night at room temp, and concd, and the product was dissolved in EtOAc, washed with 10% citric acid soln and H_2O, then dried (Na_2SO_4), and concd under reduced pressure to give a solid. This material was chromatographed on a column of Silicar CC-7 using $CHCl_3$-EtOAc (1:1) as eluent, to give the fully blocked tetrapeptide; crystn from EtOAc–hexane yielded 6.5 g (67%): mp 150°, $[\alpha]^{29}D$ −23.0° (*c* 1.5, DMF). *Anal.* ($C_{34}H_{44}N_5O_9$) C, H, N.

Z-Trp-γ-*tert*-Bu-Glu-Ala-Gly (7). To a soln of 6.5 g (0.0098 mole) of **6** in 300 ml of MeOH was added 10 ml of 1 *N* KOH and the soln was stirred for 90 min at room temp and then concd under reduced pressure. The residue was flooded with H_2O, acidified with 10% citric acid soln, and extd into EtOAc. The EtOAc soln was dried (Na_2SO_4) and concd under pressure to give the tetrapeptide free acid, crystn from EtOAc–hexane yielded 6.1 g (95%): mp 93°, $[\alpha]^{29}D$ −16.9 (*c* 2.9, DMF). *Anal.* ($C_{33}H_{42}N_5O_9$) C, H, N.

Z-Trp-γ-*tert*-Bu-Glu-Ala-Gly Pentachlorophenyl Ester (8). To a soln of 6.0 g (0.0092 mole) of the tetrapeptide free acid **7** in 150 ml of DMF was added 2.66 g (0.01 mole) of pentachlorophenol and 4.7 g (0.011 mole) of 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate. The mixt was stirred overnight at room temp and then 400 ml of H_2O was added to it. The ppt was filtered and crystd from MeOH to yield 4 g (45%): mp 170° $[\alpha]^{29}D$ −22.1° (*c* 2.0, DMF). *Anal.* ($C_{39}H_{41}Cl_5N_5O_9$) C, H, N.

Trp-γ-*tert*-Bu-Glu-Ala-Gly Pentachlorophenyl Ester·HCl (9). A fine suspension of 4.0 g (0.0044 mole) of the tetrapeptide active ester **8** and 0.8 g of 10% Pd/C in 200 ml of MeOH was treated with 0.162 g (0.0044 mole) and dry HCl in MeOH, and the suspension was hydrogenated for 2 hr. The reaction mixt was filtered and the filtrate concd. The residue was triturated with Et_2O to give 1.5 g (45%): mp 202°, $[\alpha]^{29}D$ −17.8° (*c* 0.7, DMF). *Anal.* ($C_{31}H_{36}Cl_6N_5O_7$) N.

Poly(Trp-Glu-Ala-Gly)Gly Me Ester (5). To a soln of 0.83 g (0.008 mole) of Et_3N and 1 mg of Gly Me ester·HCl in 5 ml of DMSO was added a soln of 2.2 g (0.00274 mole) of the polymn unit **9** in 22.5 ml of DMSO. The mixt was shaken for 1 week and then centrifuged to yield the fully protected polymer which was washed with three 35-ml portions of H_2O, three 35-ml portions of MeOH, and three 35-ml portions of Et_2O and dried to give 0.62 g (47%) of the blocked polymer. This material was treated with 50 ml of 90% F_3CCO_2H stirred for 50 min, and then concd under reduced pressure to yield the crude polypeptide **5**. This material was dissolved by the addn of 1 *N* NaOH to pH 7.5. The soln was dialyzed against distd H_2O overnight, and then chromatogd on Sephadex G-10 using H_2O as eluent. The high mol wt fraction was collected and dialyzed against distd H_2O and then lyophilized to yield 0.27 g (22%). *Anal.* ($C_{21}H_{24}N_5O_6 \cdot Na \cdot H_2O$) C, H, N.

Molecular Weight Determination. A calibrated column of Sephadex G-50 (2.5 × 39.0 cm) was employed for the mol wt detn. Using 0.15 *M* NaCl as eluent, 4 mg of the Na salt of poly(Trp-Glu-Ala-Gly)Gly Me ester was passed through it and the polypeptide was eluted in a vol equiv to that corresponding to a mol wt of 3×10^4.

Immunochemical Procedures. Eight rabbits were treated with poly(Tyr-Glu-Ala-Gly)Gly-*l*-^{14}C Et ester (**1**) at weekly intervals, using the immunization schedule previously described;[3] 25 days after the last injection all rabbits were bled using the std heart puncture technique. Serum from each rabbit was tested for the precipitin reaction with the homologous antigen **1**, serum from each animal gave a positive precipitin reaction. The serum from each animal was pooled and this combined serum was used for the following expts. It was assumed that antibody produced by each rabbit after the same time interval was directed against the same antigenic determinants of poly(Tyr-Glu-Ala-Gly)Gly-*l*-^{14}C Et ester (**1**).

Quantitative Precipitin Reactions. To 1-ml aliquots of the pooled rabbit serum was added incremental amts of the polypeptide **1**. Each tube was made up to a total of 2 ml with buffer (0.1 *M* NaCl–0.05 *M* $NaHCO_3$) and incubated for 1 hr at 37°, and then kept at 4° for 48 hr. The tubes were centrifuged in the cold and the ppts were washed twice with 1 ml of buffer (0.05 *M* K_2HPO_4–NaOH), pH 7.0. The total amount of protein ppt was estd by analysis for N (Kjeldahl). For each of the polypeptides **2**, **3**, **4**, and **5** quant precipitin reactions were performed using the pooled rabbit serum, which were identical with and run simultaneously with that used for the polypeptide **1**. The precipitin curves are shown in the figure.

Absorption Studies. The pooled rabbit serum was treated with quantities equal to the equiv pt amount of the heterologous polypeptides **2**, **3**, and **5**, as described above. The corresponding ppts were centrifuged out and the supernatant liquids were poured off into sep tubes. To each of these supernatant liquids was added 30 μg of the homologous antigen, poly(Tyr-Glu-Ala-Gly)Gly-*l*-^{14}C Et ester (**1**). The tubes were incubated at 37° for 1 hr, and then stood at 4° for 48 hr. The ppts were collected by centrifugation, and washed twice with 1 ml of buffer soln (0.05 *M* K_2HPO_4–NaOH), pH 7.0. The amount of protein ppt was estd by analysis for N (Kjeldahl). The amount of ppts obtained using this procedure are shown in the table. Controls in which the serum was first absorbed with the homologous antigen **1** ascertained that the homologous antigen pptd all of the antibody, since the supernatant liq gave no further precipitin reaction with 30 μg of **1** was added.

Acknowledgments. This work was supported by the National Science Foundation, The Hartford Foundation, and the State of Alabama.

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Antimalarials. 1. 2-Quinolinemethanols†

A. Markovac,* C. L. Stevens, and A. B. Ash

Ash Stevens Inc., Detroit, Michigan 48202. *Received October 18, 1971*

Ten substituted 2-quinolinemethanols were synthesized and tested against *Plasmodium berghei* in mice. Only α-di-*n*-butylaminomethyl-4-(4-chlorophenyl)-6,8-dichloro-2-quinolinemethanol was active at 640 mg/kg; the other 9 compounds were inactive.

As reported by Wiselogle,[1] the World War II antimalarial program generated 7 unsubstituted α-dialkylaminomethyl-2-quinolinemethanols wherein the amino alcohol group was varied. The synthesis of 4 of these was reported by Campbell and coworkers.[2] None of the 7 compounds possessed a quinine index higher than 0.2.[1] On the other hand, the unsubstituted 4-quinolinemethanols (ref 1, p 142) were only marginally better, but highly active antimalarials were acquired by placing substituents in various positions in the quinoline nucleus.‡ The impact was most notable with

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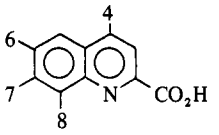
‡For World War II data on the 4-quinolinemethanols see ref 2. Recent major references include Boykin, *et al.*,[3] and Saggiomo, *et al.*[4] A complete compilation of data is maintained at the Walter Reed Army Institue of Research, Washington, D. C.

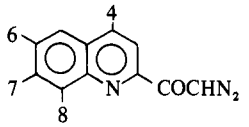
Table I. Quinaldinic Acids



No.[a]	4	6	7	8	Mp, °C dec	Recrystn solvent	Yield, %	Formula	Analyses
1	OCH_3	OCH_3	Cl	H	212-215	*b*	36[c]	$C_{12}H_{10}ClNO_4$	*b*
2	OCH_3	Cl	H	Cl	208-210	*b*	32[c]	$C_{11}H_7Cl_2NO_3$	*b*
3	H	OCH_3	Cl	H	237-238	EtOH	10[d]	$C_{11}H_8ClNO_3$	C, H, N, Cl
4	H	Cl	H	Cl	192-193	EtOH-H_2O	54[e]	$C_{10}H_5Cl_2NO_2$	C, H, N, Cl
5	$C_6H_4Cl(p)$	OCH_3	Cl	H	225-227	EtOH	34[f]	$C_{17}H_{11}Cl_2NO_3$	C, H
6	$C_6H_4Cl(p)$	Cl	H	Cl	219-220	AcOH	29[f]	$C_{16}H_8Cl_3NO_2$	C, H, N
7	$C_6H_4Cl(p)$	C_6H_5	H	H	220-221	EtOH-H_2O	25[f]	$C_{22}H_{14}ClNO_2$	C, H, N
8	$C_6H_4Cl(p)$	$C_6H_4F(p)$	H	H	200-202	EtOH	30[f]	$C_{22}H_{13}ClFNO_2$	C, H, N

[a]Synthetic methods are described in the Discussion. [b]Too insoluble to be purified. [c]From the starting amine. [d]From ethyl 7-chloro-4-hydroxy-6-methoxyquinaldinate. [e]From 6,8-dichloroquinaldine. [f]From starting aniline and 4-chlorobenzoylacrylic acid.

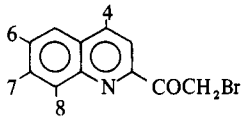
Table II. Diazomethyl 2-Quinolyl Ketones



No.	4	6	7	8	Mp, °C dec	Recrystn solvent	Yield, %[a]	Formula	Analyses
9	OCH_3	OCH_3	Cl	H	163-165	Et_2O	83	$C_{13}H_{10}ClN_3O_3$	*b*
10	OCH_3	Cl	H	Cl	198-199	CH_2Cl_2-Et_2O	86	$C_{12}H_7Cl_2N_3O_2$	C, H, N
11	H	OCH_3	Cl	H	174-176	CH_2Cl_2	76	$C_{12}H_8ClN_3O_2$	C, H
12	H	Cl	H	Cl	183-185	CH_2Cl_2	77	$C_{11}H_5Cl_2N_3O$	C, H, N
13	$C_6H_4Cl(p)$	OCH_3	Cl	H	203-205	Et_2O	81	$C_{18}H_{11}Cl_2N_3O_2$	C, H, N
14	$C_6H_4Cl(p)$	Cl	H	Cl	192-194	Et_2O	82	$C_{17}H_8Cl_3N_3O$	C, H, N
15	$C_6H_4Cl(p)$	C_6H_5	H	H	159-160	Et_2O	75	$C_{23}H_{14}ClN_3O$	C, H, N
16	$C_6H_4Cl(p)$	$C_6H_4F(p)$	H	H	174-176	Et_2O	84	$C_{23}H_{13}ClFN_3O$	C, H, N

[a]From the corresponding quinaldinic acids. [b]Photosensitive, not analyzed.

Table III. Bromomethyl 2-Quinolyl Ketones



No.	4	6	7	8	Mp, °C	Recrystn solvent	Yield, %[a]	Formula	Analyses
17	OCH_3	OCH_3	Cl	H	218-220	CH_2Cl_2-EtOH	70	$C_{13}H_{11}BrClNO_3$	C, H, N
18	OCH_3	Cl	H	Cl	204-205	CH_2Cl_2-EtOH	75	$C_{12}H_8BrCl_2NO_2$	C, H, N
19	H	OCH_3	Cl	H	178-179	CH_2Cl_2-EtOH	81	$C_{12}H_9BrClNO_2$	C, H
20	H	Cl	H	Cl	175-176	CH_2Cl_2	72	$C_{11}H_6BrCl_2NO$	C, H, N
21	$C_6H_4Cl(p)$	OCH_3	Cl	H	178-179	CH_2Cl_2-EtOH	71	$C_{18}H_{12}BrCl_2NO_2$	C, H
22	$C_6H_4Cl(p)$	Cl	H	Cl	182-183	CH_2Cl_2-Et_2O	85	$C_{17}H_9BrCl_3NO$	C, H, N
23	$C_6H_4Cl(p)$	C_6H_5	H	H	142-143	EtOH-Et_2O	73	$C_{23}H_{15}BrClNO$	C, H, N
24	$C_6H_4Cl(p)$	$C_6H_4F(p)$	H	H	180-182	EtOH-Et_2O	74	$C_{23}H_{14}BrClFNO$	C, H, N

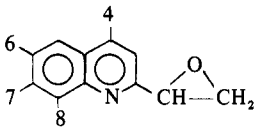
[a]From the corresponding diazomethyl ketones.

electron-withdrawing groups in the 6, 7, and 8 positions, and the activity was enhanced by the further introduction of a halophenyl group in the 2 position. In view of this singular success in the 4-quinolinemethanol series, an assessment of the impact of substituents upon antimalarial activity in the 2-quinolinemethanols appeared desirable. This need was reinforced by the phototoxicity[5] of the 4-quinolinemethanols which restricts their utility as antimalarials.

Chemistry. The synthetic route employed in this work to prepare the 2-quinolinemethanols required the acquisition of variously substituted quinaldinic acids to serve as starting materials for the introduction of the amino alcohol side chain by the well-known Lutz sequence[6] (see below).

7-Chloro-4,6-dimethoxyquinaldinic acid (**1**) and 6,8-dichloro-4-methoxyquinaldinic acid (**2**) were prepared by a 3-step sequence involving first the condensation of the corresponding anilines with ethyl oxalylacetate to give the precursors, ethyl 4-hydroxyquinaldinates, by the procedure of Surrey and Hammer.[7] Treatment of the esters with CH_2N_2 gave the 4-methoxy derivatives followed by saponification of the ester group to yield quinaldinic acids **1** and **2**. 7-Chloro-6-methoxyquinaldinic acid (**3**) was prepared by a 3-step sequence involving first the treatment of ethyl 7-chloro-4-hydroxy-6-methoxyquinaldinate with $POCl_3$ to give ethyl 4,7-dichloro-6-methoxyquinaldinate. The 4-Cl was subsequently removed selectively by hydrogenation to give

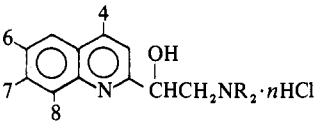
Table IV. 2-(Epoxyethyl)quinolines



No.	4	6	7	8	Mp, °C[a]	Yield, %[b]	Formula	Analyses
25	OCH_3	OCH_3	Cl	H	145–149	80	$C_{13}H_{12}ClNO_3$	*d*
26	OCH_3	Cl	H	Cl	163–165	75	$C_{12}H_9Cl_2NO_2$	C, H, N
27	H	OCH_3	Cl	H	123–125	77	$C_{12}H_{10}ClNO_2$	C, H, N
28	H	Cl	H	Cl	138–140	86	$C_{11}H_7Cl_2NO$	C, H, N
29	$C_6H_4Cl(p)$	OCH_3	Cl	H	169–170	71	$C_{18}H_{13}Cl_2NO_2$	C, H
30	$C_6H_4Cl(p)$	Cl	H	Cl	197–198	95	$C_{17}H_{10}Cl_3NO$	C, H
31	$C_6H_4Cl(p)$	C_6H_5	H	H	90–122	89	$C_{23}H_{16}ClNO$	*c*
32	$C_6H_4Cl(p)$	$C_6H_4F(p)$	H	H	Oil[d]	57	$C_{23}H_{15}ClFNO$	*d*

[a] All compds recrystd from EtOH, except **25** and **31** (EtOH–H_2O). [b] From the corresponding bromomethyl ketones. [c] Contained bromohydrin. [d] Not purified or analyzed.

Table V. α-Dialkylaminomethyl-2-quinolinemethanols



No.	4	6	7	8	R	*n*	Mp, °C[a]	Yield, %[b]	Formula[c]
33	OCH_3	OCH_3	Cl	H	1′-Bu	2	134–136	42	$C_{21}H_{33}Cl_3N_2O_3$
34a	OCH_3	Cl	H	Cl	1′-Bu	1	160–162	36	$C_{20}H_{29}Cl_3N_2O_2$
34b	OCH_3	Cl	H	Cl	1′-Hex	1	140–141	23	$C_{24}H_{37}Cl_3N_2O_2$
35	H	OCH_3	Cl	H	1′-Bu	2	126–128	24	$C_{20}H_{31}Cl_3N_2O_2$
36a	H	Cl	H	Cl	1′-Bu	1	192–194	24	$C_{19}H_{27}Cl_3N_2O$
36b	H	Cl	H	Cl	1′-Hex	1	146–148	49	$C_{23}H_{35}Cl_3N_2O$
37	$C_6H_4Cl(p)$	OCH_3	Cl	H	1′-Bu	2	190–192	33	$C_{26}H_{34}Cl_4N_2O_2$
38	$C_6H_4Cl(p)$	Cl	H	Cl	1′-Bu	1	180–181	28	$C_{25}H_{30}Cl_4N_2O$
39	$C_6H_4Cl(p)$	C_6H_5	H	H	1′-Bu	2	200–202 dec	37	$C_{31}H_{37}Cl_3N_2O$
40	$C_6H_4Cl(p)$	$C_6H_4F(p)$	H	H	1′-Bu	2	215–217 dec	37	$C_{31}H_{36}Cl_3FN_2O$

[a] All compds recrystd from CH_3CN or CH_3CN–EtOH (**35**, **36a**, **37**, **39**, and **40**). [b] From precursor epoxides and dialkylamine. [c] All analyses acceptable (0.4%) in C, H, N, and Cl, except **33** and **35**, C, H, N.

ethyl 7-chloro-6-methoxyquinaldinate. Saponification yielded **3**.

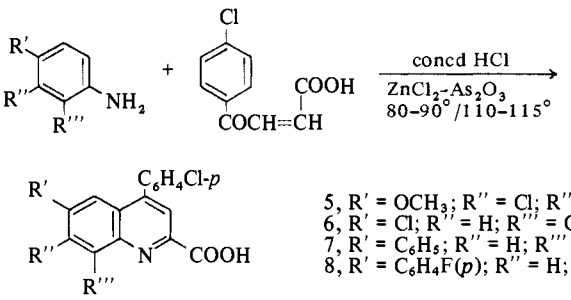
The sequence to 6,8-dichloroquinaldinic acid (**4**) was based on procedures used by Campbell and coworkers for analogous compounds.[2] 6,8-Dichloroquinaldine was prepared from crotonaldehyde and 2,4-dichloroaniline by the Doebner-Miller reaction as modified by Campbell and Schaffner for the preparation of 4-methylquinolines.[8] Bromination of 6,8-dichloroquinaldine in AcOH in the presence of NaOAc gave the α-dibromo derivative contaminated with a little tribromide in near quantitative yield. (Campbell[2] reported that bromination of quinaldine by this procedure gave α-tribromoquinaldine.) Treatment of the mixture with $AgNO_3$ in EtOH gave crude 6,8-dichloroquinoline-2-carboxyaldehyde containing some of the corresponding quinaldinic acid. Oxidation of the crude mixture with alkaline MnO_4^- gave **4**.

In the case of the 4-quinolinemethanols, as stated, antimalarial activity is markedly enhanced by the introduction of a 4-chlorophenyl group in the 2 position.‡ Accordingly, it was desirable to test this substituent effect in the present series by introducing the 4-chlorophenyl group in the corresponding 4 position. To this end, 4 variously substituted 4-(4-chlorophenyl)quinaldinic acids were prepared by a modified Skraup synthesis.[9] Appropriately substituted anilines were condensed with 4-chlorobenzoylacrylic acid[10] to yield **5**, **6**, **7**, and **8** as shown by Scheme I.

The amino alcohol side chain in the 2 position was introduced by the method of Lutz and coworkers.[6]

Biological Data. Among the 10 candidate antimalarials

Scheme I



prepared, only α-di-*n*-butylaminomethyl-4-(4-chlorophenyl)-6,8-dichloroquinolinemethanol (**38**) was active in the Rane mouse screen against *Plasmodium berghei*. § At 640 mg/kg, the average (5 mice) extension of life (Δ MST) was 6.3 days; 2 of the 5 mice survived until day 15. Two other compounds, **33** and **39**, gave a slight extension of life, 3.3 days and 1.6 days, respectively.

Experimental Section#

Quinaldinic Acids. 7-Chloro-4,6-dimethoxyquinaldinic Acid (1) and 6,8-Dichloro-4-methoxyquinaldinic Acid (2). Ethyl 7-chloro-4-

§ The antimalarial tests were performed by Dr. Leo Rane[11] of the University of Miami. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Richard E. Strube of the Walter Reed Army Institute of Research.

#Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Analyses indicated by element symbols agree with calculated values within ±0.4%.

hydroxy-6-methoxyquinaldinate, prepd in 44% yield as reported by Surrey and Hammer,[7] was dissolved in MeOH and treated with excess CH_2N_2 in Et_2O in the cold for 4 hr and the soln was stored at 5° overnight. Work-up gave ethyl 7-chloro-4,6-dimethoxyquinaldinate (84%), mp 192–194° (MeOH). *Anal.* ($C_{14}H_{14}ClNO_4$) C, H. The latter ester was suspended in MeOH–10% aqueous NaOH (1:6 v/v), refluxed 4 hr, and acidified to pH 5 (aqueous HCl). Refrigeration, filtration, and drying gave **1** (98%). Compd **2** was prepd in like manner. Treatment of ethyl 6,8-dichloro-4-hydroxyquinaldinate[7] with CH_2N_2 gave ethyl 6,8-dichloro-4-methoxyquinaldinate (83%), mp 182–184° (MeOH). *Anal.* ($C_{13}H_{11}Cl_2NO_3$) C, H. Saponification as above gave **2** (95%).

7-Chloro-6-methoxyquinaldinic Acid (3). Ethyl 7-chloro-4-hydroxy-6-methoxyquinaldinate[7] was refluxed in excess $POCl_3$ for 1 hr, cooled, and poured over ice. Filtration and drying gave ethyl 4,7-dichloro-6-methoxyquinaldinate (50%), mp 194–197° (CH_3CN). *Anal.* ($C_{13}H_{11}Cl_2NO_3$) C, H, N, Cl. The ester (12 g) was dissolved in warm, dry dioxane (600 ml) and added to a suspension of 5% Pd–$BaSO_4$ (12 g) in dioxane (150 ml). Hydrogenation was carried out at 1 atm and room temp; uptake was 1.2 equiv. The catalyst was removed, Et_3N (10 ml) was added, and the mixt was evapd. The residue was suspended in hot H_2O and filtered to yield a solid (8.6 g), mp 126–170°. This was dissolved in C_6H_6, passed through a silica gel column and eluted with C_6H_6–Et_2O (95:5). The first fraction (2.9 g) was starting material. The second fraction was ethyl 7-chloro-6-methoxyquinaldinate (3.0 g, 28%), mp 152–154° [$CHCl_3$–petr ether (bp 60–110°)]. *Anal.* ($C_{13}H_{12}ClNO_3$) Cl. The ester was refluxed in aqueous 10% NaOH–EtOH (1:1 v/v) for 3 hr. The soln was evapd and the residue was dissolved in H_2O and acidified. Filtration and drying gave **3** (74%).

6,8-Dichloroquinaldinic Acid (4). Crotonaldehyde (22.4 g) was added to a stirred mixt of 2,4-dichloroaniline hydrochloride (79.5 g), $ZnCl_2$ (6.4 g), $FeCl_3 \cdot 6H_2O$ (173 g), and EtOH (95%, 290 ml) over 1.5 hr. The mixt was stirred at reflux for 2 hr and allowed to stand overnight. EtOH was removed (aspirator) followed by azeotropic distn with C_6H_6. The residue was triturated extensively with Et_2O. The ext was dried (K_2CO_3) and filtered and Et_2O was removed. The residual oil was dissolved in hot petr ether (60–110°). Upon cooling, 17 g (25%) of crude 6,8-dichloroquinaldine was obtained, mp 106–110°. Recrystn from petr ether gave mp 110–122°. *Anal.* ($C_{10}H_7Cl_2N$) C, H, N.

Br_2 (13.6 g) was added (20 min) to a mixt of 6,8-dichloroquinaldine (6.0 g) and NaOAc (13.9 g) in AcOH (500 ml) at 70°. The temp was raised to 100° for 1 hr. After cooling, the mixt was poured over ice and filtered. The crude **α-dibromo-6,8-dichloroquinaldine** (13.5 g), mp 95–110°, was recrystd successively from EtOH and petr ether to give mp 118–119.5°. *Anal.* ($C_{10}H_5Br_2Cl_2N$) halogen as Cl: calcd, 38.30; found, 37.95.

The crude dibromide (40.4 g) in EtOH (675 ml) was mixed with a soln of $AgNO_3$ (59 g) in 50 vol % EtOH (450 ml) and the mixt was refluxed 1 hr. The mixt was filtered hot to yield crude **6,8-dichloroquinoline-2-carboxaldehyde** (18.5 g, 20%), mp 176–190°.

A mixt of the aldehyde (310 mg), $KMnO_4$ (215 mg), and aqueous KOH (2 ml, 1.6 *M*) in acetone (150 ml) was stirred 5 min, heated to boiling, dild with H_2O, and satd with SO_2. The ppt was collected, decolorized, and recrystd from EtOH–H_2O to yield 4 (220 mg, 66%).

4-(4-Chlorophenyl)-7-chloro-6-methoxyquinaldinic Acid (5). A mixt of 4-methoxy-3-chloroaniline (15.7 g), As_2O_5 (25 g), and fused $ZnCl_2$ (10 g) in concd aqueous HCl was heated with stirring to 80–90°. Powd *p*-chlorobenzoylacrylic acid[10] was added portionwise while raising the temp to 110–115°. Two layers formed sepd by decantation of the hot mixt. The lower layer was washed with aqueous HCl and poured into cold H_2O, and the mixt filtered. The collected solid was suspended in satd aqueous Na_2CO_3 soln, stirred, and filtered. The resulting Na salt of 5 was washed with H_2O and leached with Et_2O to remove unreacted starting aniline. The Na salt was then suspended in hot 5% aqueous AcOH, stirred well, and filtered. The collected solid was washed with H_2O and recrystd from EtOH–H_2O to give the title acid 5 (12 g, 34%), mp 223–226°, recrystd again from EtOH to give pure **5**.

4-(4-Chlorophenyl)-6,8-dichloroquinaldinic acid (6), 4-(4-chlorophenyl-6-phenylquinaldinic acid (7), and 4-(4-chlorophenyl)-6-(4-fluorophenylquinaldinic acid (8) were prepd by the same procedure.

Diazomethyl 2-Quinolyl Ketones. The following prepn is typical. 7-Chloro-6-methoxyquinaldinic acid (**3**) (5.5 g) was refluxed with $SOCl_2$ (50 ml) for 5 hr. Excess $SOCl_2$ was removed *in vacuo*. The crude acid chloride was azeotropically distd with C_6H_6, suspended in CH_2Cl_2, and added to a cooled (0°) Et_2O soln of CH_2N_2 (*ca.* 900 mg). After refrigeration at −10° overnight, the solvent was removed *in vacuo*. The residue was suspended in a little dry ether and filtered to give **diazomethyl 7-chloro-6-methoxy-2-quinolyl ketone (11)** (4.6 g, 70%), mp 172–174° dec. Recrystn from CH_2Cl_2 gave mp 174–176 dec.

Bromomethyl 2-Quinolyl Ketones. The following procedure is typical. Diazomethyl ketone **11** (4.2 g) was added to a hot (70°) soln of 45% aqueous HBr (10 ml) and glacial AcOH (100 ml); N_2 evolved vigorously. After 1 hr, the soln was poured into ice water. The collected ppt was suspended in satd Na_2CO_3 soln and filtered again, and the solid was washed with H_2O. After drying, the solid was suspended in EtOH, sepd, and dried to give **bromomethyl 7-chloro-6-methoxy-2-quinolyl ketone (19)** (4.1 g, 81%), mp 174–176°. Recrystn from CH_2Cl_2–EtOH gave mp 178–179°.

2-(Epoxyethyl)quinolines. The following prepn is typical. The bromomethyl ketone **19** (4 g) was suspended in hot EtOH (100 ml) and treated with $NaBH_4$ (0.4 g) in H_2O (20 ml). After 2 hr at 65°, the mixt was evapd *in vacuo*. Excess $NaBH_4$ was decompd with 10% HCl and the mixt was neutralized with $NaHCO_3$ and dild with H_2O. The ppt was collected, washed with H_2O, and dried. Recrystn from EtOH gave 7-chloro-2-(epoxyethyl)-6-methoxyquinoline (**27**) (2.4 g, 77%), mp 123–125°.

α-Dialkylaminomethyl-2-quinolinemethanols. The following prepn is typical. A soln of 2-(epoxyethyl)quinoline (**27**, 3 g) and di-*n*-butylamine (7 ml) in EtOH (70 ml) was refluxed for 18 hr. EtOH and excess amine were removed *in vacuo*. The oily residue was dissolved in Et_2O and the soln was washed with H_2O, decolorized and dried (K_2CO_3). Et_2O was evapd and the residue redissolved in a little fresh Et_2O and satd with dry HCl. The solid dihydrochloride salt (2.3 g) was filtered and washed with dry Et_2O. Recrystn from CH_3CN–EtOH gave **α-di-*n*-butylaminomethyl-7-chloro-6-methoxy-2-quinolinemethanol dihydrochloride (35)** (1.3 g, 24%), mp 126–128°.

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