7-Benz[c]acridinemethanols as Tetracyclic Analogs of the 2-Phenyl-4-quinolinemethanol Antimalarials

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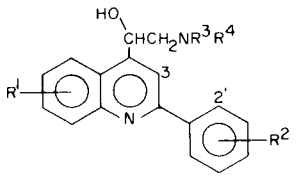
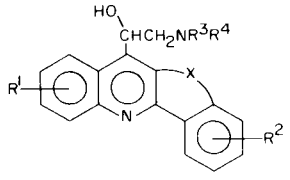
A series of new 7-benz[c]acridinemethanols and 5,6-dihydro-7-benz[c]acridinemethanols was prepared as rigid, tetracyclic analogs of the antimalarial 2-phenyl-4-quinolinemethanols. Condensation of 5,7-dichloroisatin with 6-chloro-, 7-chloro-, and 6,7-dichloro-1-tetralone furnished halogenated 5,6-dihydro-7-benz[c]acridinecarboxylic acids, which were transformed into the corresponding acid chlorides, acyl malonates, α-bromomethyl ketones, and epoxides. Fully aromatic members of the series obtained *via* dehydrogenation of the 5,6-dihydro acids were likewise converted into epoxides *via* the acylmalonate route. Although all the epoxides studied proved to be exceptionally resistant to ring-opening by di-*n*-butylamine, probably on account of steric effects, they could be cleaved readily with piperidine or morpholine. Nmr spectra of the resulting amino alcohols suggest that these compounds exist in a single preferred conformation stabilized by internal O-H· · ·N hydrogen bonding, and that free rotation about the side chain C-C bond does not occur at room temperature.

Significant levels of activity against avian plasmodial infections were shown by 2-phenyl-4-quinolinemethanols of general structure I during the extensive World War II research program on malaria (2). Unfortunately, clinical application of these agents in man was thwarted by their high degree of phototoxicity, which manifested itself as severe exfoliation of the skin upon exposure to sunlight (3). In recent years, synthetic work on 2-phenyl-4-quinolinemethanols has been revived (4) as part of a vigorous search for new drugs against certain pyrimethamine-resistant and chloroquine-resistant strains of human malaria. Attempts have been made to correlate experimental phototoxicity data (5) with electronic structure (6) in the hope of providing helpful guidelines for analog design. Thus far, however, intense efforts by numerous investigators have failed to yield the ideal combination of high antiplasmodial activity and complete absence of phototoxic response in the host.

The present paper deals with the synthesis of a series of heretofore unknown benz[c]acridinemethanols, representing one of several possible rigid, geometrically well-defined ring systems of general structure II, in which free rotation of the phenyl ring is prevented by the X-bridge. A recently published observation that quinolinemethanols of type I with substituents at the 3- and 2′-positions display decreased phototoxicity in the mouse (5a) suggested the possibility that tetracyclic analogs II might exhibit improved chemotherapeutic properties or a more favorable therapeutic index. Moreover, it was postulated that systematic modification of the X-bridge might provide information concerning the possible relationship between phototoxicity and π-orbital resonance interaction in the 2-phenylquinoline system (6).



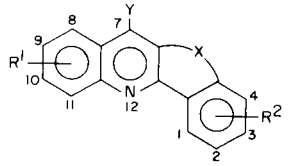
I



II

The synthetic plan followed in this program is summarized in Chart I. Entry into the benz[c]acridine ring system was achieved *via* the Pfitzinger reaction, following the precedent of several earlier investigations (7). The 5,6-dihydrobenz[c]acridine-7-carboxylic acids obtained in this manner were converted successively into acid chlorides, acyl malonates, α-bromomethyl ketones, epoxides, and amino alcohols *via* suitable modifications of the approach used by Olsen (8) to construct the *N,N*-dialkylaminoalkyl carbinol side chain in 2-phenyl-4-quinolinemethanols. Dehydrogenation of the 5,6-dihydro acids with bromine (7d) and elaboration of the side chain *via* the sequence outlined above led to the fully aromatic amino alcohols. A total

TABLE I



Compound Number	X	R^1	R^2	Y	M.p., °C	Crystn. Solvent (a)	Analyses (b) C	H	Cl	N
1	CH_2CH_2	H	H	COOH	252-254 dec. (c)	A	----	---	----	---
2	CH=CH	H	H	COOH	278-281 dec. (d)	B	----	---	----	---
3	CH_2CH_2	9,11-Cl_2	2-Cl	COOH	283-284 dec.	C	57.09 56.93	2.67 2.72	28.09 27.88	3.70 3.69
4	CH_2CH_2	9,11-Cl_2	3-Cl	COOH	269-270 dec.	C	57.09 56.98	2.67 2.62	28.09 28.19	3.70 3.66
5	CH=CH	9,11-Cl_2	3-Cl	COOH	285-286 dec.	D	57.40 57.68	2.14 2.09	28.24 28.39	3.72 3.65
6	CH_2CH_2	9,11-Cl_2	2,3-Cl_2	COOH	303-304 dec.	C	52.33 52.15	2.20 2.14	34.44 34.54	3.39 3.37
7	CH=CH	9,11-Cl_2	2,3-Cl_2	COOH	281-283 dec.	B	52.59 52.20	1.72 1.63	34.50 34.12	3.41 3.41
8	CH_2CH_2	H	H	COCl	117-119 dec.	E	73.56 73.77	4.12 4.09	12.09 12.24	4.76 4.93
9	CH=CH	H	H	COCl	122-124 dec.	E	74.10 74.01	3.46 3.46	12.15 12.13	4.80 4.76
10	CH_2CH_2	9,11-Cl_2	2-Cl	COCl	194-196 dec.	F	54.44 54.10	2.28 2.34	35.71 35.89	3.53 3.29
11	CH_2CH_2	9,11-Cl_2	3-Cl	COCl	253-254 dec.	E	54.44 54.60	2.28 2.24	35.71 35.39	3.53 3.36
12	CH=CH	9,11-Cl_2	3-Cl	COCl	236-238 dec.	F	54.71 54.96	1.79 1.67	35.89 35.62	3.55 3.45
13	CH_2CH_2	9,11-Cl_2	2,3-Cl_2	COCl	265-267 dec.	G	50.04 49.76	1.87 1.79	41.12 41.44	3.24 3.01
14	CH=CH	9,11-Cl_2	2,3-Cl_2	COCl	279-281 dec.	G	50.33 50.33	1.41 1.44	41.27 41.30	3.26 3.21
15	CH_2CH_2	H	H	$COCH(CO_2Et)_2$	92-94	H	71.90 72.18	5.57 5.51	---- ----	3.36 3.26
16	CH=CH	H	H	$COCH(CO_2Et)_2$	71-74	I	72.27 72.27	5.09 5.09	---- ----	3.37 3.51
17	CH_2CH_2	9,11-Cl_2	2-Cl	$COCH(CO_2Et)_2$	150-152	J	57.65 57.60	3.87 3.96	20.42 20.66	2.69 2.82
18	CH_2CH_2	9,11-Cl_2	3-Cl	$COCH(CO_2Et)_2$	154-157	J	57.65 57.52	3.87 3.84	20.42 (e)	2.69 2.50
19	CH=CH	9,11-Cl_2	3-Cl	$COCH(CO_2Et)_2$	161-163	K	57.87 57.82	3.49 3.60	20.50 20.65	2.70 2.57
20	CH_2CH_2	9,11-Cl_2	2,3-Cl_2	$COCH(CO_2Et)_2$	141-143	L	54.07 53.95	3.44 3.65	25.54 25.70	2.52 2.43
21	CH=CH	9,11-Cl_2	2,3-Cl_2	$COCH(CO_2Et)_2$	145-146	K	54.27 54.43	3.09 2.98	---- ----	2.53 2.36

TABLE I (continued)

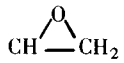
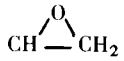
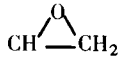
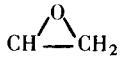
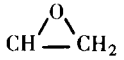
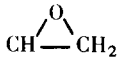
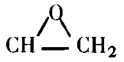
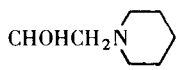
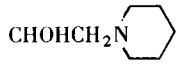
Compound Number	X	R^1	R^2	Y	M.p., °C	Crystn. Solvent (a)	Analyses (b) C	H	Cl	N
22	CH_2CH_2	H	H	$COCH_2Br$	94-96	H	64.78 64.92	4.00 3.99	(f) ----	3.97 4.05
22·HBr	CH_2CH_2	H	H	$COCH_2Br$	235-236 dec.	(g)	52.66 52.86	3.50 3.59	(h) ----	3.23 3.20
23·HBr	CH_2CH_2	H	H	$COCHBr_2$	234 dec.	(g)	44.54 44.41	2.76 2.50	(i) ----	2.73 2.61
24	CH_2CH_2	H	H	$COCH_3$	118	L	83.47 83.27	5.55 5.63	---- ----	5.13 5.05
25	CH=CH	H	H	$COCH_3$	105-107	M	84.11 84.20	4.83 4.86	---- ----	5.16 5.05
26	CH_2CH_2	H	H		82-85	H	83.48 83.32	5.53 5.39	---- ----	5.12 5.12
27	CH=CH	H	H		137-139	K	84.11 84.35	4.83 4.87	---- ----	5.16 5.19
28	CH_2CH_2	9,11-Cl_2	2-Cl		181-183 and 196-197 dec. (j)	L	60.58 60.52	3.21 3.09	28.23 28.44	3.72 3.60
29	CH_2CH_2	9,11-Cl_2	3-Cl		238-240 dec.	L	60.58 60.59	3.21 3.08	28.23 28.35	3.72 3.63
30	CH=CH	9,11-Cl_2	3-Cl		231-233 dec.	L	60.90 60.87	2.69 2.82	28.39 28.50	3.74 3.62
31	CH_2CH_2	9,11-Cl_2	2,3-Cl_2		247-248 dec.	L	55.50 55.61	2.69 2.60	34.49 34.25	3.41 3.37
32	CH=CH	9,11-Cl_2	2,3-Cl_2		270-271 dec.	O	55.77 55.63	2.22 1.94	34.66 34.92	3.42 3.21
33	CH=CH	9,11-Cl_2	2,3-Cl_2	 (7,12-dihydro)	247-251 dec.	L	55.50 55.52	2.69 2.73	34.49 34.80	3.41 3.33
34	CH_2CH_2	H	H	$CHOHCH_3$	193-196	(k)	82.87 82.75	6.22 6.28	---- ----	5.08 4.88
35	CH=CH	H	H	$CHOHCH_3$	167-168	(k)	83.48 83.26	5.53 5.50	---- ----	5.12 5.02
36	CH=CH	9,11-Cl_2	2,3-Cl_2	CH_2CH_2OH	247-251 dec.	D	55.50 55.52	2.69 2.72	34.49 34.29	3.41 3.40
37	CH_2CH_2	H	H		117-119	H	80.40 80.57	7.31 7.49	---- ----	7.81 7.81
38	CH=CH	H	H		140-142	M	80.86 80.87	6.78 6.89	---- ----	7.86 8.07

TABLE I (continued)

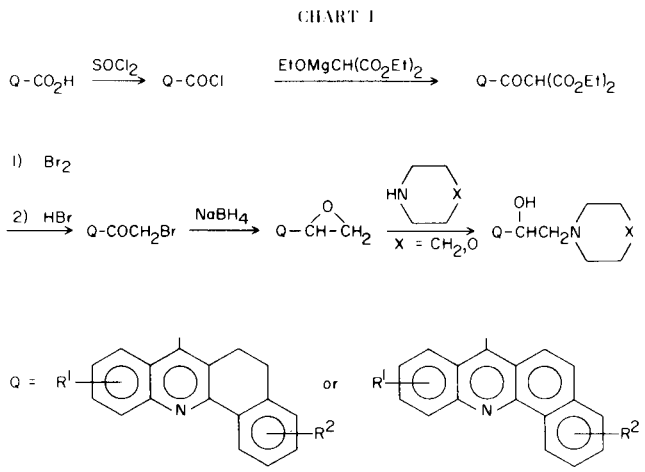
Compound Number	X	R^1	R^2	Y	M.p., °C	Crystn. Solvent (a)	Analyses (b) C	H	Cl	N
39	CH_2CH_2	9,11-Cl_2	2-Cl	$CHOHCH_2N$ 	186-188 dec.	N	62.41 62.15	5.01 5.29	23.03 22.74	6.06 5.87
40	CH_2CH_2	9,11-Cl_2	3-Cl	$CHOHCH_2N$ 	199-201 dec.	N	62.41 62.53	5.01 5.09	23.02 22.96	6.06 5.94
41	CH=CH	9,11-Cl_2	3-Cl	$CHOHCH_2N$ 	175-177 dec.	N	62.68 62.46	4.60 4.52	23.13 23.47	6.09 5.93
42	CH_2CH_2	9,11-Cl_2	2,3-Cl_2	$CHOHCH_2N$ 	198-200 dec.	N	58.08 57.72	4.46 4.27	28.57 28.85	5.64 5.39
43	CH=CH	9,11-Cl_2	2,3-Cl_2	$CHOHCH_2N$ 	204-206 dec.	N (l)	56.26 56.47	4.32 4.23	27.68 28.18	5.46 5.25
44	CH=CH	9,11-Cl_2	2,3-Cl_2	$CHOHCH_2N$  O	177-179 dec.	N	55.66 55.40	3.65 3.84	28.58 28.64	5.64 5.49
45	CH=CH	H	H	CHO	151-153 (m)	F	84.02 83.94	4.31 4.26	---- ----	5.44 5.23
46	CH_2CH_2	9,11-Cl_2	2,3-Cl_2	CHO	256 dec.	E	54.44 54.29	2.28 2.23	35.71 35.80	3.53 3.35
47	CH=CH	H	H	CH_2OH (7,12-dihydro)	157-159 (n)	F	82.73 83.07	5.78 6.05	---- ----	5.36 5.33
48	CH_2CH_2	9,11-Cl_2	2,3-Cl_2	CH_2OH	245-248 dec.	E	54.16 54.35	2.77 2.98	35.53 35.65	3.51 3.26

(a) A: methanol; B: acetic acid, water; C: ethanol; D: THF-hexane; E: benzene; F: benzene-hexane; G: thionyl chloride; H: ligroin (b.p. 60-90°); I: isopropyl ether-petroleum ether (b.p. 30-60°); J: isopropyl ether; K: ethyl acetate-hexane; L: ethyl acetate; M: ethyl acetate-ligroin (b.p. 60-90°): N: chloroform-hexane; O: THF. (b) Upper row: calculated, %; lower row: found, %. (c) Lit. (7a) m.p. 250-253° dec. (d) Lit. (7a) m.p. 261° dec. (e) Satisfactory chlorine analysis not obtained. (f) Br:Calcd., 22.69%. Found, 22.90%. (g) Reaction product analyzed without recrystallization. (h) Br: Calcd., 36.91%. Found, 36.89%. (i) Br: Calcd., 46.94%. Found, 46.83%. (j) Double melting point. (k) Purified only by column chromatography (see Experimental). (l) Analyzed as the monohydrate. (m) Lit. (31) m.p. 150°, (7d) 135°. (n) Lit. (23) m.p. 148-149°.

of eight benz[*c*]acridinemethanols were synthesized, of which four were 5,6-dihydro derivatives (II, X = -CH_2CH_2-) and four were fully aromatic (II, X = -CH=CH-). The structures and physical constants of these compounds, together with those of 40 other new benz[*c*]acridines prepared as intermediates or obtained as byproducts, are presented in Table I. Chloro-substituted targets were selected specifically for synthesis because of the high degree of biological activity shown by this particular type of substitution in the 2-phenyl-4-quinolinemethanol series (9).

Chloro-substituted 1-tetralones required for the synthesis of 5,6-dihydrobenz[*c*]acridine-7-carboxylic acids *via* the Pfitzinger reaction were obtained according to literature routes. 6-Chloro-1-tetralone and 7-chloro-1-tetralone were prepared from 6-amino-1-tetralone (10) and 7-amino-1-tetralone (11), respectively, *via* a Sandmeyer reaction. 6,7-Dichloro-1-tetralone, a compound not described prior to this investigation (12), was obtained from 3-(3′,4′-dichlorobenzoyl)propionic acid (13) by Wolff-Kishner reduction and subsequent ring closure in hot polyphosphoric acid. Condensations of 5,7-dichloroisatin with the foregoing 1-tetralones were conducted in aqueous alcoholic potassium hydroxide solution under typical Pfitzinger reaction conditions, but the low solubility of the tri- and tetra-

CHART I



chloro acids necessitated the development of somewhat modified work-up techniques for large-scale work. Whereas acids **3** and **6** were generally formed in yields of 50-80%, acid **4** could be obtained in only 10-30% yield. Aromatization of acids **4** and **6** to acids **5** and **7**, respectively, was accomplished in 70-80% yield by treatment with bromine in refluxing glacial acetic acid. Completion of the aromatization reaction was monitored by nmr spectral analysis in trifluoroacetic acid or dimethyl sulfoxide solution, which permitted the disappearance of the $-CH_2CH_2-$ to be followed. Reactions of carboxylic acids **3-7** with thionyl chloride proceeded in yields of 70-90%. The products (Table I, compounds **10-14**) differed from non-chlorinated analogs **8** and **9** in that removal of excess thionyl chloride under reduced pressure at the end of the reaction left only free bases, rather than hydrochloride salts. This was ascribed to decreased basicity of the nitrogen atom as a result of the presence of electron-withdrawing chlorine substituents (14). Conversion of **8**·HCl and **9**·HCl into the free bases was accomplished by rapid partition between chloroform and cold dilute aqueous sodium bicarbonate. The reported method of hydrogen chloride removal by azeotropic distillation with benzene (15) was found to be effective only with small samples.

Our initial plan for the elaboration of the antimalarial side chain was to convert the acids into methyl ketones by reaction with methyl lithium (the Tegner reaction) (4a), and to transform the latter into α-bromomethyl ketones. Unfortunately, pilot reactions of **1** and **2** with methyl lithium in ether at room temperature, or in tetrahydrofuran at 50°, invariably led to almost quantitative recoveries of starting materials. Because of the poor solubility characteristics of the benz[c]acridine-7-carboxylic acids, and in view of failures encountered occasionally by other investigators using the Tegner reaction (4f), we examined the possibility of employing acid chlorides instead of acids. Although the non-chlorinated methyl ketones **24** and **25** could be isolated, in several experiments, after treatment of the acid chlorides with methyl lithium in ether at 0°, the reaction proved capricious and difficult to control; even slight variations in experimental procedure gave rise to an unwanted side product whose structure was not investigated. Moreover, all efforts to apply the reaction with chlorinated analog **13** under a variety of conditions (*e.g.* at -70° in tetrahydrofuran) failed to give a methyl ketone.

Reaction of acid chlorides **8** and **14** with diazomethane and treatment with hydrobromic acid as prescribed by Lutz (15) and others (4d-4g, 4i) resulted mainly in the isolation of unchanged starting materials, or of carboxylic acids arising from hydrolysis during work-up. Infrared analysis of the crude material isolated on treatment of **8** with diazomethane at room temperature overnight, or at 5° for 9 days, revealed the presence of only a trace of diazoketone, which gave weak absorption at 2120 cm^{-1} (16).

Attempted bromination of methyl ketone **24** with sodium bromate and hydrobromic acid (15) failed to yield the desired α-bromomethyl ketone **22**, but gave instead a compound with the empirical formula $C_{19}H_{14}Br_3NO$. The nmr spectrum of this material, taken in dimethyl sulfoxide solution, indicated complete disappearance of the methyl group and retention of the CH_2CH_2 bridge, but showed no signal in the τ 5.0-6.0 region corresponding to the $COCH_2Br$ function. Instead, a singlet was noted at τ 2.57 which was in accord with the presence of a $COCHBr_2$ group. Thus, the bromination product was formulated as the α,α-dibromomethyl derivative, **23**·HBr. Although parallel trial runs with methyl ketone **25** suggested that monobromination could be achieved in the aromatic series, numerous attempts to effect selective monobromination in the dihydro series were unsuccessful.

The introduction of a single bromine atom in the side chain was finally realized *via* the acyl malonate route pioneered by Walker and Hauser (17) and recently utilized for the synthesis of quinolinemethanols by Olsen (8). As shown in Chart I, acid chlorides were condensed with diethyl ethoxymagnesium malonate in tetrahydrofuran, and the resulting activated ketodiesters were subjected to bromination in chloroform and direct acid-catalyzed hydrolysis and decarboxylation. The acyl malonates (Table I, compounds **15-21**) were obtained for the most part in yields of 70-90%. Higher yields resulted from acid chlorides with electron-withdrawing chloro substituents. Infrared spectra of the acyl malonates taken in the solid state as well as in chloroform solution exhibited strong carbonyl absorption at 1750 cm^{-1} and a characteristic pair of peaks at 1640 cm^{-1} and 1610 cm^{-1} ascribable to the internally hydrogen-bonded form of a β-ketoester. Nmr spectra in deuteriochloroform solution displayed an interesting non-

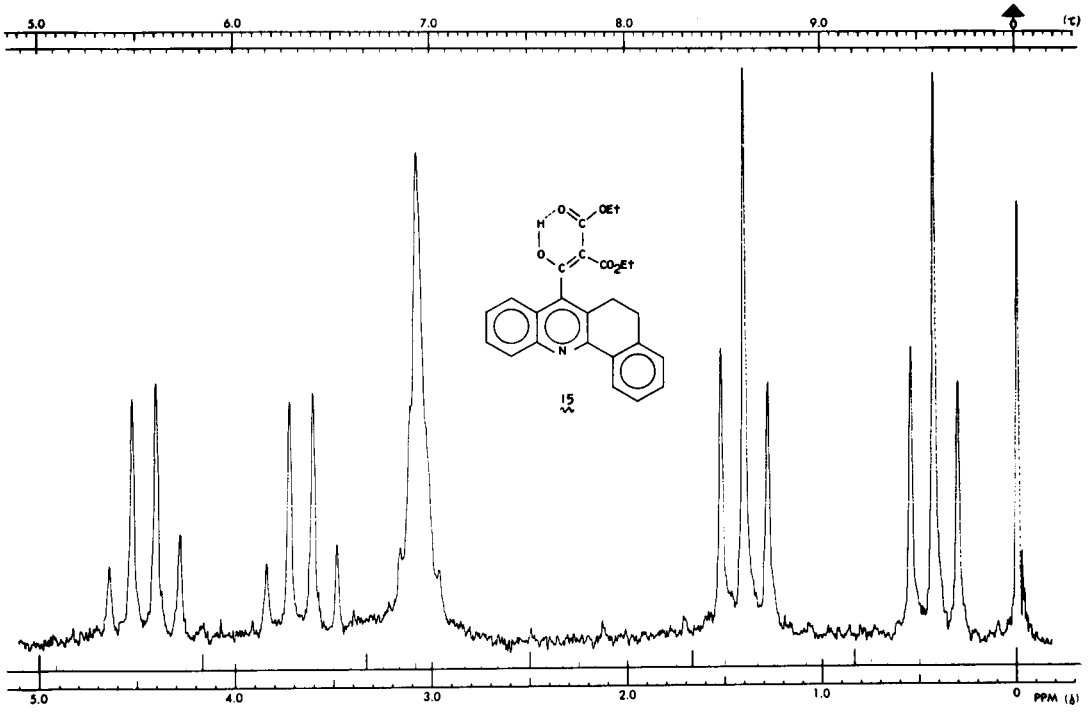


Figure 1

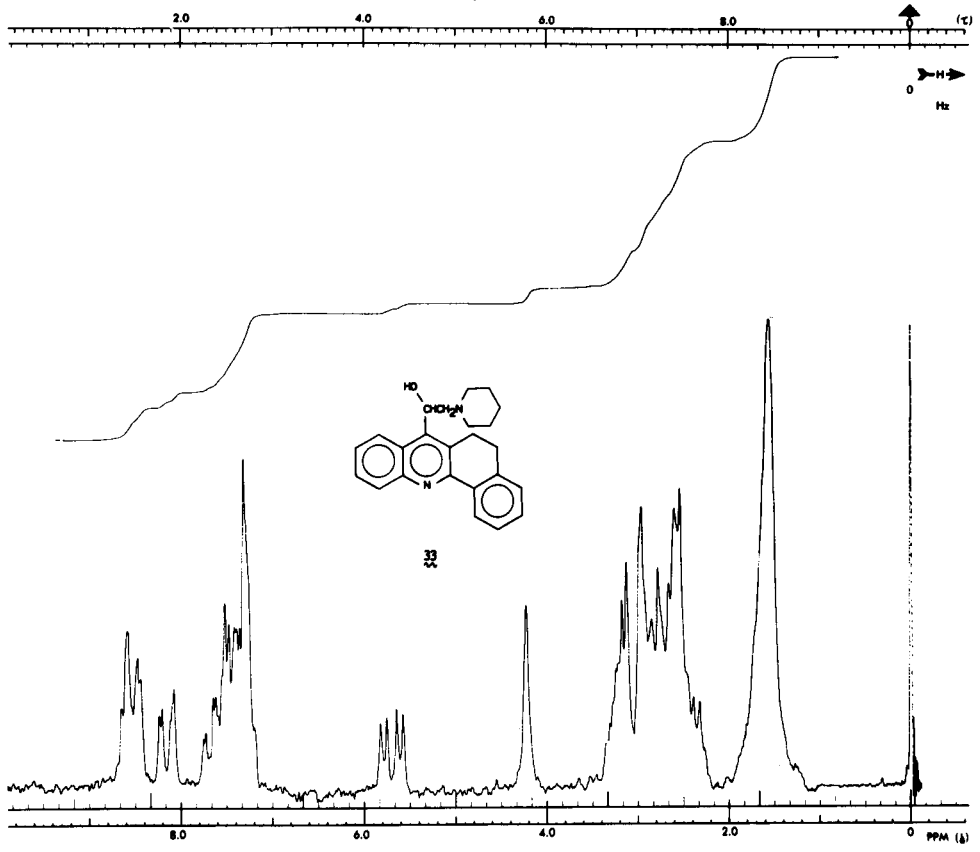


Figure 2

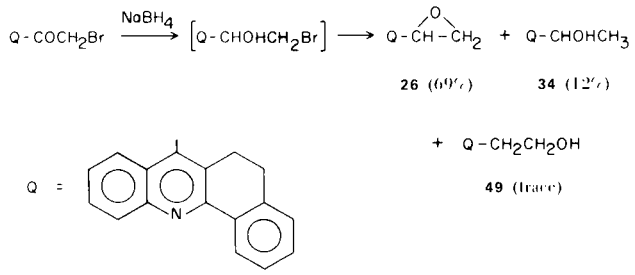
equivalence of the two ester functions. A typical illustration is the spectrum of compound **15** shown in Figure 1. In addition to the CH_2CH_2 signal at τ 6.93 (broad singlet, with fine structure), there were two methylene quartets centered at τ 5.55 and τ 6.35 and two methyl triplets centered at τ 8.60 and τ 9.58, respectively. The abnormally high magnetic field of one of the ethyl group signals suggests shielding by the ring current associated with the π electrons of the quinoline ring. Convincing support for this view was provided by molecular models, which showed the sterically least hindered configuration to be one having the non-associated ester function above the plane of the quinoline ring.

Bromination of the acyl malonates in chloroform solution proceeded rapidly and without concomitant attack at the benzylic positions of the bridge. Hydrolysis and decarboxylation of the unpurified bromoketodiesters was performed in a mixture of hydrobromic and acetic acids under reflux. Nmr spectra of the crude decarboxylated products showed a preponderance (75-85%) of the expected α-bromomethyl ketones, together with minor amounts (15-25%) of the corresponding methyl ketones which proved to be difficult to separate by conventional techniques of crystallization or chromatography. Formation of methyl ketones at the expense of α-bromomethyl ketones was markedly time-dependent, and could never be eliminated as a side reaction. Optimum α-bromomethyl ketone/methyl ketone ratios were realized only when refluxing of the chloroform solution did not exceed 30 minutes. Overall yields calculated on the basis of the starting acyl malonates fell in the 65-85% range. In the sole instance in which an analytically pure specimen of α-bromomethyl ketone was obtained (Table I, compound **22**), purification required multiple recrystallization from ligroin.

Methyl ketones are known to be byproducts in the synthesis of α-bromomethyl ketones *via* the acyl malonate route, and are believed to originate by disproportionation of the α-bromomethyl ketones (2 Q-$COCH_2Br$ + HBr → Q-$COCH_3$ + Q-$COCHBr_2$). It is assumed that this side reaction takes place mainly during the hydrolysis and decarboxylation step. Moreover, since hydrogen bromide is liberated during bromination, disproportionation may occur to a small extent at this stage as well. It is therefore of interest that, in the present series, no evidence of α,α-dibromomethyl ketone formation was noted. Although the disproportionation mechanism appears to be excluded, the origin of the methyl ketones remains unclear.

Because of the effort required to effect complete separation of the α-bromomethyl and methyl ketones, the synthesis of epoxides *via* sodium borohydride reduction (18) and treatment with alkali (Chart I) was usually carried out with unpurified mixtures. As anticipated, the epoxides (Table I, compounds **26-32**) were accompanied by secondary alcohols resulting from reduction of the methyl ketones and further reduction of the epoxides themselves (*vide infra*). The difference in polarity between the epoxides and alcohols permitted fractionation at this stage by column chromatography on silica gel. The epoxides were obtained in 50-75% yield (calculated on the basis of the estimated amount of α-bromomethyl ketone in α-bromomethyl ketone/methyl ketone mixture used), and were identified by their nmr spectra, which displayed features characteristic of the epoxide ring in styrene oxide (19). For example, the spectrum of epoxide **27** showed a methinyl triplet at τ 5.42 (with some fine structure probably due to coupling with the neighboring aromatic protons at C-6 and C-8) and a typical eight peak ABX pattern consisting of two widely spaced pairs of doublets at τ 6.59 and τ 7.10, respectively. Secondary alcohols accompanying the epoxides were distinguished by the appearance of a methyl doublet at higher field. Thus, the spectrum of alcohol **34** showed a methyl doublet at τ 8.22 (J = 6.5 Hz), as well as a methinyl multiplet at τ 3.93 and a broad hydroxyl singlet at τ 5.33 which disappeared on addition of a drop of deuterioacetic acid. The CH_2CH_2 bridge gave rise, in this instance, to a well-defined A_2B_2 pattern consisting of two triplets at τ 7.20 and τ 6.68.

It is of interest that, whereas sodium borohydride reduction of α-bromomethyl ketones had been expected to yield bromohydrins, tlc analysis actually disclosed extensive spontaneous cyclization to epoxides even before the addition of aqueous alkali (4f, 4g). Analysis of the course of reaction was performed with a sample of α-bromomethyl ketone **22** known to contain no trace of methyl ketone **24**. Column chromatography on silica gel led only to the isolation of epoxide **26**, secondary alcohol **34**, and a minute amount of another, slower-moving alcohol to which structure **49** was assigned; no trace of bromohydrin was detected either by tlc or column chromatography. The formulation of compound **49** was based upon its nmr spectrum, which contained a multiplet at τ 7.05 corresponding to the methylene protons of the bridge, a typical A_2B_2 pattern consisting of two triplets at τ 6.13 and τ 6.65 which could be ascribed to the methylene protons of the side chain, and a broad hydroxyl singlet at τ 7.80 which disappeared in the presence of deuterioacetic acid. Secondary alcohol **34** was crystalline and only sparingly chloroform-soluble, whereas primary alcohol **49** was an oil dissolving readily in chloroform and other non-polar solvents. The spontaneous formation of epoxides during sodium borohydride reduction of the α-bromomethyl ketones, as well as the apparent ability of the epoxides to undergo further reduction to primary and secondary alcohols, are phenomena that have not been cited previously in the quinolinemethanol series.



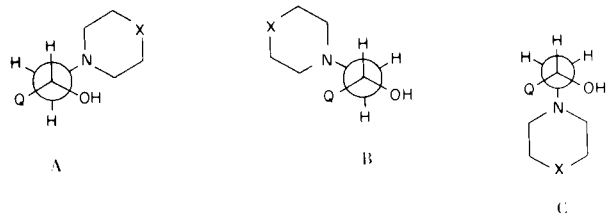
It is also of interest that, whereas epoxides **26-31** were generated without complication on reduction of the corresponding α-bromomethyl ketones with sodium borohydride at room temperature, attempted preparation of the fully aromatic tetrachloro epoxide **32** under these conditions unexpectedly gave the 7,12-dihydro derivative **33** (Table I). The structure of **33** was deduced on the basis of microanalysis and spectral characteristics. The ultraviolet absorption spectrum (see Experimental) indicated 7,12-reduction of the benz[*c*]acridine moiety; the nmr spectrum in deuteriopyridine solution showed multiplets at 7.38 (2*H*), 6.78 (1*H*), and 5.76 (1*H*) consistent with the epoxide ring. Further exposure of **33** to the action of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in tetrahydrofuran solution gave the desired **32**.

Trial experiments aimed at the development of satisfactory general conditions for the final step of the synthesis of *N,N*-dialkylaminoalkyl carbinol derivatives (Chart I) were performed with epoxide **27** as a model. Most unexpectedly, and in contrast to the reported ease of similar reactions with non-bridged quinolinemethanol epoxides (4), attempts to effect condensation of **27** with di-*n*-butylamine met consistently with failure. Reactions were conducted with or without *N,N*-dimethylformamide as a solvent, as well as in the presence or absence of small amounts of di-*n*-butylamine hydrobromide as a catalyst. Heating **27** with di-*n*-butylamine in *N,N*-dimethylformamide at 100° for 22 hours and then at 160° for 4 hours gave a mixture containing a large proportion of unreacted starting material, together with four other compounds whose separation was not attempted. In another experiment, conducted at 90°, aliquots subjected periodically to tlc and infrared analysis indicated gradual thermal isomerization of the epoxide into a carbonyl compound. However, even after two weeks at 90°, no product having the characteristics of an amino alcohol was detected. The apparent lack of reactivity of the epoxide ring in **27** was ascribed to steric hindrance.

Replacement of di-*n*-butylamine with piperidine, a much more potent nucleophile (20), allowed epoxide **27** to be transformed into amino alcohol **38** in 77% yield after just 6 hours at 110°. In similar fashion, the remaining epoxides gave amino alcohols **37** and **39-43**, respectively, in yields of 70-95%; epoxide **32** also yielded amino alcohol **44** on reaction with morpholine.

A novel reaction was discovered when the 7,12-dihydro epoxide **33** was treated with piperidine in an effort to prepare the corresponding amino alcohol. Instead of the anticipated product, there was obtained a 76% yield of 3,9,11-trichloro-7-(2-hydroxyethyl)benz[*c*]acridine (**36**). The identity of this material was established on the basis of its microanalysis and spectral characteristics. The nmr spectrum, taken in deuteriopyridine solution, displayed features similar to those of alcohol **43**, including methylene signals at τ 5.75 and τ 6.05 (two-proton multiplets). Formally, this appears to be an internal disproportionation process wherein the 7,12-dihydrobenz[*c*]acridine moiety undergoes oxidation and the epoxide ring is reduced; however, the exact mechanistic aspects of this unusual reaction remain to be investigated in fuller detail.

Nmr spectra of amino alcohols **37-44** furnished significant information concerning the stereochemistry of the piperidinomethyl or morpholinomethyl carbinol side chain. For example, the spectrum of compound **37** (Figure 2) showed, in addition to various aromatic and methylene signals, a characteristic doublet of doublets centered at τ 4.30, corresponding to the methinyl proton in an ABX system. Inasmuch as a system of this type requires the protons of the adjacent methylene group to be magnetically non-equivalent, it appears likely that the side chain exists preferentially in a unique stereochemical conformation, and that free rotation about the carbon-carbon single bond does not occur at ordinary temperatures. Consideration of the three possible stereochemical projections depicted below led us to select **A** as the most probable conformation for these compounds. This structure is favored not only because it permits maximum separation of bulky groups, but also because it provides an opportunity for stabilization *via* hydrogen bonding of the hydroxyl proton to the piperidine or morpholine nitrogen.



A possible alternative synthesis of the epoxides also explored during this investigation was the reaction of benz[*c*]acridine-7-carboxaldehydes with sulfur ylides (21). Following the initiation of our program, Duncan and coworkers (22) reported the preparation of several azaphenanthrene epoxides *via* the ylide reaction, but did not comment upon the potentialities of their approach with respect to quinoline-4-carboxaldehydes, acridine-9-carbox-

aldehydes, or other compounds of similar structure. Accordingly, the synthesis of aldehydes **45** and **46** (Table I) was carried out as described below, starting from acids **2** and **6**.

Reduction of acid **2** with lithium aluminum hydride in tetrahydrofuran gave the known 7,12-dihydro derivative **47** (23), identified on the basis of spectral evidence. The ultraviolet spectrum showed strong resemblance to that of *N*-phenyl-1-naphthylamine (24). The nmr spectrum, taken in deuteriochloroform solution, showed the expected AB_2 pattern, consisting of a triplet centered at τ 5.74 and a doublet centered at τ 6.33. In addition, singlets at τ 3.16 and τ 8.46 were present, corresponding to the amino and hydroxy protons, respectively. Addition of deuterium oxide caused disappearance of these peaks after a few minutes. Treatment of **47** with selenium dioxide in acetic acid led to oxidation of the alcohol function and concurrent aromatization. The resulting aldehyde **45**, previously made by oxidation of 7-methylbenz[c]acridine (7d), was characterized by the appearance, in the nmr spectrum in deuteriochloroform solution, of a sharp singlet at τ 1.18 and by the absence of all methylene or methinyl absorption.

Treatment with diborane in tetrahydrofuran transformed acid **6** into alcohol **48** in 95% yield, and oxidation of the latter with dimethyl sulfoxide in the presence of dicyclohexylcarbodiimide and phosphoric acid (25) gave aldehyde **46**. The nmr spectrum of the alcohol, taken in deuteriopyridine solution, showed the side chain methylene as a singlet at τ 4.85 and the bridge methylenes as an A_2B_2 pattern centered at τ 7.00. The spectrum of the aldehyde, in the same solvent, showed the disappearance of the side chain methylene, the retention of the bridge methylenes, and the appearance of a sharp singlet at τ 1.00.

Despite numerous trials, all attempts to obtain epoxides **27** and **31** from aldehydes **45** and **46** *via* the ylide route met with failure. Aldehyde **45** was allowed to react with dimethyl sulfonium methylide in tetrahydrofuran at 0° and -50°, and with dimethyl sulfoxonium methylide in dimethyl sulfoxide at room temperature. Deep red solutions were formed in every instance, which were reminiscent of the color observed earlier in reactions of the acid chlorides with methyl lithium (26). When tlc analysis revealed the presence of as many as eight compounds in the crude product, and infrared as well as nmr spectra failed to show any epoxides in the mixture, work on the ylide approach was terminated.

Biological Activity.

The benz[c]acridinemethanols prepared during the course of this work were tested for antimalarial activity according to the standardized evaluation procedure described previously in the literature (27). Against *Plasmodium berghei* in the mouse, amino alcohol **41** brought about a significant prolongation in survival time (T/C = 17.2/6.1 days) at a dose of 20 mg./kg. At doses of 40 to 320 mg./kg., this compound was curative (*i.e.* 60-day survival) in all test animals, and no toxic deaths were observed. The 5,6-dihydro analog **40** was active at 40 mg./kg. (T/C = 14.2/6.1 days) and curative at higher doses. No significant activity was observed against *Plasmodium gallinaceum* in chicks. More detailed antimalarial data for amino alcohols **37-44**, as well as the results of phototoxicity studies being conducted by Dr. W. E. Rothe, Walter Reed Army Institute of Research, will be reported at a later date.

EXPERIMENTAL (28)

6-Chloro-1-tetralone.

To a suspension of 6-amino-1-tetralone (10) (106 g., 0.66 mole) in a mixture of concentrated hydrochloric acid (200 ml.) and water (130 ml.) was added at 0-5° with stirring a solution of sodium nitrite (46 g., 0.67 mole) in water (150 ml.), followed by cuprous chloride (75 g., 0.75 mole) in concentrated hydrochloric acid (600 ml.). The temperature was gradually raised to 60° in order to complete the reaction. Steam distillation, extraction of the distillate with chloroform (2 x 200 ml.), decolorization with charcoal, drying, solvent removal, and vacuum distillation afforded 50 g. (42% yield) of colorless liquid, b.p. 102-104° (0.25 mm.) [lit. (29) b.p. 167-169° (18 mm.)]; nmr (deuteriochloroform), τ 7.83 (multiplet, 3-CH_2), τ 7.35 and τ 7.05 (triplets, 2-CH_2 and 4-CH_2), τ 2.72 (multiplet, C-5 and C-7 protons), τ 2.05 (doublet, J = 9 Hz, C-8 proton). The *oxime* derivative melted at 145.5-146° (ethanol) (30).

4-(3,4-Dichlorophenyl)butanoic Acid.

To a solution of potassium hydroxide (120 g., 2.2 moles) in diethylene glycol (640 ml.) at 70° was added 4-(3,4-dichlorophenyl)-4-oxobutanoic acid (13) (160 g., 0.65 mole) and 95% hydrazine (48 g., 1.1 moles). After 1 hour of stirring under reflux, the condenser was removed and the internal reaction temperature was allowed to rise to 170°. The condenser was replaced, and the reaction maintained at 170° for 2 hours, cooled, and poured into ice water (4 liters) and concentrated hydrochloric acid (280 ml.). After overnight refrigeration, the gummy solid was collected on a filter, washed with water (4 x 800 ml.), and dried; 17 g. (84% yield), m.p. 63-65°. Analytically pure material, m.p. 67-68.5°, was obtained by crystallization from chloroform-ligroin (b.p. 30-60°) or benzene.

Anal. Calcd. for $C_{10}H_{10}Cl_2O_2$: C, 51.50; H, 4.29. Found: C, 51.44; H, 4.35.

6,7-Dichloro-1-tetralone.

4-(3,4-Dichlorophenyl)butanoic acid (100 g., 0.43 mole) was heated in polyphosphoric acid (1 kg.) at 80° for 1 hour with occasional stirring. The mixture was poured into ice water (2 liters), and the gummy precipitate was filtered, washed with dilute hydrochloric acid, and crystallized from aqueous alcohol. If desired, the product can be isolated from the ice water mixture by repeated extraction with chloroform, rinsing of the combined chloroform layers with 10% sodium bicarbonate and then water, treatment with charcoal, and evaporation to dryness. Analytically pure 6,7-dichloro-1-tetralone had m.p. 106.5-107.5°; nmr (deuteriochloroform), τ 7.75 (multiplet, 3-CH_2), τ 7.25 and τ 7.00 (triplets, 2-CH_2 and 4-CH_2), τ 2.56 (singlet, C-5 proton), and τ 1.82 (singlet, C-8 proton).

Anal. Calcd. for $C_{10}H_8Cl_2O$: C, 55.81; H, 3.72; Found:

C, 55.99; H, 3.73.

The *oxime* derivative had m.p. 204-205° (ethanol).

Anal. Calcd. for $C_{10}H_9Cl_2NO$: C, 52.17; H, 3.91. Found: C, 52.31; H, 3.96.

The *2,4-dinitrophenylhydrazone* melted at 257° (ethanol-ethyl acetate).

Anal. Calcd. for $C_{16}H_{12}Cl_2N_4O_4$: C, 48.68; H, 3.04. Found: C, 48.76; H, 3.02.

Carboxylic Acids (**1-7**).

Pfitzinger Reactions. Preparation of Compound **4**.

A mixture of 6-chloro-1-tetralone (36 g., 0.2 mole), 5,7-dichloroisatin (ROC/RIC Chemical Corp., Sun Valley, Calif.) (43 g., 0.2 mole), absolute ethanol (200 ml.), and 33% aqueous potassium hydroxide (100 ml.) was stirred under reflux for 48 hours. After evaporation to dryness under reduced pressure, the residue was washed repeatedly with benzene and treated with 20% acetic acid (250 ml.) and water (850 ml.) to convert the potassium salt into the free acid. The crude acid was digested with boiling 10% sodium hydroxide (200 ml.), water (1500 ml.) was added, and the boiling mixture was decolorized with charcoal and filtered. Acidification of the filtrate with concentrated hydrochloric acid (50 ml.) gave **4** as a yellow powder (59 g., 78% yield). Analytically pure material was obtained by crystallization from ethanol. In the synthesis of acid **6**, several passages through the sodium salt were required in order to effect purification. In the synthesis of **3**, material purified *via* the sodium salt also had to be crystallized from a large volume of aqueous acetone.

Aromatization Reactions. Preparation of Compound **7**.

A mixture of acid **5** (44 g., 0.11 mole), bromine (43 g., 0.27 mole), and glacial acetic acid (400 ml.) was stirred under reflux for 24 hours, additional bromine (43 g., 0.27 mole) was added, and reflux was resumed. After a total of 48 hours, the mixture was poured into water (3.5 liters) and refrigerated. The product (36 g., 82% yield) was obtained as a light yellow solid.

Carboxylic Acid Chlorides (**8-14**).

The carboxylic acid was refluxed with excess thionyl chloride (3 ml./g. for compounds **8** and **9**; 10-12 ml./g. for compounds **10-14**) for 4-6 hours. In the preparation of **8** and **9**, excess thionyl chloride was removed under reduced pressure, the residue was partitioned between chloroform and cold dilute aqueous sodium bicarbonate, and the dried chloroform layer was evaporated under reduced pressure. Compounds **11**, **13** and **14** crystallized directly from the cooled thionyl chloride reaction mixture; compounds **10** and **12** crystallized only after dilution with ether.

Acyl Malonates (**15-21**). Preparation of Compound **20**.

A mixture of magnesium turnings (1.1 g., 0.044 g. atom), absolute ethanol (4 ml.), carbon tetrachloride (1 ml.) and dry tetrahydrofuran (80 ml., dried over Linde type 3A molecular sieves) was heated to reflux with stirring. A solution of diethyl malonate (7.0 g., 0.044 mole) in absolute ethanol (8 ml.) and tetrahydrofuran (60 ml.) was then added dropwise during 30 minutes, and refluxing and stirring were continued for another 30 minutes. The solution was cooled and transferred during 30 minutes *via* a pressure-compensated dropping funnel to a rapidly stirred suspension of compound **13** (17 g., 0.04 mole) in boiling tetrahydrofuran (500 ml.). After another 3 hours, the solution was concentrated under vacuum to one-third volume and poured into ice (400 g.) and concentrated sulfuric acid (40 ml.). The mixture was extracted with chloroform, the extracts were filtered to remove some fluffy insoluble material, and the chloroform solution was washed with water and dried. Evaporation under reduced pressure left 19.3 g. (87%) of light tan solid.

α-Bromomethyl Ketones.

Reactions performed using compound **19** are illustrative. To a stirred, refluxing solution of **19** (16 g., 0.03 mole) in chloroform (150 ml.) was added dropwise during 15 minutes a solution of bromine (5.3 g., 0.033 mole) in chloroform (30 ml.). After another 15 minutes the chloroform was evaporated under reduced pressure, and the reddish-brown solid was dissolved in a mixture of glacial acetic acid (175 ml.) and 48% aqueous hydrobromic acid (30 ml.). After being refluxed with stirring for 30 minutes, the solution was cooled and poured into ice and water (400 ml.), and the precipitated yellow solid was filtered, washed with water and dried; 13 g., m.p. 215-219° dec. Nmr analysis (deuteriopyridine) indicated the presence of about 75% α-bromomethyl ketone (τ 4.78, $COCH_2Br$) and 25% methyl ketone (τ 7.15, $COCH_3$). The other acyl malonates (**15-18, 20, 21**) likewise gave high yields of solids containing about 80-85% α-bromoketone and 15-20% methyl ketone. The only α-bromoketone yielding to ready purification was compound **22** which could be obtained pure by repeated recrystallization from ligroin. α-Bromoketone/methyl ketone mixtures were used without further purification for the formation of epoxides.

Epoxides (**26-33**).

Preparation of Compound **30**.

To a stirred solution of the foregoing α-bromoketone/methyl ketone mixture (7.5 g., calculated by nmr analysis to contain 5.9 g., 0.013 mole, of α-bromoketone) in tetrahydrofuran (130 ml.) and water (40 ml.) (95% ethanol was used as solvent for the nonchlorinated bromoketone mixtures) was added powdered sodium borohydride (6.5 g., 0.017 mole) in portions, over a period of 10 minutes. After 30 minutes at room temperature, a solution of potassium hydroxide (9.7 g., 0.017 mole) in water (50 ml.) was added. After another 20 minutes, most of the tetrahydrofuran was removed under reduced pressure and water (50 ml.) was added. The precipitated yellow solid (5.6 g.) was dissolved in warm benzene and chromatographed on 250 g. of silica gel (Baker 3405) using benzene or chloroform as the eluent. The epoxide was eluted rapidly in the first few fractions, the alcohols being retained on the column. Evaporation of the benzene eluates gave the epoxide (3.5 g., 73% yield based on α-bromoketone) as a yellow solid.

Preparation of Compound **32**.

When the α-bromoketone/methyl ketone mixture derived from acyl malonate **21** was subjected to the foregoing reaction and work-up conditions, the product isolated in 65% yield after column chromatography on silica gel (elution with benzene) was the 7,12-dihydro epoxide **33** (see Table I). A sample recrystallized from ethyl acetate gave pale yellow needles; nmr (deuteriopyridine) τ 7.38 (multiplet, 2*H*), 6.78 (multiplet, 1*H*), 5.76 (multiplet, 1*H*); uv λ max (abs. ethanol) 267 nm (ϵ, 29,870), 287 nm (ϵ, 16,980), 303 nm (ϵ, 11,230), 351 nm (ϵ, 9,080), 373 nm (infl., ϵ, 6,420). A mixture of **33** (2.1 g., 0.0051 mole) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (2.3 g., 0.01 mole) in tetrahydrofuran (50 ml.) was stirred under reflux for 15 minutes, cooled, and filtered. Recrystallization of the ethanol-washed solid (2.0 g., 96% yield) from tetrahydrofuran gave **32** in the form of pale yellow needles.

Amino Alcohols (**37-44**).

The epoxides were dissolved in excess piperidine or morpholine (12-15 ml./g.) and heated under reflux for 6-7 hours. After removal

of excess amine under reduced pressure, recrystallization of the solid residues from appropriate solvents (Table I) gave the pure amino alcohols in yields of 70-95%.

3,9,11-Trichloro-7-(2-hydroxyethyl)benz[c]acridine (**36**).

A mixture of epoxide **33** (1.72 g., 0.0041 mole) and piperidine (20 ml.) was refluxed for 7 hours. Removal of the amine under vacuum left a reddish-brown solid which was dissolved in chloroform (10 ml.). Addition of *n*-hexane (10 ml.) and cooling gave 1.3 g. (76% yield) of cream-colored solid; nmr (deuteriopyridine) τ 6.05 (multiplet, 2*H*), 5.75 (multiplet, 2*H*); uv λ max (abs. ethanol) 287 nm (ϵ, 65,100), 302 nm (ϵ, 54,400), 332 nm (infl., ϵ, 5,540), 346 nm (infl., ϵ, 7,590), 360 nm (ϵ, 8,440), 372 nm (ϵ, 9,700), 390 nm (ϵ, 7,270).

5,6-Dihydro-7-hydroxymethyl-2,3,9,11-tetrachlorobenz[c]acridine (**48**).

To a stirred solution of compound **6** (17 g., 0.040 mole) in ice-cold dry tetrahydrofuran (200 ml.) was added 80 ml. of a 1.0 *M* solution of diborane in tetrahydrofuran (Alfa Inorganics, Inc.) over a period of 15 minutes. After 3 hours at room temperature, ethanol (15 ml.) was added, followed by 6 *N* hydrochloric acid (30 ml.). The mixture was stirred for 15 minutes, concentrated under reduced pressure to a volume of about 100 ml. and poured into 10% aqueous sodium hydroxide (200 ml.) containing some cracked ice. After 2 hours, the tan solid was filtered off, washed with water, and dried; 15 g. (95% yield).

5,6-Dihydro-2,3,9,11-tetrachlorobenz[c]acridine-7-carboxaldehyde (**46**).

To a stirred solution of compound **48** (0.2 g., 0.005 mole) and dicyclohexylcarbodiimide (0.3 g., 0.0015 mole) in dry dimethyl sulfoxide (10 ml.) was added 0.05 ml. of a 1.0 *M* solution of phosphoric acid in dimethyl sulfoxide. After 24 hours at 80°, the solution was cooled, and ethyl acetate (20 ml.) was added, followed by oxalic acid (0.09 g., 0.001 mole). After being stirred for 15 minutes, the mixture was filtered, and the filtrate was poured into 2% aqueous sodium hydroxide (50 ml.) solution and extracted with chloroform. The extracts were washed with water, dried, concentrated under reduced pressure to a volume of about 25 ml., and filtered through a column of silica gel (15 g.), using chloroform as the eluent. Evaporation of the eluate gave aldehyde **46** (0.13 g., 66% yield) as a yellow solid.

7,12-Dihydro-7-hydroxymethylbenz[c]acridine (**47**).

To a cooled, stirred solution of lithium aluminum hydride (3.8 g., 0.1 mole) in dry tetrahydrofuran (400 ml.) was added compound **2** (14 g., 0.05 mole) over a period of 15 minutes. The mixture was then refluxed for 4 hours, cooled, and treated dropwise with ethyl acetate (10 ml.), followed by saturated aqueous sodium chloride (20 ml.). The mixture was filtered through Celite, and the filtrate was concentrated to a red oil under reduced pressure. The oil was dissolved in dichloromethane, and the solution was washed twice with 5% aqueous sodium hydroxide, rinsed with water, and dried. Evaporation left alcohol **47** (9.6 g., 74% yield); uv λ max (95% ethanol), 258 nm (ϵ, 19,200), 275 nm (infl., ϵ, 12,250), 283 nm (infl., ϵ, 9,580), and 345 nm (ϵ, 9,180).

Benz[c]acridine-7-carboxaldehyde (**45**).

A mixture of compound **47**, (4.1 g., 0.016 mole), selenium dioxide (3.5 g., 0.032 mole), and glacial acetic acid (75 ml.) was heated, with stirring, at 100° for 3 hours. The mixture was cooled, and filtered through Celite, and the filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform, and the solution was washed with 5% aqueous sodium hydroxide and with water. Evaporation of the dried organic layer left the crude aldehyde as an orange solid (2.5 g., 61% yield). For purification, the solid was dissolved in benzene and filtered through silica gel (50 g.). Elution with benzene afforded **45** as a yellow solid. When the crude product was filtered through alumina, a Cannizzaro reaction occurred on the column, 7-hydroxymethylbenz[c]acridine being eluted with benzene instead of the desired aldehyde. This compound, when recrystallized from benzene-hexane, had m.p. 160-164° [lit. (**23**) m.p. 165°]; nmr (deuteriopyridine), τ 4.18 (singlet, CH_2OH).

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