lized from a mixture of ethanol, acetone, and ether. The water-soluble, dark maroon solid weighed 9.8 g. (56%), m.p. >325°. The sample was allowed to equilibrate in the air prior to analysis.

Anal. Calcd. for $C_{26}H_{28}N_4O_6 \cdot 2HCl \cdot 0.75H_2O$: C, 53.93; H, 5.48; N, 9.68; H_2O, 2.33. Found: C, 53.82; H, 5.81; N, 9.88; H_2O, 2.61.

4-(3-Chloro-9-acridinylamino)-α-amino-*o*-cresol 10-Oxides

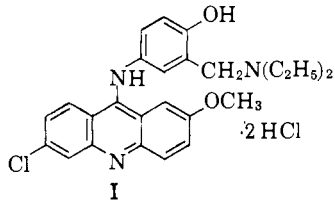
EDWARD F. ELSLAGER AND FRANK H. TENDICK

Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan

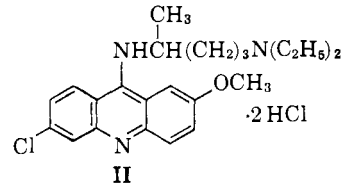
Received June 14, 1962

A group of 4-(3-chloro-9-acridinylamino)-α-amino-*o*-cresol 10-oxides has been prepared by the condensation of a 3,9-dichloroacridine 10-oxide with the appropriate 4-amino-α-amino-*o*-cresol hydrochloride in phenol. Several compounds exhibited good activity against *Entamoeba histolytica in vitro* and *Plasmodium lophurae* in the chick.

During investigations of malaria conducted in the United States during World War II, 4-(6-chloro-2-methoxy-9-acridinylamino)-α-diethylamino-*o*-cresol dihydrochloride (I) was synthesized in these laboratories[1] and was demonstrated to be qualitatively similar to quin-



I



II

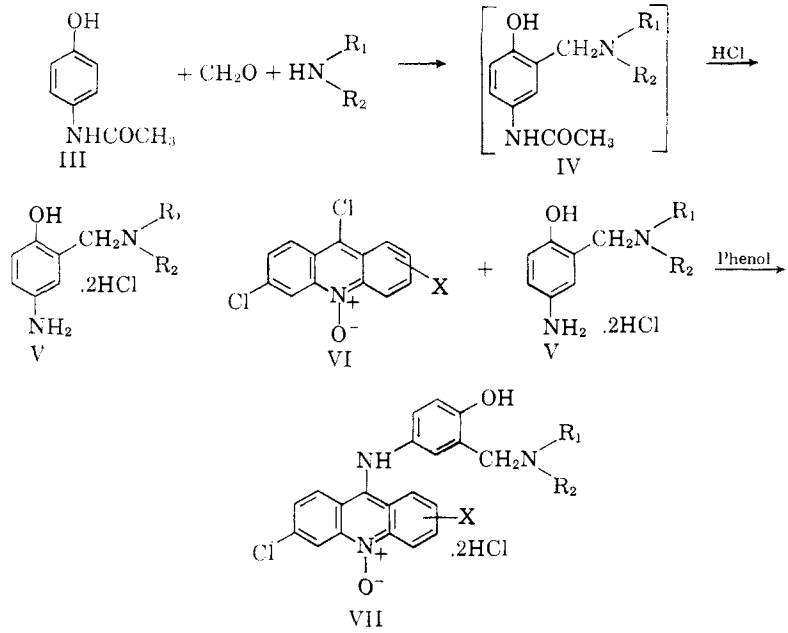
acrine (II) in over-all antimalarial potency.[2] It was of interest to synthesize various 4-(3-chloro-9-acridinylamino)-α-amino-*o*-cresol 10 oxides (VII) for biological evaluation. Details of the synthetic work are described in the present communication.

The 4-(3-chloro-9-acridinylamino)-α-amino-*o*-cresol 10-oxides (VII) (Table II) were prepared by allowing a 3,9-dichloroacridine 10-

(1) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb and A. L. Rawlins, *J. Am. Chem. Soc.*, **70**, 1363 (1948).

(2) F. Y. Wiselogle, "A Survey of Antimalarial Drugs, 1941–1945," J. T. Edwards, Ann Arbor, Mich., 1946, pp. 373, 1361.

oxide[3] (VI) to react with the appropriate 4-amino-α-amino-o-cresol hydrochloride (V) in phenol (methods I and II). Condensation of 4′-hydroxyacetanilide (III) with formaldehyde and the appropriate amine gave the corresponding 4-acetamido-α-amino-o-cresols (IV) which were not isolated but were hydrolyzed directly to the intermediate 4-amino-α-amino-o-cresol hydrochlorides (V) (Table I).[1] In several cases the crude 4-amino-α-amino-o-cresol hydrochlorides were used without further purification.

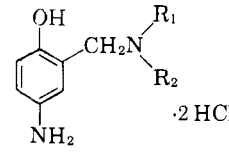


Absorption in the ultraviolet and low wave length visible range was used to assist in the characterization of the 4-(3-chloro-9-acridinylamino)-α-amino-o-cresol 10-oxides. A comparison of the spectrum of a representative 9-aminoacridine 10-oxide and of the corresponding des N-oxide in 0.1 N hydrochloric acid is shown in Fig. 1. The solid line represents 4-(6-chloro-2-methoxy-9-acridinylamino)-α-diethylamino-o-cresol 10-oxide dihydrochloride and the broken line 4-(6-chloro-2-methoxy-9-acridinylamino)-α-diethylamino-o-cresol dihydrochloride. Formation of the 10-oxide bond causes a general bathochromic shift combined with a modest decrease in intensity of the most intense band and a general decrease in resolution.

(3) E. F. Elslager, R. E. Bowman, F. H. Tendick, D. J. Tivey and D. F. Worth, *J. Med. Pharm. Chem.*, **5**, 1159 (1962).

Table I

4-Amino-α-(mono and dialkylamino)-o-cresol, Hydrochlorides[a]



NR_1R_2	M.p., °C.[b]	Yield[c] purified, %	Purification[d] solvent
$N(CH_2)_4$	215	91	A
$NH(CH_2)_9CH_3$	110	83	B
$N[(CH_2)_2OH]_2$	207	58	C
$N[(CH_2)_2]_2NCH_3$	130	97	D
$N[(CH_2)_2]_2NC_6H_4Cl$[e,f]	260	38	D

	Analyses					
	Carbon, %		Hydrogen, %		Nitrogen, %	
Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
$C_{11}H_{16}N_2O \cdot 2HCl$	49.82	49.51	6.84	7.19	10.57	10.61
$C_{17}H_{30}N_2O \cdot 2HCl$	58.11	58.39	9.18	9.40	7.97	7.98
$C_{11}H_{18}N_2O_3 \cdot 2HCl$	44.15	44.10	6.73	6.92	9.36	9.50
$C_{12}H_{19}N_3O \cdot 3HCl$	43.58	43.13	6.71	7.31	12.71	12.69
$C_{17}H_{20}ClN_3O \cdot 2HCl$	52.25	52.05	5.68	5.88	10.75	10.82

[a] All compounds are off-white solids. [b] M.p. dec. [c] Over-all yield based on 4′-hydroxyacetanilide. [d] A, ethanol–ether; B, ethanol–acetone–ether; C, ethanol–ethyl acetate; D, methanol–ether. [e] C_6H_4Cl represents the *o*-chlorophenyl radical. [f] In this case the intermediate 4-acetamino-α-[N′-(*o*-chlorophenyl)piperazinyl]-*o*-cresol was isolated, purified and characterized; off-white crystals (65.6 g., 45.6%), m.p. 154–155° from ethyl acetate. *Anal.* Calcd. for $C_{19}H_{22}ClN_3O_2$: C, 63.41; H, 6.16; N, 11.68. Found: C, 63.62; H, 6.37; N, 11.76.

The 4-(3-chloro-9-acridinylamino)-α-amino-*o*-cresol 10-oxides (VII) described in the present communication were tested by Dr. Paul E. Thompson and co-workers of these laboratories against trophozoite-induced *P. lophurae* in the chick[4] and against *Entamoeba histolytica in vitro*.[5] Compounds 1, 2, 4, 6, 7, 8 and 10 were more active than quinacrine against *P. lophurae* in the chick; compounds 4 and 10 caused much less staining of mouse tissues than quinacrine. Eleven compounds were amebicidal *in vitro* at concentrations of 20 to 400 μg./ml.[6]

Acknowledgment.—The authors take this opportunity to thank Dr. Loren M. Long for encouragement in this investigation and Dr. Paul E. Thompson, Miss Anita Bayles, Mrs. Sheila Herbst, Dr.

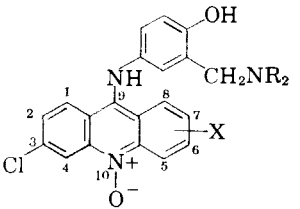
(4) P. E. Thompson, J. E. Meisenhelder, H. H. Najarian and A. Bayles, *Am. J. Trop. Med. Hyg.*, **10**, 335 (1961).

(5) For a description of test methods, see P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles and A. R. Cook, *Antibiotics and Chemotherapy*, **5**, 433 (1955).

(6) P. E. Thompson, A. Bayles, S. Herbst, H. Najarian and B. Olszewski, unpublished results, Parke, Davis and Co.

TABLE II

4-(3-CHLORO-9-ACRIDINYLAMINO)-α-AMINO-*o*-CRESOL 10-OXIDES[a]



Compound	NR_2	X	M.p., °C.[b]	Yield purified, %	Procedure	Purification solvent[c]	Formula	Analyses: Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$N(CH_2)_4$	6-Cl	230-231	45	II	A	$C_{24}H_{29}Cl_2N_3O_2 \cdot 2HCl \cdot 1.5H_2O$	52.00	52.11	4.73	4.66	7.58	7.59
2	$N(C_2H_5)_2$	6-Cl	140-142	77	I	B	$C_{24}H_{33}Cl_2N_3O_2 \cdot 0.5H_2O$	61.94	62.48	5.20	5.64	9.03	8.62
3	$N(C_2H_5)_2$	-H	135-140	81	II	C	$C_{24}H_{24}ClN_3O_2 \cdot 2HCl$	58.25	58.01	5.30	5.88	8.49	8.40
4	$N(CH_3)_2$	7-OCH_3	138-140	43	I	B	$C_{25}H_{24}ClN_3O_3 \cdot 0.75H_2O$	64.79	64.78	5.55	5.73	9.07	8.70
5	$N[(CH_2)_2]_2O$	7-OCH_3	264-265	60	II	D	$C_{26}H_{24}ClN_3O_4 \cdot 2HCl \cdot 0.5H_2O$	54.80	54.97	4.97	5.20	7.67	7.93
6	$N(C_2H_5)_2$	6-CH_3	210-211	58	II	E	$C_{26}H_{26}ClN_3O_2 \cdot 2HCl \cdot 2H_2O$	55.10	55.25	5.92	5.87	7.71	7.78
7	$NHCH_2CH(CH_3)_2$	7-OCH_3	220-221	27	II	C	$C_{26}H_{26}ClN_3O_3 \cdot 2HCl \cdot 1.5H_2O$	54.40	54.13	5.66	5.80	7.61	7.70
8	$N(C_2H_5)_2$	7-OCH_3	173-174	72	I	B	$C_{25}H_{26}ClN_3O_3$	66.44	66.03	5.80	6.13	9.30	9.20
9	$N[(CH_2)_2OH]_2$	7-OCH_3	179-181	24	II	F	$C_{25}H_{26}ClN_3O_5 \cdot 2HCl \cdot 2H_2O$	50.64	50.77	5.44	5.72	7.09	7.17
10	$N(CH_2)_5$	7-OCH_3	185-186	63	I	B	$C_{26}H_{26}ClN_3O_3 \cdot 0.5H_2O$	66.02	66.59	5.76	6.05	8.88	8.77
11	$N[(CH_2)_2]_2NCH_3$	7-OCH_3	230-231	11	II	E	$C_{26}H_{27}ClN_4O_3 \cdot 3HCl \cdot 1.5H_2O$[d]	50.74	50.80	5.40	5.71	9.10	9.57
12	$N[(CH_2)_2OCH_3]_2$	7-OCH_3	225-226	4	II	E	$C_{27}H_{30}ClN_3O_5 \cdot 2HCl$	55.14	55.27	5.54	5.60	7.18	6.92
13	$NH(CH_2)_9CH_3$	6-Cl	200-205	54	II	D	$C_{30}H_{25}Cl_2N_3O_2 \cdot 2HCl \cdot 0.5H_2O$	57.88	57.66	6.15	5.89	6.75	6.92
14	$N[(CH_2)_2]_2NC_6H_4Cl$[e]	7-OCH_3	211-212	64	I	G	$C_{39}H_{28}Cl_2N_4O_3 \cdot 0.5H_2O$	63.70	63.71	5.00	4.97	9.59	9.59
15	$NH(CH_2)_9CH_3$	7-OCH_3	175-176	51	II	C	$C_{31}H_{38}ClN_3O_3 \cdot 2HCl$	61.13	61.15	6.62	6.80	6.90	6.83

[a] Compounds vary from deep orange to nearly black in color. [b] Melted dec. [c] A, methanol-acetone; B, ethanol-water; C, ethanol-acetone-water; D, methanol-acetone-water; E, ethanol-acetone; F, methanol; G, ethanol. [d] Water determination (Karl Fischer): calcd.: 1.39; found: 4.46. [e] C_6H_4Cl represents the *o*-chlorophenyl radical.

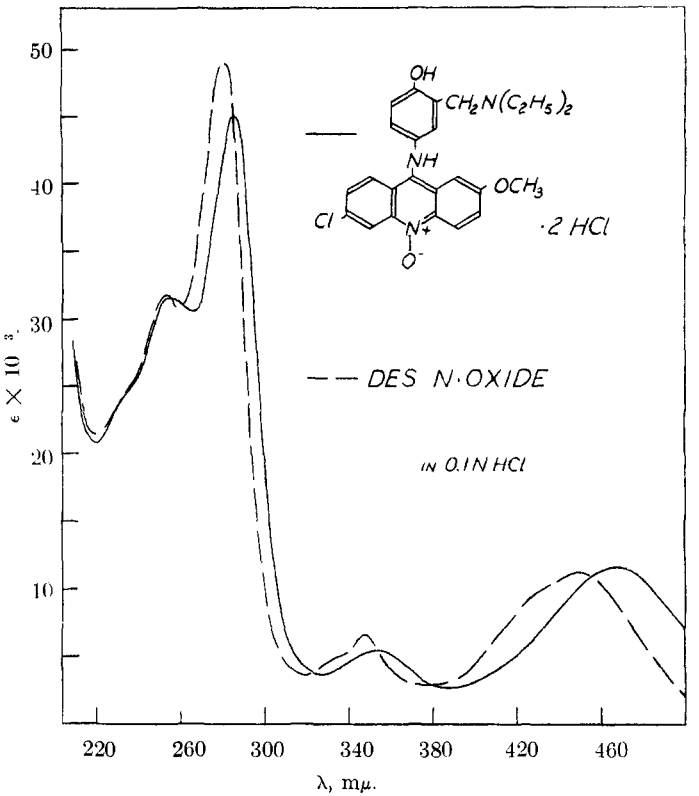


Fig. 1.—Absorption in 0.1 *N* HCl solution, taken with a Cary-11 spectrophotometer.

Haig Najarian and Miss Bronislawa Olszewski for the biological testing. The authors are also indebted to Mr. Charles E. Childs and associates for the microanalyses and to Dr. J. M. Vandenbelt and associates for determination of the infrared and ultraviolet absorption spectra.

Experimental[7]

General Method for Preparing 4-Amino-α-(mono- and dialkylamino)-o-cresol Hydrochlorides (V) (Table I).—A mixture of 105 g. (1 mole) of diethanolamine, 30 g. (1 mole) of paraformaldehyde and 100 ml. of ethanol was warmed until a clear solution was obtained; it was then added to a solution of 151 g. (1 mole) of 4′-hydroxyacetanilide in 100 ml. of ethanol. The resulting mixture was boiled under reflux on the steam bath for 3 hr. Most of the ethanol was removed by distillation and 500 ml. of 18% hydrochloric acid was added. The mixture was

(7) Melting points are uncorrected.

concentrated to a small volume on the steam bath and the residue was dried by azeotropic distillation of several portions of ethanol and benzene. The residue was dissolved in a 50% methanol-ethanol mixture and a 50% mixture of anhydrous ether and ethyl acetate was added to precipitate the product. The precipitate was digested with boiling ethanol, the mixture was allowed to cool, and the product was collected by filtration and dried *in vacuo* at 50°. The desired 2,2'-(5-aminosalicylimino)diethanol weighed 175 g. (58%), m.p. 207° dec.

Methods for Preparing 4-(3-Chloro-9-acridinylamino)-α-amino-*o*-cresol 10-Oxides (VII) (Table II). Method I.—A mixture of 12.8 g. (0.044 mole) of 6,9-dichloro-2-methoxyacridine 10-oxide,[3] 11.7 g. (0.044 mole) of 4-amino-α-diethylamino-*o*-cresol dihydrochloride,[1] and 25 g. of phenol was heated at 130–140° for 1.5 hr., cooled, and poured into a mixture of 5 ml. of concd. hydrochloric acid and 200 ml. of acetone with vigorous stirring. After 18 hr., the mixture was diluted with anhydrous ether and the solid was collected by filtration, dissolved in warm water, and filtered. The filtrate was made alkaline with ammonium hydroxide and the base was collected by filtration and dried *in vacuo* at 45°. Crystallization from ethanol (decolorizing charcoal) gave 14.3 g. (72%) of 4-(6-chloro-2-methoxy-9-acridinylamino)-α-diethylamino-*o*-cresol 10-oxide as deep maroon crystals, m.p. 173–174° dec.

Method II.—A mixture of 14.6 g. (0.055 mole) of 4-amino-α-1-pyrrolidinyl-*o*-cresol dihydrochloride and 25 g. of phenol was heated *in vacuo* on the steam bath for 1 hr.; 3,6,9-trichloroacridine 10-oxide[3] (14.9 g., 0.05 mole) then was added and the mixture was stirred and heated at 125–135° for 2 hr. Upon cooling, the reaction mixture was poured into 800 ml. of acetone with vigorous stirring and the crude hydrochloride salt was collected by filtration and dried *in vacuo*. The product was dissolved in water and the solution was made alkaline with excess ammonium hydroxide. The solid base was extracted with chloroform and the combined chloroform extracts were dried over anhydrous potassium carbonate. The drying agent was removed by filtration and the chloroform solution was evaporated to dryness *in vacuo*. The crude base was dissolved in boiling ethanol (decolorizing charcoal), the ethanol solution was concentrated to a small volume, and excess concd. hydrochloric acid was added. The orange hydrochloride salt was collected by filtration and crystallized twice from a methanol–acetone mixture. The desired 4-(3,6-dichloro-9-acridinylamino)-α-(1-pyrrolidinyl)-*o*-cresol 10-oxide dihydrochloride sesquihydrate weighed 12.5 g. (45%), m.p. 230–231° dec.