fore evaluated further. It should be noted that without the $-CH_2P(O)(CH_3)_2$ moiety, the starting arylpiperazines leading to **1**, **4**, and **7** when tested in the SHR model at 100 mg/kg po caused death in all animals within 5 hr, preceeded by a short period of hyperexcitability and convulsions.

A dose–response study in the SHR revealed the MED's for **1**, **4**, and **7** to be 2.5, 10, and 25 mg/kg, respectively. For comparison, guanethidine was found to have an MED of 5.0 and hydralazine of 2.5 mg/kg.

All three compounds were examined in the acute anesthetized (pentobarbital) dog and only a short transitory hypotension was observed at iv doses up to 20 mg/kg.

Thus, although these compounds were uninteresting in lowering blood pressure in acute experiments on dogs, they did show a significant hypotensive effect in spontaneous hypertensive rats.

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Micro-Tech Laboratories, Inc., Skokie, Ill. Spectral data (ir and nmr) of new compounds were in accord with structure.

The arylpiperazines used as starting materials were purchased from Aldrich Chemical Co., Milwaukee, Wis.

General Dimethylphosphinylmethyl Alkylation Procedure. A stirred mixture of the arylpiperazine† (0.10 mol), chloromethyldimethylphosphine oxide[5] (0.11 mol), and triethylamine (0.11 mol) as HCl acceptor in 300 ml of C_6H_6 was refluxed under N_2 for 10–24 hr. The mixture was then filtered while hot to remove precipitated $Et_3N{\cdot}HCl$. The filtrate was concentrated to a small volume (*ca.* 50 ml), and work-up was continued as follows.

(1) If the crystalline product separated voluminously during concentration, it was filtered, washed with C_6H_6, dried, and recrystallized from the solvent indicated in Table I (compounds **1**, **4**, and **6**).

(2) If the product was very soluble in C_6H_6, the remainder of the solvent was removed *in vacuo* to a waxy crystalline solid which was triturated with ether or hexane, filtered, dried, and recrystallized (compounds **5** and **8**). Sometimes an oil was obtained which was induced to crystallize by scratching or freezing (compounds **3** and **9**).

(3) When a residual oil could not be solidified, it was dissolved in ether or EtOH and added to a cold 5 *N* solution of ethanolic HCl. The precipitated salt was filtered, washed with ether, dried, and recrystallized (compounds **2** and **7**).

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†The arylpiperazines leading to compounds 2–4 were purchased as the mono- or dihydrochloride salts requiring an additional 1 or 2 equiv of Et_3N in the alkylation procedure in order to liberate the piperazine base *in situ*.

Antimalarials. 3. Fluorenemethanols†

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The medicinal chemistry of compounds containing the fluorene nucleus continues to be of interest. Clinical studies of tilorone [2,7-bis[2-(diethylamino)ethoxy]-9-fluorenone dihydrochloride] as a broad-spectrum antiviral agent and antitumor agent have been reviewed.[1,2] Alkylaminoalkyl esters of fluorenone-2,7-dicarboxylic acid have been reported to be potent antiviral agents and interferon inducers.[3] Quaternary nitrogen-substituted choline ester derivatives of fluorene have neuromuscular blocking activity.[4] A series of 4-(3-alkylamino-2-hydroxypropoxy)-9-fluorenones have β-adrenergic blocking and antiarrythmic activity and inhibit blood platelet aggregation.[5,6] Fluorene-2-acetic acids and analogs are potent antiinflammatory agents.[7] In the botanical field attention has been drawn to the morphactins[8,9] which are synthetic growth regulators derived from fluorene-9-carboxylic acid.

Prior to the present work 11 nonhalogenated 2-fluorenemethanols had been tested as antimalarials[10] and weak activity observed in 2 of them; it was suggested[11] that "another position for the side chain might have been more advantageous." In addition to these, 16 other derivatives of fluorene, 9-fluorenone, and 9-fluorenol (none of them an aminoalkylmethanol) were described in the Wiselogle treatise;[12] none were active.

More recently 1-, 2-, 3-, and 4-aminofluorenes and halogenated derivatives were condensed with diphenic anhydride to give 32 diphenamic acids and the related imides. Weak antimalarial activity was observed in the single case of *N*-(2-fluorenyl)diphenimide.[13]

At the time our work began it was already apparent that a nitrogen-containing ring structure was not a necessary feature for high antimalarial activity; the phenanthrenemethanols were known to be among the most active antimalarials.[14,15]

Chemistry. The synthesis routes to the compounds listed in Table I involved conversion of the carboxyl group in the appropriate fluorene- or fluorenenonecarboxylic acid to the desired di-*n*-butylaminomethylmethanol side chain by the procedure used previously.[16] The syntheses of **1**, **4**, and **7** were uncomplicated. During the synthesis of **2** $NaBH_4$ reduction of bromomethyl 9-keto-4-fluorenyl ketone gave 9-hydroxy-4-fluorenylethylene oxide, the immediate precursor of **2**. However, during the analogous synthesis of **5** the reduction of bromomethyl 2,7-dichloro-9-keto-4-fluorenyl ketone gave a mixture of oxides containing 9-keto and 9-hydroxy groups, respectively. When the 9-hydroxy oxide was separated from the mixture and characterized we attempted to convert it to **5** in the usual way but obtained impure **6**. Because of this difficulty we made **5** by the sodium borohydride reduction of the free base of **6**. The 9-keto oxide precursor of **6** was easily obtained by simply allowing the borohydride reduction of the bromomethyl ketone to proceed in the presence of air. 9-Keto-4-fluorenylethylene oxide, the precursor of **3**, was made by oxidation of the 9-hydroxy oxide by manganese dioxide.[17]

When the conventional synthesis was applied to fluorene-9-carboxylic acid we were unable to prepare the nec-

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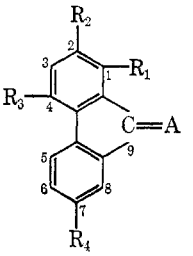
Table I. α-(*N*,*N*-Di-*n*-butylaminomethyl)fluorenemethanols



Compd	A	R_1[a]	R_2	R_3[a]	R_4	Mp, °C	Yield,[b] %	Formula	Analyses[c]
1	H, H	SC	H	H	H	144–150 dec	50	$C_{23}H_{31}NO \cdot HBr$	C, H, Br, N[d]
2	H, OH	H	H	SC	H	58–66 dec	55	$C_{23}H_{31}NO_2 \cdot HCl \cdot H_2O$	C, H, Cl, N[e]
3	O	H	H	SC	H	174–177 dec	83	$C_{23}H_{29}NO_2 \cdot HCl$	C, H, Cl, N[f]
4	H, H	H	H	SC	H	115–118 dec	82	$C_{23}H_{31}NO \cdot HCl$	C, H, Cl, N[f]
5	H, OH	H	Cl	SC	Cl	135–145 dec	59[g]	$C_{23}H_{29}Cl_2NO_2 \cdot HCl$	C, H, Cl, N[f]
6	O	H	Cl	SC	Cl	193–198 dec	65	$C_{23}H_{27}Cl_2NO_2 \cdot HCl$	C, H, Cl, N[f]
7	H, H	H	Cl	SC	Cl	99–103 dec[h]	75	$C_{23}H_{29}Cl_2NO \cdot HCl$	C, H, Cl, N[f]

[a] The symbol SC indicates $-CHOHCH_2N(n\text{-}C_4H_9)_2$. [b] Figures are for reaction of the oxide with di-*n*-butylamine. [c] Values for the elements indicated were within 0.4% of theroetical values. [d] HBr salt was precipitated from Et_2O solution of base. [e] Hygroscopic HCl salt precipitated from Et_2O solution of base. [f] HCl salt precipitated from dry Et_2O solution of base. [g] See Experimental Section for synthesis procedure. [h] When prepared in another laboratory the compound was also obtained with mp 168–171°. Both lower and higher melting forms gave the same oxalate salt, mp 104–105°, which on reconversion to the hydrochloride gave only the higher melting form, mp 171.0–172.5° (R. E. Olsen, Cordova Chemical Co., personal communication).

Table II. Antimalarial Activity[a]

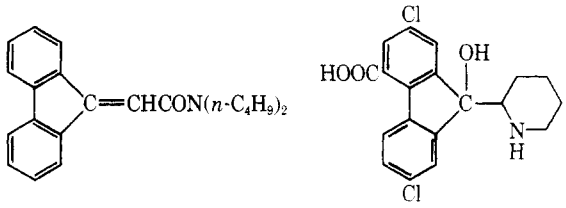
	Increase in mean survival time, days, and no. of cures (C) at dosage, mg/kg						
Compd[b]	10	20	40	80	160	320	640
5					7.3 active	11.3 active	15.1 active
6	5.1	8.1 active	10.5 active	12.9 active	2C	5C	
7	5.9	10.5 active	2C	5C	5C	5C	

[a] Test procedure was described in *J. Med. Chem.*, **11**, 1225 (1968). [b] Arabic numerals refer to compounds in Table I.

essary diazomethyl ketone intermediate. In an alternative synthesis ethyl fluorenylideneacetate[18] was hydrolyzed to fluorenylideneacetic acid[19,20] and the latter converted to I by a recently described procedure.[21] We were then unable to carry out a proposed hydroboration and reduction of I to the desired aminomethylmethanol.

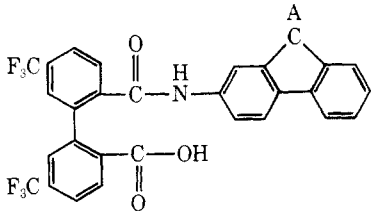
Compound II was prepared during an unsuccessful attempt to apply the Boykin reaction[22] to 2,7-dichlorofluorenone-4-carboxylic acid. The reaction of 2-pyridyllithium occurred at the 9-keto group rather than at the carboxyl group to give the 9-(2-pyridyl) precursor of II, from which II was obtained by reduction.

Because of the well-known enhancement of antimalarial activity by trifluoromethyl groups we planned to prepare fluorenemethanols containing these groups. For convenience we chose to start with the recently described[23] 5,5′-bis(trifluoromethyl)diphenic acid, which we prepared by an improved procedure. Unfortunately, we were unable to cyclize the acid to the desired 1,6-bis(trifluoromethyl)-fluorenone-4-carboxylic acid by any technique that did not also cause hydrolysis of the trifluoromethyl groups, an observation that is similar to that reported[24] for other diphenic acids containing strong electron-attracting groups. As an alternative the 5,5′-bis(trifluoromethyl)diphenic acid was converted to its anhydride and the latter was condensed with 2-aminofluorene and 2-aminofluorenone to give III and subsequently IV, all of which belong to a series in which antimalarial activity had been reported.[13]

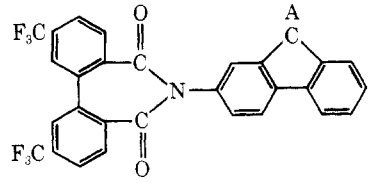


I

II



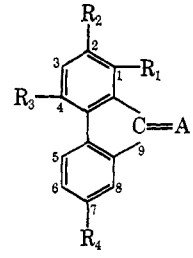
IIIa, A = H, H
b, A = O



IVa, A = H, H
b, A = O

Pharmacology. Antimalarial activity data (Table II) show that the chlorinated fluorenemethanols **5**–**7** are curative in mice; however, none was curative in the chick at 160–320 mg/kg (see footnote 12 in ref 16 for protocol). The lower state of oxidation at the 9 position appears to contribute the greater activity. All of the other compounds listed in Table I, compounds I–IV, and all intermediates

Table III. Fluorenylethylene Oxides



Compd	A	R_1	R_2	R_3	R_4	Mp, °C	Recrystn solvent	Yield,[a] %	Formula	Analyses
8	H, H	-CH—CH_2 (EO)	H	H	H	64–67	Sublimed, 60° (0.1 mm)	60	$C_{15}H_{12}O$	C, H
9	H, OH	H	H	EO	H	111–112		73	$C_{15}H_{12}O_2$	C, H
10	O	H	H	EO	H	142–143	C_6H_6–C_6H_{14}	82	$C_{15}H_{10}O_2$	C, H
11	H, H	H	H	EO	H	57–59[b]		99	$C_{15}H_{12}O$	C, H
12	H, OH	H	Cl	EO	Cl	150–164	C_6H_6–C_6H_{14}	36	$C_{15}H_{10}Cl_2O_2$	C, H, Cl
13	O	H	Cl	EO	Cl	153–155		50	$C_{15}H_8Cl_2O_2$	C, H, Cl
14	H, H	H	Cl	EO	Cl	128–132[c]		82	$C_{15}H_{10}Cl_2O$	C, H, Cl

[a] Yields are for purified material; yields of crude were usually quantitative. [b] A portion sublimed at 60° (0.1 mm) had mp 63–65°. [c] A portion recrystallized from C_6H_{14} had mp 132–134°.

were inactive. No compound was toxic at or below 640 mg/kg, the highest dose tested. The inactivity of III and IV, despite the presence of trifluoromethyl groups, shows that the earlier observation of activity in this series was not significant.

Compounds **7** and II were also tested for true causal prophylactic activity against *Plasmodium gallinaceum* in chicks;[25] **7** gave 4/5 cures and 0/5 deaths at 10 mg/kg; II was inactive.

Experimental Section

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., and by the late Dr. S. M. Nagy (Belmont, Mass.). Satisfactory uv and ir spectra were recorded for all compounds examined for antimalarial activity and for most intermediates. No attempt was made to separate the diastereoisomeric mixtures **2** and **5**.

Fluorenecarboxylic Acids. Fluorene-1-carboxylic acid (Aldrich) and fluorenone-4-carboxylic acid (Aldrich) were used as received. Fluorene-4-carboxylic acid was prepared by the Wolff-Kishner reduction of the available keto acid.[26] 2,7-Dichlorofluorenone-4-carboxylic acid was prepared (mp 256–260°, 91%) by a literature procedure.[27] The precursor, 5,5′-dichlorodiphenic acid[28] (mp 262–273°, 86%), was prepared by an improved procedure based on that for diphenic acid itself.[28] 2,7-Dichlorofluorene-4-carboxylic acid was prepared by the Wolff-Kishner reduction of the keto compound by a procedure similar to that used for the unchlorinated keto acid; after recrystallization (AcOH) it was obtained in 68% yield, mp 257–263°.‡

5,5′-Bis(trifluoromethyl)diphenic acid was prepared (94%) from 3,6-bis(trifluoromethyl)-9-phenanthroic acid (supplied by the Walter Reed Army Institute of Research) by a dichromate oxidation procedure used previously[30] for the oxidation of phenanthrenequinone to diphenic acid. After precipitation from dilute aqueous $NaHCO_3$ it had mp 233–235° (lit.[23] mp 232–234°). None of eight techniques used for the cyclization of diphenic acids gave the desired 1,6-bis(trifluoromethyl)fluorenone-4-carboxylic acid; attack of the trifluoromethyl groups with formation of HF was observed under all conditions that allowed the formation of a fluorenone. 5,5′-Bis(trifluoromethyl)diphenic anhydride (mp 139–141°, 97%) was prepared by refluxing a solution of 5 g of the acid in 30 ml of Ac_2O for 4 hr. *Anal.* ($C_{16}H_6F_6O_3$) C, H.

Acid Chlorides. Fluorene-1-carbonyl chloride,[31] fluorene-4-carbonyl chloride,[32] and fluorenone-4-carbonyl chloride[33],§ were prepared by reaction with $SOCl_2$. 2,7-Dichlorofluorene-4-carbonyl chloride (mp 145–150°) and 2,7-dichlorofluorenone-4-carbonyl chloride (mp 163–167°) were not additionally characterized. All chlorides were obtained in 90–100% yields.

Diazomethyl Ketones. The five novel compounds were prepared in the usual way[34] from the acid chlorides listed above and were not purified with the exception of **diazomethyl 2,7-dichloro-9-keto-4-fluorenyl ketone,** which had mp 157° dec (C_6H_6–C_6H_{14}). *Anal.* ($C_{15}H_6Cl_2N_2O_2$) C, H, Cl, N.

Bromomethyl Ketones. These intermediates were made in the usual way[34] by addition of cold saturated ethereal HBr to a suspension of the diazomethyl ketone in benzene. **Bromomethyl 1-fluorenyl ketone** (79%) had mp 131–132° (C_6H_6–C_6H_{14}). *Anal.* ($C_{15}H_{11}BrO$) C, H, Br. **Bromomethyl 2,7-dichloro-9-keto-4-fluorenyl ketone** (80%) had mp 175–176° (C_6H_6–C_6H_{14}). *Anal.* ($C_{15}H_7BrCl_2O_2$) C, H, Br, Cl. **Bromomethyl 2,7-dichloro-4-fluorenyl ketone** (93%) had mp 124–128° (C_6H_{14}–$CHCl_3$). *Anal.* ($C_{15}H_9BrCl_2O$) C, H, Br, Cl. **Bromomethyl 9-keto-4-fluorenyl ketone** (93%) had mp 71–75°, not additionally characterized. **Bromomethyl 4-fluorenyl ketone** was a red oil, not additionally characterized.

Fluorenylethylene Oxides. Compounds 8, 11, and 14 (Table III) were prepared by the reduction of the appropriate bromomethyl ketones by $NaBH_4$ in MeOH suspension followed by an alkaline work-up.[16] Compound **9** was prepared similarly by reduction of crude bromomethyl 9-keto-4-fluorenyl ketone, the reaction involving concurrent reduction of the 9-keto group.

9-Keto-4-fluorenylethylene Oxide (10). To a solution of 3.7 g (0.016 mol) of **9** in 350 ml of C_6H_6 there was added 14.5 g (0.16 mol) of manganese dioxide (General Metallic Oxides, Grade No. 37) and the mixture was refluxed for 5.5 hr under a Dean-Stark trap, in which the collection of a little water was observed. The hot suspension was filtered and the filtrate taken to dryness.

2,7-Dichloro-9-hydroxy-4-fluorenylethylene oxide (12) and 2,7-dichloro-9-keto-4-fluorenylethylene oxide (13) were obtained as a mixture by the $NaBH_4$ reduction of bromomethyl 2,7-dichloro-9-keto-4-fluorenyl ketone. In one run colorless **12** was isolated by recrystallization of the mixture; it was sensitive to air under alkaline conditions and could not be used for the synthesis of **5**, giving instead impure **6**. In a second run the crude reaction mixture was allowed to stand in contact with air for several days without addition of aqueous NaOH and deposited bright yellow **13**; no attempt was made to develop a higher yield process.

α-(*N,N*-Di-*n*-butylaminomethyl)fluorenemethanols. With the exception of **5** all compounds in Table I were prepared by the reaction of the appropriate oxide with di-*n*-butylamine, using a procedure described previously.[16]

α-(Di-*n*-butylaminomethyl)-2,7-dichloro-9-hydroxy-4-fluorenemethanol Hydrochloride (5). $NaBH_4$ (2 g) was added during 10 min to a stirred solution of 1.7 g (0.004 mol) of the free base of **6** in 100 ml of MeOH at 0°. Two additional 2-g portions were then

‡ Schildo and Sieglitz[29] used a different route and recorded mp 262–263°.
§ We observed mp 137–139°.

added similarly. The reaction mixture became colorless. The crude product was precipitated by addition of water. The broad melting point of the derived HCl salt was consistent with the presence of a mixture of diastereoisomers.

N,N-Di-n-butylfluorenylideneacetamide (I). Ethyl fluorenylideneacetate[18] was hydrolyzed to the acid[19,20] and the latter converted to the title compound by a procedure described recently[21] for the direct conversion of carboxylic acids to amides. The crude product in $CHCl_3$ was washed with 5% HCl and recovered from the dry ($MgSO_4$) solution as 9.1 g (61%) of a red oil. The oil was twice distilled at 220° (0.01 mm) (bulb-to-bulb) and obtained as a viscous yellow oil. *Anal.* ($C_{23}H_{27}NO$) C, H; N: calcd, 4.20; found, 3.70.

Unsuccessful attempts were made to identify the products obtained by hydroboration with disiamylborane.[35]

2,7-Dichloro-9-hydroxy-9-(2-pyridyl)-4-fluorenecarboxylic Acid. The crude material (mp 224–232°) was obtained in 22% yield from 2,7-dichlorofluorenone-4-carboxylic acid under the conditions of the Boykin reaction.[22] A sample for analysis (CH_3CN) had mp 250–252° dec. *Anal.* ($C_{19}H_{11}Cl_2NO_3$) C, H, Cl, N.

2,7-Dichloro-9-hydroxy-9-(2-piperidyl)-4-fluorenecarboxylic Acid Hydrochloride (II). The pyridyl intermediate was hydrogenated in EtOH–HCl over Adams' PtO_2 in the usual way to give a yellow solid which, after trituration with CH_3CN, became colorless (95%, mp 244–245° dec). *Anal.* ($C_{19}H_{18}Cl_3NO_3$) C, H, Cl, N.

N-(2-Fluorenyl)-5,5′-bis(trifluoromethyl)diphenamic Acid (IIIa). 5,5′-Bis(trifluoromethyl)diphenic anhydride was allowed to react with 2-aminofluorene in a general procedure[13] to give the amic acid (74%), mp 240–242°. *Anal.* ($C_{29}H_{17}F_6NO_3$) H, N; C: calcd, 64.32; found, 63.72.

Compound IIIb was prepared similarly from 2-aminofluorenone and obtained in quantitative yield: mp 276–279°. *Anal.* ($C_{29}H_{15}F_6NO_4$) H, N; C: calcd, 62.71; found, 62.06.

N-(2-Fluorenyl)-5,5′-bis(trifluoromethyl)diphenimide (IVa). The amic acid IIIa was cyclized by Ac_2O–AcONa[13] to give the imide in 98% yield: mp 310–313°. *Anal.* ($C_{29}H_{15}F_6NO_2$) H, N; C: calcd, 66.54; found, 65.96.

Compound IVb was prepared similarly from IIIb: mp 322–325°. *Anal.* ($C_{29}H_{13}F_6NO_3$) C, H, N.

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Antimalarials. 4. Tetrahydroquinolinemethanols†

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The undesirable phototoxicity of potent antimalarials in the substituted 2-phenyl-4-quinolinemethanol series has been discussed by us[1] and by others.[2] Our unsuccessful efforts to decrease phototoxicity (without at the same time decreasing antimalarial activity) involved four structural modifications.[1] More recently some success was achieved with compounds in which the 2-phenyl substituent was separated from the quinoline nucleus by CH_2, CO, and CF_2 groups.[2] When the 2-phenyl groups were replaced by aryloxy or arylamino groups there was a little to a moderate effect on both phototoxicity and antimalarial activity.[3] When the 2-phenyl groups were replaced by thienyl groups phototoxicity remained; when they were replaced by methyl or *tert*-butyl groups phototoxicity decreased but antimalarial activity did also.[4]

Our earlier[1] reduction of the well-known 6,8-dichloro-2-phenyl-α-(2-piperidyl)-4-quinolinemethanol (I) gave the 1,2,3,4-tetrahydro derivative II which was less phototoxic than I, but whose evaluation was complicated by the fact that II was toxic to mice at 50 mg/kg ip.

In order to subject our hypothesis to a more satisfactory evaluation we have now prepared IV–VI from III (variously known as SN15068 or WR 30090) by the route shown.

At the time the work began III was known to have about half the antimalarial activity of I but was much less toxic because it did not cause depletion of catecholamines with related effects.[5] It was thought that the unacceptably high phototoxicity of III in mice would prevent its clinical use, although the reported[6] minimum effective phototoxic dose in swine was just 25 mg/kg po, identical with that of qui-

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