3-Chloro-9-(4-diethylamino-1-methylbutylamino)-acridine 10-Oxide and other 9-Aminoacridine N-Oxides

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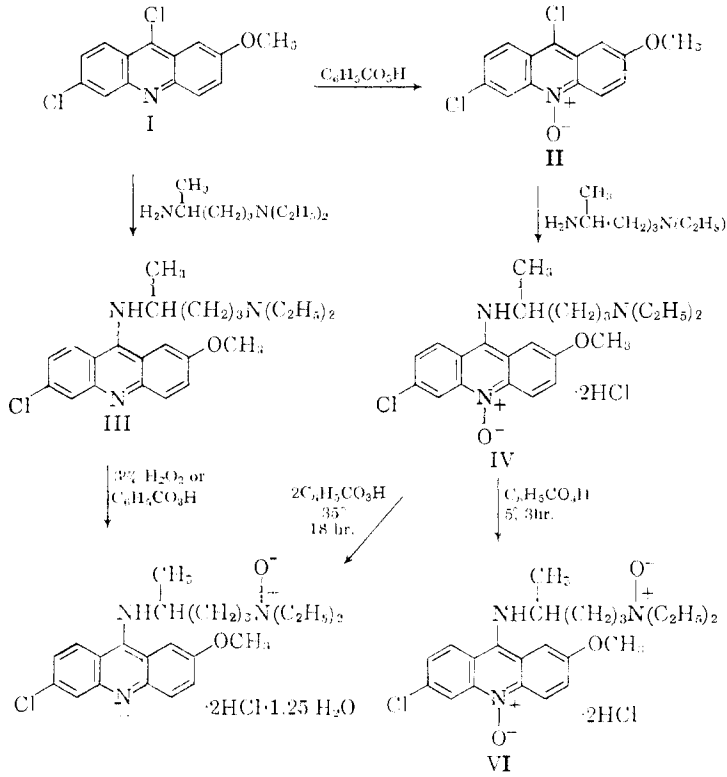
Authentic samples of quinacrine N^{ω}-oxide, 10-oxide, and N^{ω},10-dioxide have been prepared for antiparasitic testing, together with a variety of 9-(mono and dialkylaminoalkylamino)acridine 10-oxides. The latter compounds were prepared by the condensation of the appropriate 9-chloroacridine 10-oxide with a mono or dialkylaminoalkylamine in phenol. 3-Chloro-9-(4-diethylamino-1-methylbutylamino)acridine 10-oxide dihydrochloride exhibits promising antimalarial activity in experimental animals and in man.

In 1946 Linsker and Bogert[1] reported the isolation of an oxidation product of quinacrine (III) that was assigned the N^{ω},10-dioxide structure VI. This N-oxide was prepared in the hope that it would exhibit a more favorable chemotherapeutic index than quinacrine. These hopes were not realized, however, and biological tests demonstrated that N-oxidation exerted a deleterious effect on the chemotherapeutic properties of quinacrine. Thus, the so-called N^{ω},10-dioxide proved to be only one-half, one-third, and one-fifth as active as quinacrine against *Plasmodium gallinaceum* in the chick, *P. lophurae* in the duck, and *P. cathemerium* in the duck, respectively.[2] Studies in mice showed no significant difference in toxicity between the two compounds.[1,2]

Attempts by other investigators[3] to oxidize acridines to acridine 10-oxides with aqueous hydrogen peroxide have been unsuccessful. The apparent discrepancy between these reports and the quinacrine N^{ω},10-dioxide structure assigned by Linsker and Bogert prompted us to reinvestigate this problem. We repeated the oxidation of quinacrine base with cold 3% hydrogen peroxide according to the procedure described by Linsker and Bogert, and isolated the product as

(1) F. Linsker and M. T. Bogert, *J. Am. Chem. Soc.*, **68**, 192 (1946).
(2) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. T. Edwards, Ann Arbor, Mich., 1946.
(3) A. Albert, "The Acridines," Edward Arnold and Co., London, 1951.



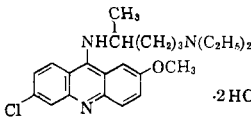
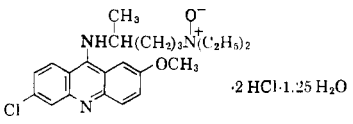
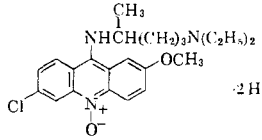
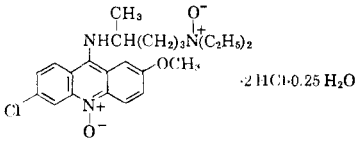
the yellow dihydrochloride salt, m.p. 182–184° dec. after recrystallization from dilute hydrochloric acid (reported m.p.[1] 184–186° dec.). The oxidation product absorbed at the same wave lengths as quinacrine dihydrochloride in the ultraviolet region (Table I), indicating that it was not an acridine 10-oxide. Microanalytical results, including Karl Fischer water titrations (Table I), were in excellent agreement with the hydrated quinacrine N$^{\omega}$-oxide dihydrochloride (V).

Several years later, Pushkareva and Varuhina[4] reported that the oxidation of quinacrine base with perbenzoic acid in chloroform gave a product identical with that reported by Linsker and Bogert. Again, the quinacrine N$^{\omega}$,10-dioxide structure (VI) was assumed, but no evidence was presented to support the assigned structure. Upon repeating this work, we isolated a product that was identical with the hydrated N$^{\omega}$-oxide (V) obtained previously using aqueous hydrogen peroxide. Similarly, 3,6-dichloro-9-(4-diethylamino-1-methylbutyl-

(4) Z. V. Pushkareva and L. V. Varuhina, *Doklady Akad. Nauk USSR*, **103**, 257 (1955).

TABLE I

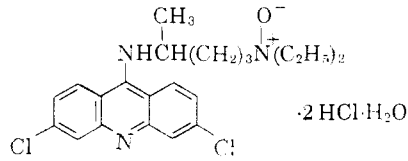
PROPERTIES OF QUINACRINE AND QUINACRINE N-OXIDES

Structure	Ultraviolet absorption spectra in 0.1 *N* HCl λ	E_1^1	Analyses, % Calcd.	Found
 ·2HCl	444	181	C, 58.41	
	425	191	H, 6.82	
	343	100	N, 8.89	
	280	1112	H_2O, 0.00	
	222	444		
Quinacrine, dihydrochloride				
 ·2 HCl·1.25 H_2O	444	178	C, 54.02	54.14
	425	190	H, 6.80	6.91
	343	100	N, 8.22	8.46
	280	1095	H_2O, 4.40	4.51
	222	426		
So-called quinacrine N^{ω}, 10-dioxide, dihydrochloride; correct structure, quinacrine N^{ω}-oxide, dihydrochloride, 1.25 hydrate.				
 ·2 HCl	464	179	C, 56.50	56.37
	444	209	H, 6.60	6.81
	349	88	N, 8.60	8.66
	285	1090	H_2O, 0.00	0.00
	226	500		
Quinacrine 10-oxide, dihydrochloride				
 ·2 HCl·0.25 H_2O	465	187	C, 54.23	54.39
	446	197	H, 6.43	6.42
	349	82	N, 8.25	8.37
	285	1025	H_2O, 0.88	0.99
	227	466		
Quinacrine N^{ω},10-dioxide, dihydrochloride				

amino)acridine N^{ω}-oxide dihydrochloride hydrate (VII) was prepared from 3,6-dichloro-9-(4-diethylamino-1-methylbutylamino)acridine[5] and perbenzoic acid in chloroform.

When it became evident that the product was not the desired quinacrine N^{ω},10-dioxide we initiated the synthesis of authentic samples of quinacrine 10-oxide (IV) and quinacrine N^{ω},10-dioxide (VI). Oxidation of 6,9-dichloro-2-methoxyacridine (I) with per-

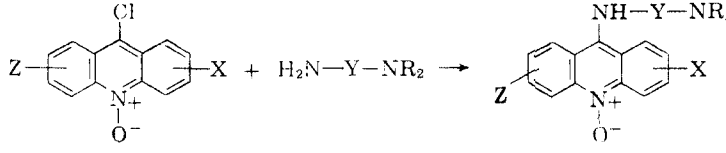
(5) D. P. Spalding, G. W. Moersch, H. S. Mosher and F. C. Whitmore, *J. Am. Chem. Soc.*, **68**, 1596 (1946).



VII

benzoic acid in chloroform gave 6,9-dichloro-2-methoxyacridine 10-oxide (II) (Table II). The ultraviolet absorption spectrum of this intermediate showed a bathochromic shift, indicating the formation of the 10-oxide. Condensation of II with N^1,N^1-diethyl-1,4-pentanediamine using phenol as a solvent afforded quinacrine 10-oxide dihydrochloride (IV). The ultraviolet spectrum of this compound also exhibited a strong shift to higher wave lengths (Table I), indicating that the N-oxide function was retained during the reaction. Oxidation of quinacrine 10-oxide (IV) with excess perbenzoic acid in chloroform at 35° caused deoxygenation of the 10-oxide function and quinacrine N^{ω}-oxide (V) was obtained. However, oxidation with one mole of perbenzoic acid at 3–5° gave the desired quinacrine N^{ω},-10-dioxide (VI); the ultraviolet spectrum of this product also showed a pronounced shift to higher wave lengths (Table I).

The three N-oxides of quinacrine were tested against *P. lophurae* in chicks by Dr. P. E. Thompson and co-workers of these laboratories.[6,7] Among them, quinacrine 10-oxide dihydrochloride (IV) exhibited unexpectedly high activity; it was approximately 11.5 times as active as quinine and 4 times as active as quinacrine. Furthermore, the drug caused less tissue staining than quinacrine. These findings encouraged the synthesis of a variety of substituted 9-(mono- and dialkylaminoalkylamino)acridine 10-oxides for antiparasitic testing (IX, where X and Z represent hydrogen, chloro, methyl, methoxy, nitro, or phenyl and Y represents an alkylene radical) (Tables III through V). The compounds were synthesized by the condensation of the appropriate substituted 9-chloroacridine 10-oxide



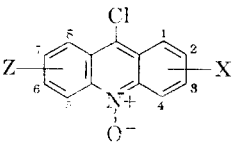
VIII IX

(6) P. E. Thompson, A. Bayles, D. A. McCarthy and B. J. Olszewski, unpublished results, Parke, Davis and Co.

(7) For a description of test methods, see P. E. Thompson, J. E. Meisenhelder, H. H. Najarian and A. Bayles, *Am. J. Trop. Med. Hyg.*, **10**, 335 (1961).

TABLE II

SUBSTITUTED 9-CHLOROACRIDINE 10-OXIDES[a]

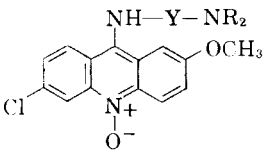


X, Z	M.p., °C.[b]	Yield purified, %	Purification solvent[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
3-Cl	167–169[d]	41	A	$C_{13}H_7Cl_2NO$	59.12	59.22	2.67	2.77	5.31	5.24
3-Cl,6-CH_3	172–174	43	A	$C_{14}H_9Cl_2NO$	60.46	60.17	3.26	3.32	5.04	4.95
2-C_6H_5,6-Cl	209–211	62	A	$C_{19}H_{11}Cl_2NO$	67.08	67.09	3.26	3.52	4.12	3.93
3,6-Cl	236–238	43	B	$C_{13}H_6Cl_3NO$[e]	52.29	52.58	2.03	2.10	4.69	4.96
2-OCH_3	199–200	78	C	$C_{14}H_{10}ClNO_2$	64.74	64.57	3.88	4.04	5.39	5.42
2-OCH_3,6-Cl	234–235[f]	81	C	$C_{14}H_9Cl_2NO_2$[g]	57.2	57.4	3.1	2.8	4.8	5.1
3-NO_2	225	71	D	$C_{13}H_7ClN_2O_3$	56.8	56.7	2.6	2.7	10.2	10.1

[a] All compounds were orange solids. [b] All m.p. dec. [c] A, chloroform-acetone; B, acetone; C, chloroform; D, benzene. [d] Voronina, *et al.*, *Zhurnal Obshchei Khimii*, **30,** 3476 (1960), report m.p. 167–168°. [e] Cl, calcd., 35.63; found, 36.09. [f] Pushkareva and Varulhina, *Doklady Akad. Nauk USSR*, **103,** 257 (1955), report m.p. 236° dec. [g] Cl, calcd., 24.1; found, 24.8.

TABLE III

6-CHLORO-9-(MONO- AND DIALKYLAMINOALKYLAMINO)-2-METHOXYACRIDINE 10-OXIDES[a]



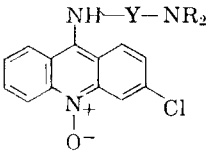
—Y—NR$_2$	M.p., °C.[b]	Yield purified, %	Procedure	Purif. solvent[c,d]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Water, % Calcd.	Water, % Found
$(CH_2)_2NH(CH_2)_2OH$	207	43	I	A	$C_{18}H_{20}ClN_3O_3 \cdot 2HCl \cdot 1.5H_2O$	46.82	47.13	5.46	5.83	9.10	9.18	5.85	6.48
$(CH_2)_3NH(CH_2)_2OH$	215–217	58	I	A	$C_{19}H_{22}ClN_3O_3 \cdot 2HCl \cdot 0.5H_2O$	49.85	49.47	5.50	5.69	9.18	9.10	1.97	2.06
$(CH_2)_2NHCH_2CHOHCH_3$	170	31	V	F	$C_{19}H_{22}ClN_3O_3 \cdot 2HCl \cdot 1.5H_2O$	47.96	48.20	5.72	5.87	8.83	9.07	5.68	5.53
$(CH_2)_2N(CH_2)_4$	231–232	33	V	A	$C_{20}H_{24}ClN_3O_2 \cdot 2HCl \cdot H_2O$	51.90	52.28	5.66	5.75	9.08	9.08	3.89	3.52
$(CH_2)_2N[(CH_2)_2]_2NH$	235	17	V	F	$C_{20}H_{25}ClN_4O_2 \cdot 3HCl \cdot 1.5H_2O$	45.90	46.20	5.59	5.98	10.71	10.59	5.16	5.46
$(CH_2)_3NHCH(CH_3)_2$	225	55	V	B	$C_{20}H_{24}ClN_3O_2 \cdot 2HCl \cdot 1.8H_2O$	50.12	50.08	6.22	6.25	8.77	8.86	6.77	6.87
$(CH_2)_3N(CH_2)_4$	237–238	37	III	A	$C_{21}H_{24}ClN_3O_2 \cdot 2HCl \cdot 1.1H_2O$	52.70	53.09	5.94	6.05	8.78	8.83	4.14	4.73
$(CH_2)_2N(CH_2)_5$	207–209	53	V	C	$C_{21}H_{24}ClN_3O_2 \cdot 2HCl \cdot 1.3H_2O$	52.30	52.65	5.98	6.02	8.71	8.89	4.86	5.45
$(CH_2)_3N(C_2H_5)_2$	244–246	59	I	E	$C_{21}H_{26}ClN_3O_2 \cdot 2HCl$	54.73	54.39	6.12	6.45	9.12	9.15		
$(CH_2)_2NCH_3(CH_2)_3CH_3$	207–208	14	III	C	$C_{21}H_{26}ClN_3O_2 \cdot 2HCl \cdot H_2O$	52.67	52.84	6.32	6.01	8.78	8.79	3.76	4.08
$CH_2CHOHCH_2N(C_2H_5)_2$	167	11	VI	B	$C_{21}H_{26}ClN_3O_3 \cdot H_2O$[f]	59.78	59.76	6.69	6.66	9.96	9.80	4.27	4.55

$(CH_2)_3N[(CH_2)_2OH]_2$	218–222	32	I	A	$C_{21}H_{26}ClN_3O_4 \cdot 2HCl$	51.17	51.33	5.73	5.88	8.53	8.34		
$(CH_2)_2N(CH_2\text{-}CH=CH_2)_2$	196–199	51	V	C	$C_{22}H_{24}ClN_3O_2 \cdot 2HCl \cdot H_2O$	54.05	54.15	5.77	6.06	8.60	8.68	3.69	3.95
$(CH_2)_3N(CH_2)_5$	253	24	V	B	$C_{22}H_{26}ClN_3O_2 \cdot 2HCl \cdot 1.8H_2O$	52.29	52.76	6.30	6.19	8.32	8.51	6.42	7.13
$(CH_2)_3NC_5H_{10}O$[g]	248	47	V	B	$C_{22}H_{26}ClN_3O_3 \cdot 2HCl \cdot 0.2H_2O$	53.66	53.64	5.81	5.88	8.53	8.56	0.73	0.85
$(CH_2)_3N[(CH_2)_2]_2NCH_3$	238–239	78	V	C	$C_{22}H_{27}ClN_4O_2 \cdot 3HCl \cdot 1.7H_2O$	47.61	47.75	6.07	6.09	10.10	10.13	5.47	5.76
$(CH_2)_3N[(CH_2)_2]_2N\text{-}(CH_2)_2OH$	226–228	76	V	F	$C_{23}H_{29}ClN_4O_3 \cdot 3HCl \cdot 2H_2O$	46.79	46.94	6.15	6.18	9.49	9.59	6.10	6.23
$CHCH_3(CH_2)_3N(C_2H_5)_2$	221–223	49	I	D	$C_{23}H_{30}ClN_3O_2 \cdot 2HCl$	56.50	56.37	6.60	6.81	8.60	8.66		
$CHCH_3(CH_2)_3NC_2H_5\text{-}(CH_2)_2OH$	215	43	V	F	$C_{23}H_{30}ClN_3O_3 \cdot 2HCl \cdot H_2O$	52.83	52.75	6.55	6.54	8.03	7.81		
$CHCH_3(CH_2)_3N\text{-}[(CH_2)_2OH]_2$	225	31	V	B	$C_{23}H_{30}ClN_3O_4 \cdot 2HCl \cdot 0.5H_2O$	52.13	52.39	6.28	6.39	7.93	8.07	1.70	1.60
$(CH_2)_5N(CH_2)_5$	245	56	V	F	$C_{24}H_{30}ClN_3O_2 \cdot 2HCl$	57.55	57.33	6.44	6.55	8.39	8.53		
$(CH_2)_2N]CH_2CH\text{-}(CH_3)_2]_2$	215–216	21	V	C	$C_{24}H_{32}ClN_3O_2 \cdot 2HCl \cdot 1.5H_2O$	54.39	54.86	7.04	6.87	7.93	8.01	5.10	5.48
$(CH_2)_3NHCHC_2H_5\text{-}(CH_2)_3CH_3$	217–219	37	I	D	$C_{24}H_{32}ClN_3O_2 \cdot 2HCl$	57.32	56.98	6.83	6.76	8.36	8.30		
$(CH_2)_3NH(CH_2)_3N\text{-}[(CH_2)_2OH]_2$	201–202	77	V	C	$C_{24}H_{33}ClN_4O_4 \cdot 3HCl \cdot 2.3H_2O$	45.91	45.76	6.52	6.48	8.92	8.96	6.60	6.65
$(CH_2)_3NHCH]CH_2N\text{-}(CH_3)_2]_2$	203–205	84	V	C	$C_{24}H_{34}ClN_5O_2 \cdot 4HCl \cdot 3.2H_2O$	43.44	43.49	6.74	6.76	10.56	10.36	8.69	8.72
$(CH_2)_3NH(CH_2)_7CH_3$	227–228	69	V	C	$C_{26}H_{34}ClN_3O_2 \cdot 2HCl$	58.09	58.25	7.02	6.92	8.13	8.22		
$(CH_2)_3NC_{10}H_{19}N$[h]	192–194	47	V	C	$C_{27}H_{36}ClN_4O_2 \cdot 3HCl \cdot 0.8H_2O$	53.44	53.05	6.58	6.33	9.23	9.60	2.37	2.04
$(CH_2)_3NCH_3(CH_2)_9\text{-}CH_3$	187–189	33	V	C	$C_{28}H_{40}ClN_3O_2 \cdot 2HCl$	60.16	60.03	7.57	7.64	7.52	7.54		

[a] All compounds were yellow or orange as the hydrochloride salts and red as the bases. [b] All m.p. dec. [c] A, methanol; B, methanol-acetone; C, ethanol–acetone; D, ethanol; E, methanol–water; F, methanol-ethanol–acetone. [d] A small amount of hydrochloric acid was added to the solvents used for purification of the hydrochloride salts. [e] By Karl Fischer method. [f] N. M. Voronina, *et al.*, *Zhur. Obshchei Khimii*, **30**, 3476 (1960), report the dihydrochloride salt, m.p. 235–236°. [g] $NC_5H_{10}O$ represents the 3-hydroxypiperidino radical. [h] $NC_{10}H_{19}N$ represents the 3-(1-methyl-2-pyrrolidinyl)piperidino radical.

TABLE IV

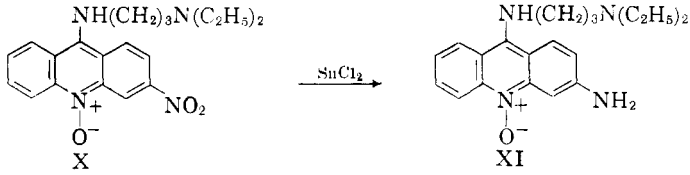
3-CHLORO-9-(MONO- AND DIALKYLAMINO-ALKYLAMINO)ACRIDINE 10-OXIDES[a]



—Y—NR_2	M.p., °C.[b]	Yield purif., %	Procedure	Purif. solvent[c,d]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Water, %[e] Calcd.	Water, %[e] Found
$(CH_2)_3N(CH_3)_2$	233–236	32	II	B	$C_{18}H_{20}ClN_3O \cdot 2HCl \cdot 0.3H_2O$	52.97	52.92	5.58	5.65	10.30	10.24	1.32	1.15
$(CH_2)_2N(C_2H_5)_2$	245–248	42	II	B	$C_{19}H_{22}ClN_3O \cdot 2HCl$	54.75	54.47	5.80	5.74	10.08	10.04		
$(CH_2)_3N(CH_2)_4$	231	51	IV	D	$C_{20}H_{22}ClN_3O \cdot 2HCl \cdot 0.3H_2O$	55.32	55.17	5.71	5.84	9.68	9.67	1.24	1.25
$(CH_2)_3N(C_2H_5)_2$	224–226	35	II	A	$C_{20}H_{24}ClN_3O \cdot 2HCl \cdot 0.7H_2O$	54.17	54.44	6.23	6.38	9.48	9.26	2.84	3.14
$(CH_2)_3N(CH_2)_5$	251	55	II	B	$C_{21}H_{24}ClN_3O \cdot 2HCl \cdot 0.8H_2O$	55.14	55.07	6.13	6.06	9.19	9.22	3.15	2.95
$(CH_2)_3NC_5H_{10}O$[f]	165–167	34	VI	D	$C_{21}H_{24}ClN_3O_2$	65.36	65.46	6.27	6.38	10.89	10.92		
$(CH_2)_3N[(CH_2)_2]_2NCH_3$	200–225	56	II	A	$C_{21}H_{25}ClN_4O \cdot 3HCl \cdot 3H_2O$	46.00	46.47	6.25	6.29	10.22	10.14	9.86	9.70
$(CH_2)_4N(CH_2)_6$	242–243	30	V	C	$C_{22}H_{26}ClN_3O \cdot 2HCl \cdot 0.5H_2O$	56.72	56.67	6.27	6.17	9.02	9.15	1.93	1.88
$(CH_2)_5N(CH_2)_4$	220–221	44	V	E	$C_{22}H_{26}ClN_3O \cdot 2HCl \cdot 0.7H_2O$	56.06	56.08	6.40	6.56	8.98	9.07	2.70	2.73
$(CH_2)_3N[(CH_2)_2]_2N(CH_2)_2OH$	171–172	35	VI	D	$C_{22}H_{27}ClN_4O_2 \cdot 0.3H_2O$	62.86	62.99	6.62	6.65	13.33	13.39	1.28	1.28
$CHCH_3(CH_2)_3N(C_2H_5)_2$	223–225	85	II	B	$C_{22}H_{29}ClN_3O \cdot 2HCl$	57.58	57.48	6.59	6.72	9.16	9.06		
$CHCH_3(CH_2)_3N[(CH_2)_2OH]_2$	100	44	V	B	$C_{22}H_{29}ClN_3O_3 \cdot 2HCl \cdot 0.7H_2O$	52.45	52.60	6.34	6.43	8.34	8.20	2.50	2.78
$(CH_2)_3NH(CH_2)_3N[(CH_2)_2OH]_2$	210–213	45	V	E	$C_{23}H_{31}ClN_4O_3 \cdot 3HCl \cdot 0.5H_2O$	48.86	48.71	6.24	6.50	9.91	9.78	1.59	1.55
$(CH_2)_2NH(CH_2)_7CH_3$	243–245	48	II	B	$C_{24}H_{32}ClN_3O \cdot 2HCl \cdot 0.4H_2O$	58.35	58.37	7.10	7.31	8.50	8.62	1.46	1.16
$(CH_2)_3NCH_3(CH_2)_9CH_3$	208–209	23	V	C	$C_{27}H_{38}ClN_3O \cdot 2HCl \cdot H_2O$	59.28	59.43	7.74	7.62	7.68	7.71	3.29	2.96

[a] All compounds were yellow to orange as the hydrochloride salts and red as the bases. [b] All m.p. dec. [c] A, methanol; B, methanol-acetone; C, ethanol-acetone; D, ethanol; E, methanol-ethanol-2-propanol. [d] A small amount of hydrochloric acid was added to the solvent used for the purification of the hydrochloride salts. [e] By Karl Fischer method. [f] $NC_5H_{10}O$ represents the 3-hydroxypiperidino radical.

(VIII, where X and Y represent hydrogen, chloro, methyl, methoxy, nitro, or phenyl) (Table II) with a mono or dialkylaminoalkylamine in phenol (methods I through VI).[8] 6-Chloro-2-methoxy-9-(octylamino)acridine 10-oxide and 6-chloro-9-(*o*-chlorobenzylamino)-2-methoxyacridine 10-oxide were prepared in a similar manner from 6,9-dichloro-2-methoxyacridine 10-oxide and octylamine and *o*-chlorobenzylamine, respectively. 3 - Amino - 9 - (3 - diethylaminopropylamino)acridine 10-oxide (XI) was prepared by the reduction of 9-(3-diethylaminopropylamino)-3-nitroacridine 10-oxide (X) with stannous chloride in glacial acetic acid; the diaminoacridine was purified as the picrate salt.



The 9-chloroacridine 10-oxides (VIII) were obtained by oxidation of the corresponding 9-chloroacridines with perbenzoic acid in chloroform. Many of the intermediate 9-chloroacridines have been described previously[3,5]; 6,9-dichloro-2-phenylacridine and 3,9-dichloro-6-methylacridine were prepared by phosphorus oxychloride ring-closure of 4-chloro-N-(4-diphenyl)anthranilic acid and 4-chloro-N-(*m*-tolyl)anthranilic acid, respectively.

A majority of the intermediate polyamines have been described previously[9,10] or are commercially available.[11–16] N-Decyl-N-

(8) During the latter stages of this work, Pushkareva and Varuhina[4] reported an independent synthesis of quinacrine 10-oxide from 6-chloro-2-methoxy-9-phenoxyacridine 10-oxide and N^1, N^1-diethyl-1,4-pentanediamine.

(9) F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 223 (1958).

(10) E. F. Elslager, F. W. Short, M. J. Sullivan and F. H. Tendick, *ibid.*, **80**, 451 (1958).

(11) 2-[(4-Aminopentyl)ethylamino]ethanol and 2,2′-(4-aminopentylimino)diethanol were obtained through the courtesy of Dr. C. M. Suter and Dr. B. F. Tullar of the Sterling-Winthrop Research Institute, Rensselaer, N. Y.

(12) The authors are indebted to Dr. Franklin Johnston and Dr. G. W. Fowler of the Union Carbide Chemical Co., South Charleston 3, W. Va., for the samples of 2-(2-aminoethylamino)-ethanol, 2-(3-aminopropylamino)ethanol, and 1-(2-aminoethyl)piperazine.

(13) 1-(3-Aminopropyl)-3-(1-methyl-2-pyrrolidinyl)piperidine was obtained through the courtesy of Dr. E. Monroe, Dow Chemical Co., Midland, Michigan.

(14) 1-[(2-Aminoethyl)amino]-2-propanol and 4-(3-aminopropyl)-1-piperazineethanol were obtained through the courtesy of the Wyandotte Chemical Co., Wyandotte, Michigan.

(15) N,N-Dimethyl-1,3-diaminopropane, N,N-diethyl-1,3-diaminopropane, and 2,2′-(3-aminopropylimino)diethanol were obtained through the courtesy of the American Cyanamid Co., New York 20, N. Y.

TABLE

OTHER SUBSTITUTED 9-(MONO- AND DIALKYLAMINOALKYLAMINO)ACRIDINE 10-OXIDES[a]

—Y—NR$_2$	X	Z	M.p., °C.[b]	Yield purified, %	Procedure	Purification[c,d] solvent
$(CH_2)_2NH(CH_2)_2OH$	2-OCH_3	H	214	28	V	D
$(CH_2)_3NH(CH_2)_2OH$	2-OCH_3	H	209	21	V	D
$CHCH_3(CH_2)_3N(C_2H_5)_2$	2-OCH_3	H	209	40	IV	B
$(CH_2)_3N(CH_3)_2$	3-Cl	6-Cl	254	41	V	D
$CHCH_3(CH_2)_3N(C_2H_5)_2$	3-Cl	6-Cl	216–218	87	I	A
$(CH_2)_4N(CH_2)_5$	3-Cl	6-Cl	221–222	22	I	B
$CHCH_3(CH_2)_3N(C_2H_5)_2$	2-C_6H_5	6-Cl	176	34	VI	C
$(CH_2)_3NH(CH_2)_2CH_3$	2-C_6H_5	6-Cl	224	45	V	A

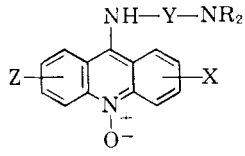
[a] All compounds were yellow or orange as the dihydrochloride salts and red as the bases. [b] All m.p. dec. [c] A, methanol–acetone; B, ethanol–acetone; C, ethanol–water; D, methanol–ethanol–acetone.

methyl-1,3-propanediamine, N^2-(3-aminopropyl)-N^1,N^1,N^3,N^3-tetramethyl-1,2,3-propanetriamine and 2,2′-[3-[(3-aminopropyl)amino]-propylimino]diethanol were prepared by catalytic hydrogenation of the corresponding nitriles in the presence of Raney cobalt catalyst.

The 9-(mono and dialkylaminoalkylamino)acridine 10-oxides were active against a variety of parasites, bacteria and fungi, including *P. lophurae*, *Entamoeba histolytica*, *Trichomonas vaginalis*, *Syphacia obvelata*, *Aspiculuris tetraptera*, *Hymenolepis nana*, *Streptococcus pyogenes* (C 203), *Staphylococcus aureus* (UC-76), *Mycobacterium tuberculosis* (H37RV), *Candida albicans*, *Cryptococcus neoformans*, *Nocardia asteroides*, and *Trichophyton interdigitale*.[6,17,18] Many of the 9-amino-

(16) N^1,N^1-Diethyl-1,4-pentanediamine was purchased from the Winthrop Laboratories, New York 18, N. Y.; 1-(5-aminopentyl)piperidine was purchased from the Organic Preparations Stocks, University of Illinois, Urbana, Ill.; 1-(3-aminopropyl)-4-methylpiperazine was purchased from the Aldrich Chemical Co., Milwaukee, Wis.; N,N-diethylethylenediamine and 1-amino-3-diethylamino-2-propanol were purchased from Distillation Products Industries, Rochester, N. Y.; N-isopropyl-1,3-diaminopropane, N-butyl-N-methylethylenediamine, N,N-diallylethylenediamine, N,N-diisobutylethylenediamine, 1-(2-aminoethyl)pyrrolidine, 1-(3-aminopropyl)pyrrolidine, 1-(5-aminopentyl)pyrrolidine, 1-(2-aminoethyl)piperidine, 1-(3-aminopropyl)piperidine and 1-(3-aminopropyl)hexamethyleneimine were purchased from the Sapon Laboratories, Valley Stream, N. Y.

V



Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Water, %[e] Calcd.	Found
$C_{18}H_{21}N_3O_3 \cdot 2HCl \cdot 1.5H_2O$	50.60	51.00	6.13	6.33	9.83	10.10	6.32	7.29
$C_{19}H_{23}N_3O_3 \cdot 2HCl \cdot 0.7H_2O$	53.45	53.86	6.23	6.53	9.84	9.85	2.95	2.90
$C_{23}H_{31}N_3O_3 \cdot 2HCl \cdot 0.8H_2O$	58.92	58.95	7.44	7.63	8.96	9.03	3.07	3.18
$C_{21}H_{23}Cl_2N_3O \cdot 2HCl$	52.85	52.72	5.28	5.64	8.80	8.66		
$C_{22}H_{27}Cl_2N_3O \cdot 2HCl \cdot 0.5H_2O$	52.60	52.34	6.02	6.55	8.37	8.36		
$C_{23}H_{27}Cl_2N_3O \cdot 2HCl \cdot 0.5H_2O$	53.71	53.55	5.88	6.09	8.17	7.98		
$C_{28}H_{32}ClN_3O$	72.78	72.93	6.98	6.90	9.09	9.07		
$C_{30}H_{36}ClN_3O \cdot 2HCl \cdot 0.5H_2O$	62.99	63.32	6.87	6.89	7.35	7.50	1.58	1.64

[d] A small amount of hydrochloric acid was added to the solvents used for purification of the hydrochloride salts. [e] By the Karl Fischer method.

acridine 10-oxides were more active than quinacrine against trophozoite-induced *P. lophurae* infections in chicks and ten compounds were 6 to 24 times as active as quinine. These results are especially noteworthy because none of the hundreds of acridines examined for antimalarial activity in the past[2,19] has been shown to be superior to quinacrine as an antimalarial drug.

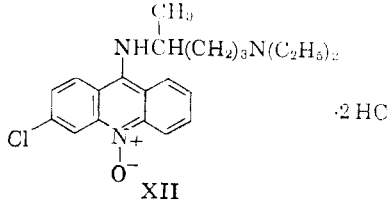
The most promising compound tested was 3-chloro-9-(4-diethylamino-1-methylbutylamino)acridine 10-oxide dihydrochloride (CI-423) (XII).[20] Comparative testing by the drug-diet method against trophozoite-induced *P. lophurae* infections in chicks demonstrated the drug to be approximately 16 times as active as quinine, 4 times as active as quinacrine, and one-half as active as amodiaquine. In rhesus monkeys, comparisons on a single or multiple oral dose basis

(17) M. W. Fisher and A.L. Erlandson, unpublished results, Parke, Davis and Co.

(18) A. B. Hillegas, unpublished results, Parke, Davis and Co.

(19) G. R. Coatney, W. C. Cooper, N. B. Eddy, and J. Greenberg, "Survey of Antimalarial Agents," Public Health Service Publication No. 193, U. S. Government Printing Office, Washington 25, D. C., 1953.

(20) P. E. Thompson, J. E. Meisenhelder, H. H. Najarian and A. Bayles, *Am. J. Trop. Med. Hyg.*, **10** 335 (1961).



XII

against trophozoite-induced *P. cynomolgi* infections showed the compound to be distinctly more potent than either quinacrine or amodiaquine in rapidly suppressing the acute parasitemia and curing the animals. In contrast to quinacrine, XII did not induce visible staining of the skin of mice or rats when given for respective periods of 2 and 4 weeks. These observations suggest that XII has the further advantage over quinacrine of being unlikely to stain the skin.[20]

Pre-clinical toxicity studies in animals[21] and *observations on the* tolerance of the drug by human volunteers[22] demonstrated that XII was tolerated sufficiently well for trial in the treatment of human malaria. Reports from initial field trials in Liberia and in Southern Rhodesia indicate that XII is approximately as active as amodiaquine against *P. falciparum* and *P. malariae* and is tolerated well.[23,24] The drug appears to hold considerable promise as an antimalarial drug, particularly in single dose therapy.[24]

Acknowledgment.—The authors take this opportunity to thank Dr. Loren M. Long for encouragement in this investigation, Dr. Paul E. Thompson, Miss Anita Bayles, Mrs. Sheila Herbst, Dr. D. A. McCarthy, Dr. Haig Najarian, Miss Bronislawa Olszewski, Dr. David Worley, Dr. M. W. Fisher, Dr. A. L. Erlandson, and Dr. A. B. Hillegas for the biological evaluation of these compounds, and Mrs. Elinor L. Benton, Miss Ann M. Ehrenfeld, Miss Joan M. Multhaup and Mrs. Doris R. Thomas for synthesizing several of the compounds described herein. The authors also are indebted to Mr. Charles E. Childs and associates for the microanalyses, and to Dr. J. M. Vandenbelt and associates for determination and interpretation of the infrared and ultraviolet absorption spectra.

Experimental[25]

3-(Decylmethylamino)propionitrile.—A mixture of 60 g. (1.13 moles) of acrylo-

(21) R. J. McAlpine, unpublished results, Parke, Davis and Co.

(22) K. O. Courtney, unpublished data in the files of Parke, Davis and Company, Ann Arbor, Michigan.

(23) A. E. Gunders, *W. Afr. Med. J.*, in press.

(24) E. T. Reid, R. J. Fraser and F. B. Wilford, Malaria and Bilharzia Research Laboratory, Salisbury, Southern Rhodesia, manuscript in preparation.

(25) Melting points are uncorrected.

nitrile, 62.5 g. (0.365 mole) of decylmethylamine, and 5 drops of 40% aqueous benzyltrimethylammonium hydroxide solution was stirred and heated at 50–60° for 0.5 hr. A second 62.5 g. (0.365 mole) portion of decylmethylamine was added over a period of 0.5 hr., then an additional 20 g. (0.378 mole) of acrylonitrile. The mixture was heated on the steam bath for 6 hr. and allowed to stand at room temperature for 48 hr. Acrylonitrile (40 g., 0.756 mole) was added and the mixture was heated on the steam bath for an additional 50 hr. period. Upon cooling, the liquid was filtered to remove insolubles, low boiling components were removed *in vacuo* on the steam bath, and the residue was distilled *in vacuo* through a 23-cm. Vigreux column. 3-(Decylmethylamino)propionitrile was obtained as a colorless liquid, b.p. 100–103° (0.15 mm.), $n^{25}D$ 1.4474; yield, 142 g. (87%).

Anal. Calcd. for $C_{14}H_{28}N_2$: C, 74.94; H, 12.57; N, 12.48. Found: C, 74.82; H, 12.74; N, 12.82.

N-Decyl-N-methyl-1,3-propanediamine.—3-(Decylmethylamino)propionitrile (140 g., 0.625 mole) was reduced catalytically with Raney cobalt according to the procedure described previously for the preparation of 1-(3-aminopropyl)-3-piperidinol.[10,26] N-Decyl-N-methyl-1,3-propanediamine was obtained as a colorless liquid, b.p. 81–83° (0.10 mm.), $n^{25}D$ 1.4512; yield, 114 g. (80%).

Anal. Calcd. for $C_{14}H_{32}N_2$: N, 12.27. Found: N, 12.28.

N^2-(3-Aminopropyl)-N^1,N^1,N^3,N^3-tetramethyl-1,2,3-propanetriamine.—Acrylonitrile (143 g., 2.68 moles) was added to 388 g. (2.68 moles) of N^1,N^1,N^3,N^3-tetramethyl-1,2,3-propanetriamine[27] at 40–50° with stirring over a period of 0.5 hr. The temperature was maintained at 40–50° for 2 hr. and the reaction mixture was allowed to stand at room temperature for 18 hr. Low boiling materials were removed *in vacuo* on the steam bath and the crude 3-{[2-dimethylamino-1-(dimethylaminomethyl)ethyl]amino}propionitrile was hydrogenated catalytically with Raney cobalt as described previously.[10,26] The crude amine was distilled *in vacuo* through a 18 cm. Vigreux column to give 318 g. (60%) of a colorless liquid, b.p. 83–86° (0.8 mm.), $n^{25}D$ 1.4612.

Anal. Calcd. for $C_{10}H_{27}N_4$: C, 59.06; H, 13.38; N, 27.55. Found: C, 59.54; H, 13.00; N, 27.91.

2,2'-{3-[(3-Aminopropyl)amino]propylimino}diethanol.—To 518 g. (3.2 moles) of 2,2'-(3-aminopropylimino)diethanol[15] was added at 20–30° with stirring 170 g. (3.2 moles) of acrylonitrile over a period of 0.5 hr. A mild exothermic reaction occurred. The mixture was allowed to stand at room temperature for 18 hr. and subsequently was stirred and heated on the steam bath *in vacuo* for 2 hr. The residual crude 3-{{3-[bis(2-hydroxyethyl)amino]propyl}amino}propionitrile was then hydrogenated catalytically with Raney cobalt as described previously.[10,26] The crude amine was distilled *in vacuo* through a 18 cm. Vigreux column to give 365 g. (52%) of a pale yellow liquid, b.p. 184–186° (0.3 mm.), $n^{25}D$ 1.5031.

Anal. Calcd. for $C_{10}H_{25}N_3O_2$: C, 54.76; H, 11.49; N, 19.16. Found: C, 54.87; H, 11.55; N, 19.07.

4-Chloro-N-(4-diphenyl)anthranilic Acid.—A mixture of 111.5 g. (0.66 mole) of 4-aminodiphenyl, 114.6 g. (0.6 mole) of 2,4-dichlorobenzoic acid, 82.8 g. (0.6 mole) of anhydrous potassium carbonate, 3 g. of copper powder and 800 ml. of 1-pentanol was boiled under reflux with mechanical stirring for 6 hr. Water was

(26) The authors are indebted to Mr. William Pearlman of the Parke, Davis High Pressure Laboratory who developed the Raney cobalt procedure used, and carried out the hydrogenations.

(27) N^1,N^1,N^3,N^3-Tetramethyl-1,2,3-propanetrianine was obtained through the courtesy of the Commercial Solvents Corp., New York 16, N. Y.

removed from the reaction mixture by means of a Dean-Stark water separator. A solution of 70 g. of potassium hydroxide in 100 ml. of water was then added and the mixture was steam-distilled, the residue diluted with water, and filtered. The filtrate was made slightly acid with dil. hydrochloric acid and the crude acid was collected by filtration and washed with water. The wet filter-cake was digested with 1.5 l. of boiling ethanol and the mixture was cooled. The precipitate was collected by filtration, washed with petroleum ether, and dried *in vacuo* at 60°. Crystallization from chlorobenzene (decolorizing charcoal) gave 129.5 g. (67%) of pale yellow needles, m.p. 245–246°.

Anal. Calcd. for $C_{19}H_{14}ClNO_2$: C, 70.48; H, 4.36; N, 4.32. Found: C, 70.20; H, 4.26; N, 4.37.

4-Chloro-N-(*m*-tolyl)anthranilic acid.—Utilizing the procedure described above for the preparation of 4-chloro-N-(4-diphenyl)anthranilic acid, 191 g. (1 mole) of 2,4-dichlorobenzoic acid, 134 g. (1.25 mole) of *m*-toluidine and 138 g. (1 mole) of potassium carbonate afforded 159.2 g. (60%) of 4-chloro-N-(*m*-tolyl)anthranilic acid, yellow needles from chlorobenzene (decolorizing charcoal), m.p. 197–199°.

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62. Found: C, 64.22; H, 4.85.

6,9-Dichloro-2-phenylacridine.—A mixture of 124.5 g. (0.37 mole) of 4-chloro-N-(4-diphenyl)anthranilic acid and 475 ml. of phosphorus oxychloride was warmed gently on the steam bath until an exothermic reaction began. After the reaction subsided, the mixture was stirred and heated on the steam bath for 2 hr. and approximately one-half of the phosphorus oxychloride was removed *in vacuo*. Dry chloroform (250 ml.) then was added to the residue and the chloroform mixture was poured slowly with vigorous stirring into a large excess of ammonium hydroxide and ice. After 1 hr., 500 ml. of chloroform was added and the mixture was filtered. The yellow solid weighed 50 g., m.p. 237–240°. The chloroform layer was separated and was washed with water, dried over anhydrous potassium carbonate, and concentrated until crystallization began. The yellow crystals were collected by filtration and dried, 61 g., m.p. 240–242°. The yellow solids were combined and crystallized from chlorobenzene (decolorizing charcoal); the yellow needles thus obtained weighed 103 g. (83%), m.p. 239–241°.

Anal. Calcd. for $C_{19}H_{11}Cl_2N$: C, 70.38; H, 3.42; N, 4.32; Cl, 21.87. Found: C, 70.21; H, 3.35; N, 4.26; Cl, 21.66.

3,9-Dichloro-6-methylacridine.—Utilizing the procedure described above for the preparation of 6,9-dichloro-2-phenylacridine, 26.2 g. (0.1 mole) of 4-chloro-N-(*m*-tolyl)anthranilic acid and 80 ml. of phosphorus oxychloride afforded 16 g. of mixed chloroacridine isomers. Fractional crystallization of the mixture from benzene gave 5.3 g. (20%) of pale yellow crystals, m.p. 203° dec. For analysis, a small sample was recrystallized from acetone to give long fibrous needles, m.p. 206° dec.

Anal. Calcd. for $C_{14}H_9Cl_2N$: C, 64.14; H, 3.46; N, 5.34. Found: C, 64.19; H, 3.59; N, 5.30.

Quinacrine N^{10}-Oxide Dihydrochloride Hydrate (V).—To a solution of 34.0 g. (0.085 mole) of quinacrine base in 500 ml. of chloroform maintained below 35° was added slowly with stirring a solution of 12.8 g. (0.093 mole) of perbenzoic acid[28] in 250 ml. of chloroform. The reaction mixture was allowed to stand at room temperature for 18 hr. and was washed successively with two 500 ml.

(28) H. Gilman and A. H. Blatt, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, New York, 1946, p. 431.

portions of 10% sodium carbonate and with water. The chloroform layer was dried over anhydrous potassium carbonate, the drying agent was collected by filtration, and the chloroform was removed *in vacuo* in the presence of platinum foil. The oily residue was dissolved by heating with a mixture of water and 85 ml. of concd. hydrochloric acid and the acid solution was filtered and allowed to cool. The crude salt was collected by filtration, washed successively with dil. hydrochloric acid and acetone, and dried *in vacuo* at 45° for 18 hr. Two recrystallizations from 5% hydrochloric acid gave 24.5 g. (57%) of yellow crystals, m.p. 182–184° dec.

3,6-Dichloro-9-(4-diethylamino-1-methylbutylamino)acridine N$^{\omega}$-Oxide Dihydrochloride Hydrate (VII).—Utilizing the procedure described above for the preparation of quinacrine N$^{\omega}$-oxide dihydrochloride, 40.5 g. (0.1 mole) of 3,6-dichloro-9-(4-diethylamino-1-methylbutylamino)acridine[5] was allowed to react with perbenzoic acid (16.0 g., 0.116 mole). Crystallization of the crude hydrochloride salt from 2-propanol gave 17.1 g. (33%) of a bright yellow solid, m.p. 182–190° dec.

Anal. Calcd. for $C_{22}H_{27}Cl_2N_3O \cdot 2HCl \cdot H_2O$: C, 51.67; H, 6.11; N, 8.22; H_2O, 3.52. Found: C, 52.02; H, 6.30; N, 8.18; H_2O, 3.74.

General Method for Preparing 9-Chloroacridine 10-Oxides.—A solution of 61.3 g. (0.247 mole) of 3,9-dichloroacridine[29] in 1.5 l. of chloroform was cooled to 25° and to it was added in one portion a cool solution of 37.5 g. (0.272 mole) of perbenzoic acid[28] in 450 ml. of chloroform. The solution was allowed to stand at room temperature for 18 hr. during which time the color of the solution changed from orange to deep green. A test with starch–iodide paper indicated the absence of peracid. The chloroform solution was washed successively with two 1 l. portions of 10% aqueous sodium carbonate solution and three 1 l. portions of water, dried over anhydrous potassium carbonate, and concentrated to 500 ml. The crude product was precipitated by the addition of 2 l. of anhydrous ether, collected by filtration, and dried *in vacuo* at 60° for 18 hr. Crystallization from chloroform–acetone (decolorizing charcoal) gave 26.8 g. (41%) of orange crystals, m.p. 167–169°.

Methods for Preparing 9-(Mono- and dialkylaminoalkylamino)acridine 10-Oxides (Tables III–V).—The 9-(mono- and dialkylaminoalkylamino)acridine 10-oxide salts listed in Tables I and III–V and described in the following procedures were often hygroscopic and in that state were difficult to analyze. Therefore, the salts were allowed to equilibrate in the air prior to microanalysis and Karl Fischer water determinations were used to determine the amount of water of hydration.

Method I.—A mixture of 14.8 g. (0.05 mole) of 6,9-dichloro-2-methoxyacridine 10-oxide, 45 g. of phenol and 6.3 g. (0.06 mole) of 2-[(2-aminoethyl)amino]ethanol was stirred and heated on the steam bath for 2 hr. The cooled reaction mixture was poured into a solution of 20 ml. of concd. hydrochloric acid in 750 ml. of acetone. The solid which separated was collected by filtration, washed with acetone and dried. Recrystallization from methanol containing a few drops of concd. hydrochloric acid gave 2-[2-(6-chloro-2-methoxy-9-acridinylamino)ethylamino]ethanol 10-oxide dihydrochloride as an orange, hygroscopic solid. This was dried at 60° *in vacuo* and then exposed to the atmosphere for 18 hr. until it was no longer hygroscopic; yield, 10.0 g. (43%), m.p. 207° dec.

(29) Aldrich Chemical Company, Milwaukee, Wisconsin.

Method II.—A mixture of 20.0 g. (0.076 mole) of 3,9-dichloroacridine 10-oxide, 50 g. of phenol and 9.5 g. (0.082 mole) of N,N-diethylethylenediamine was heated and stirred on the steam bath for 3 hr. The cooled reaction mixture was poured into an excess of cold, aqueous sodium hydroxide and the oily base which separated was extracted with chloroform. The combined chloroform extracts were washed successively with dilute sodium hydroxide and water and dried over anhydrous potassium carbonate. Concentration of the chloroform solution, dilution with ether, and addition of excess anhydrous hydrogen chloride gave the crude dihydrochloride salt. Recrystallization from a mixture of methanol and acetone containing a few drops of concd. hydrochloric acid gave 3-chloro-9-(2-diethylaminoethylamino)acridine 10-oxide dihydrochloride. Yield was 13.3 g. (42%); m.p. 245–248° dec. after drying and subsequent exposure to the atmosphere.

Method III.—A mixture of 23 g. (0.078 mole) of 6,9-dichloro-2-methoxyacridine 10-oxide, 70 g. of phenol and 11 g. (0.086 mole) of 1-(3-aminopropyl)pyrrolidine was stirred and heated on the steam bath for 3 hr. After cooling the reaction solution was poured into a solution of 30 ml. of concd. hydrochloric acid in 2 l. of acetone. The yellow precipitate was collected by filtration and washed thoroughly with acetone and anhydrous ether. This crude product was dissolved in 1 l. of hot water, treated with decolorizing charcoal, and poured into excess dil. ammonium hydroxide. The red oil which separated was extracted with chloroform. The combined chloroform extracts were washed well with water and dried over anhydrous potassium carbonate. The deep red solution was concentrated to 150 ml., diluted with 500 ml. of dry ether, and excess dry hydrogen chloride added. The yellow precipitate was collected by filtration and dried. Crystallization from methanol, to which a few drops of hydrochloric acid was added, gave 6-chloro-2-methoxy-9-[3-(1-pyrrolidinyl)propylamino]acridine 10-oxide dihydrochloride as a yellow, hygroscopic powder; yield 14 g. (37%); m.p. 237–238° dec. after drying at 60° *in vacuo* and subsequent exposure to the atmosphere.

Method IV.—A mixture of 60 g. (0.23 mole) of 3,9-dichloroacridine 10-oxide, 32 g. (0.25 mole) of 1-(3-aminopropyl)pyrrolidine and 150 g. of phenol was heated and stirred on the steam bath for 3 hr. The cooled reaction mixture was treated with excess base and extracted with chloroform as in method II. The dried chloroform solution was concentrated to dryness and the dark red residue dissolved in ethanol. Excess hydrogen chloride was added and the solution diluted with acetone. The yellow precipitate was collected by filtration and recrystallized from ethanol to give 3-chloro-9-[3-(1-pyrrolidinyl)propylamino]acridine 10-oxide dihydrochloride; yield, 50 g. (51%); m.p. 231° dec. after drying at 60° *in vacuo* and exposure to the atmosphere for 24 hr.

Method V.—A mixture of 27.7 g. (0.094 mole) of 6,9-dichloro-2-methoxyacridine 10-oxide, 20.5 g. (0.090 mole) of N-decyl-N-methyl-1,3-propanediamine and 65 g. of phenol was heated and stirred on the steam bath for 3 hr. After cooling, the reaction mixture was dissolved in ethanol and an excess of concd. hydrochloric acid added. The crude product precipitated upon the addition of a large volume of acetone. This was collected by filtration, washed well with acetone and hot water, and treated with excess ammonium hydroxide. The mixture was extracted with chloroform and the combined chloroform extracts were dried over anhydrous potassium carbonate and then concentrated to an oil. This was dissolved in ethanol, excess hydrochloric acid was added and crystallization induced by the addition of acetone. The product, 6-chloro-9-[3-(decylmethylamino)propylamino]-2-methoxyacridine 10-oxide dihydrochloride, was obtained

as a bright yellow solid; yield 16.7 g. (33%); m.p. 187–189° dec. after drying and equilibration with the atmosphere.

Method VI.—A mixture of 21 g. (0.080 mole) of 3,9-dichloroacridine 10-oxide, 16 g. (0.087 mole) of 4-(3-aminopropyl)-1-piperazineethanol and 60 g. of phenol was heated and stirred on the steam bath for 3 hr. The crude dihydrochloride was precipitated with acetone, treated with excess sodium hydroxide and the base extracted with chloroform as described in method III. Concentration of the dried chloroform solution left a red solid which was recrystallized from ethanol to give 4-[3-(3-chloro-9-acridinylamino)propyl]-1-piperazineethanol 10-oxide; yield, 11.7 g. (35%); m.p. 171–172° dec.

6-Chloro-2-methoxy-9-(octylamino)acridine 10-Oxide Monohydrochloride.—Utilizing Method IV above, 6,9-dichloro-2-methoxyacridine 10-oxide (14.7 g., 0.05 mole), octylamine (6.5 g., 0.05 mole) and phenol (25 g.) afforded 7.6 g. (36%) of product as bright yellow crystals from ethanol, m.p. 208–209° dec.

Anal. Calcd. for $C_{22}H_{27}ClN_2O_2 \cdot HCl$: C, 62.41; H, 6.66; N, 6.62. Found: C, 62.24; H, 6.71; N, 6.81.

6-Chloro-9-(*o*-chlorobenzylamino)-2-methoxyacridine 10-Oxide.—6,9-Dichloro-2-methoxyacridine 10-oxide (29.4 g., 0.1 mole) and *o*-chlorobenzylamine (14.2 g., 0.1 mole) were stirred and heated with 50 g. of phenol and the crude product was worked up according to Method VI above. The crude product was crystallized from ethanol to give 17.5 g. (44%) of dark red crystals, m.p. 170° dec.

Anal. Calcd. for $C_{21}H_{16}Cl_2N_2O_2$: C, 63.16; H, 4.04; N, 7.01. Found: C, 63.16; H, 4.17; N, 6.92.

3-Amino-9-(3-diethylaminopropylamino)acridine 10-Oxide (XI).—A mixture of 9.0 g. (0.033 mole) of 9-chloro-3-nitroacridine 10-oxide, 10.0 g. (0.08 mole) of N,N-diethyl-1,3-propanediamine and 50 g. of phenol was stirred and heated at 120° for 2 hr. Upon cooling, the reaction mixture was poured into excess 2 *N* sodium hydroxide solution and the precipitate that separated was collected by filtration, washed with water, and dried. The crude 9-(3-diethylaminopropylamino)-3-nitroacridine 10-oxide (9.5 g.) was suspended in 150 ml. of glacial acetic acid and treated with 28.5 g. (0.15 mole) of anhydous stannous chloride in 150 ml. of glacial acetic acid at room temperature. After 0.5 hr., the precipitate was collected by filtration and decomposed with 10 *N* sodium hydroxide solution. The product was extracted with ethyl acetate and the combined ethyl acetate extracts were evaporated to dryness *in vacuo*. The deep red base thus obtained weighed 5.0 g., m.p. 80–90°. It was dissolved in 6 ml. of ethanol and the solution was treated with a solution of 8.5 g. of picric acid in 8 ml. of ethanol at 50°. The precipitate that separated was collected by filtration and crystallized from ethanol; yellow needles (6.0 g., 28% over-all), m.p. 202–204°.

Anal. Calcd. for $C_{20}H_{26}N_4O \cdot 2C_6H_3N_3O_7$: C, 48.2; H, 4.0; N, 17.6. Found: C, 48.6; H, 4.4; N, 17.3.

Quinacrine N$^{\omega}$,10-dioxide Dihydrochloride (VI).—A solution of 30.0 g. (0.0722 mole) of quinacrine 10-oxide in 500 ml. of chloroform was cooled to 5° and to it was added dropwise over a period of 55 min. a solution of 13.8 g. (0.0722 mole) of perbenzoic acid in 200 ml. of chloroform while maintaining the temperature at 3–5°. The reaction mixture was allowed to stand at 0 to 5° for 3 hr., 2 l. of anhydrous ether was added, and anhydrous hydrogen chloride was bubbled into the mixture. The yellow precipitate that separated was collected by filtration, washed with anhydrous ether and dried *in vacuo*. The crude material was crystallized four times from 1 l. portions of 5% hydrochloric acid, collected by fil-

tration, washed with acetone and dried *in vacuo* at 50°; yield, 21.1 g. 158%, m.p., 208–211° dec.

Anal. Calcd. for $C_{23}H_{30}ClN_3O_3 \cdot 2HCl \cdot 0.25H_2O$: C, 54.23; H, 6.43; N, 8.25; Cl^-, 13.92; H_2O, 0.88. Found: C, 54.39; H, 6.42; N, 8.37; Cl^-, 13.91; H_2O, 0.99.

Mono- and Difluorination of Steroids at C-16 through Enamine Intermediates

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Reaction of 17-oxosteroids with 4-pipecoline followed by treatment of the crude reaction product with perchloryl fluoride leads to 16,16-difluoro- and 16-monofluoro-17-oxosteroids. The reaction very likely proceeds through an enamine intermediate.

Recent reports[1,2] of the fluorination of steroids at C-16 by use of perchloryl fluoride have shown that this reagent can be used with suitable intermediates such as the 16-hydroxymethylene[1] and 16-ethoxalyl[2] derivatives of 17-oxosteroids. The present report concerns the application of the enamine procedure[3] to the same over-all transformation.

When applied to C-17, formation of enamines proved difficult and required far more vigorous conditions than at other positions.[4] Partial reaction at this position was accomplished by use of a high boiling amine, 4-pipecoline, with 3-methoxyestra-1,3,5(10)-trien-17-one or 3β-hydroxyandrost-5-en-17-one. Though enamine formation in this study proceeded at best to approximately 50% completion, it is hoped that improved procedures can be found. These observations are in essential agreement with those of Herr and Heyl,[5] who noted that enamines from 17-oxosteroids and pyrrolidine could not be prepared except for the unusual case of adrenosterone in which

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