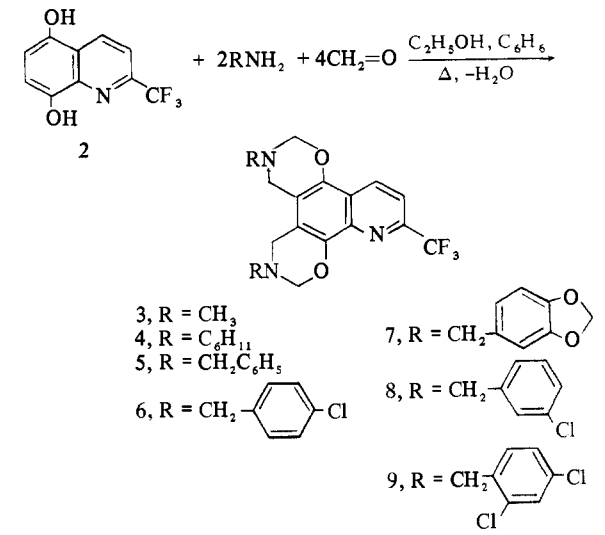
comparable to that of the corresponding aminomethylnaphthol, in this instance, 1,5-dihydroxy-2,6-bis(cyclohexylaminomethyl)naphthalene. This relationship suggested that aminomethylnaphthols might be *in vivo* degradation products of the oxazines. To extend this work we prepared several bisoxazine derivatives 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

Scheme I



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.

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-