9-Amino-2,3-dimethoxy-6-nitroacridine 10-Oxides

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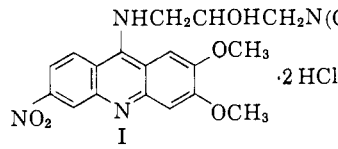
Several 9-amino-2,3-dimethoxy-6-nitroacridine 10-oxides were synthesized for antibacterial evaluation. They were prepared by the condensation of 9-chloro-2,3-dimethoxy-6-nitroacridine 10-oxide with the appropriate amine in phenol. 1-Diethylamino-3-(2,3-dimethoxy-6-nitro-9-acridinylamino)-2-propanol 10-oxide dihydrochloride exhibited more promising antibacterial properties than the corresponding des-N-oxide and was less toxic.

It has been reported that 1-diethylamino-3-(2,3-dimethoxy-6-nitro-9-acridinylamino)-2-propanol dihydrochloride (Nitroakridin 3582) (I) and combinations containing it (Entozon, Rutenol) exhibit

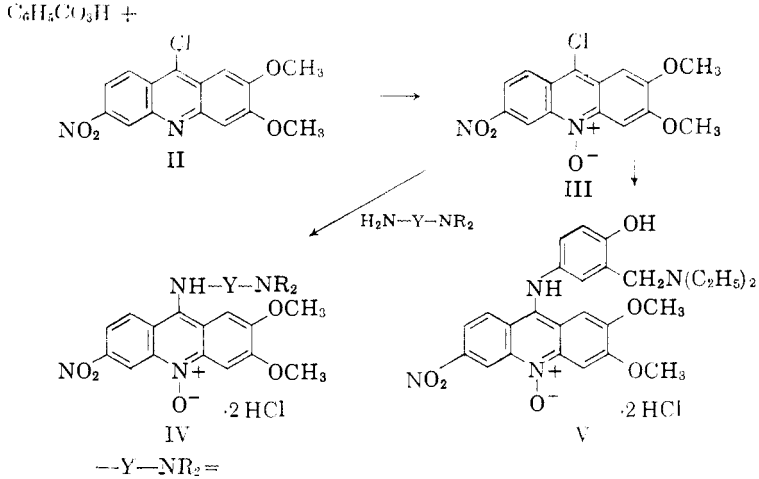


I

activity against bacteria, rickettsia, viruses, trichomonads and babesiidae.[1] It was of interest to prepare several 9-amino-2,3-dimethoxy-6-nitroacridine 10-oxides for biological evaluation in comparison with I.

The condensation of 9-chloro-2,3-dimethoxy-6-nitroacridine 10-oxide (III) with N^1,N^1-diethyl-1,4-pentanediamine,[2] 1-amino-3-diethylamino-2-propanol[3] and 2-(3-aminopropylamino)ethanol[4] in phenol gave 9-(4-diethylamino-1-methylbutylamino)-2,3-dimethoxy-6-nitroacridine 10-oxide dihydrochloride (IVa), 1-diethylamino-3-(2,3-dimethoxy-6-nitro-9-acridinylamino)-2-propanol 10-oxide dihydrochloride (IVb) and 2-[3-(2,3-dimethoxy-6-nitro-9-acridinylamino)propylamino]ethanol 10-oxide dihydrochloride (IVc), respectively. α-Diethylamino-4-(2,3-dimethoxy-6-nitro-9-acridinylamino)-*o*-cresol 10-oxide dihydrochloride (V) was prepared in a similar manner

(1) For a brief review and literature summary, see E. A. Steck, J. S. Buck and L. T. Fletcher, *J. Am. Chem. Soc.*, **79**, 441 (1957).
(2) Purchased from the Winthrop Laboratories, New York, N.Y.
(3) Purchased from Distillation Products, Rochester, N.Y.
(4) Supplied through the courtesy of the Union Carbide Chemicals Co., New York, N.Y.



—Y—NR_2 =
(a) —$CHCH_3(CH_2)_3N(C_2H_5)_2$
(b) —$CH_2CH(O)HCH_2N(C_2H_5)_2$
(c) —$(CH_2)_3NHCH_2CH_2OH$

from III and 4-amino-α-dimethylamino-*o*-cresol dihydrochloride.[5] Oxidation of 9-chloro-2,3-dimethoxy-6-nitroacridine (II)[6] with perbenzoic acid in chloroform afforded the intermediate 9-chloro-2,3-dimethoxy-6-nitroacridine 10-oxide (III) in 51% yield.

A comparison of the antibacterial activity of the 9-amino-2,3-dimethoxy-6-nitroacridine 10-oxide dihydrochlorides with 1-diethylamino - 3 - (2,3 - dimethoxy - 6 - nitro - 9 - acridinylamino) - 2 - propanol dihydrochloride was made by Dr. M. W. Fisher and Dr. A. L. Erlandson of these laboratories. The *in vitro* test results are summarized in Table I. The reference compound I was outstanding only

TABLE I

In Vitro ANTIBACTERIAL ACTIVITY OF 9-AMINO-2,3-DIMETHOXY-6-NITROACRIDINE 10-OXIDES

Test organism	Min. inhib. concn. (μg./ml.) for compound: I	IVa	IVb	IVc	V
C203 *Streptococcus*	2.50	0.16	0.01	0.01	2.50
UC-76 *Staphylococcus*	0.31	>20	1.25	10.0	>20
AD *Klebsiella*	>20	>20	>20	>20	>20
MGH-1 *Proteus vulgaris*	>20	>20	>20	>20	>20
#20 *Pseudomonas*	>20	>20	>20	>20	>20
V-31 *Salmonella*	>20	>20	>20	>20	>20
Mycobacterium tuberculosis H27Rv	1.25	5.0	0.31	5.0	10.0

(5) 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).

(6) Purchased from the Aldrich Chemical Co., Milwaukee, Wis.

by virtue of the fact that it was the most active compound *vs.* staphylococci. The corresponding 10-oxide (IVb) was over-all the most impressive compound, being the most active of the series against tubercle bacilli and streptococci while retaining very respectable activity *vs.* staphylococci. None of the compounds showed activity against the four Gram-negative bacilli at 20 μg./ml. or less. In mice, 1-diethylamino-3-(2,3-dimethoxy-6-nitro-9-acridinylamino)-2-propanol 10-oxide dihydrochloride (IVb) was the most promising compound tested. It was active against C203 *Streptococci* when administered either subcutaneously or orally and against UC-76 *Staphylococci* when given subcutaneously. The 9-amino-2,3-dimethoxy-6-nitroacridine 10-oxide hydrochlorides were less toxic than 1 - diethylamino - 3 - (2,3 - dimethoxy - 6 - nitro - 9 - acridinylamino)-2-propanol dihydrochloride in mice.

Acknowledgment.—The authors are indebted to Dr. Loren M. Long for encouragement in this investigation and to Dr. M. W. Fisher and Dr. A. L. Erlandson for the biological testing. We also thank Mr. Charles E. Childs and associates for the microanalyses and Dr. J. M. Vandenbelt and associates for the determination of the infrared and ultraviolet absorption spectra.

Experimental[7]

9-Chloro-2,3-dimethoxy-6-nitroacridine 10-Oxide (III).—A solution of 24.3 g. (0.176 mole) of perbenzoic acid[8] in 500 ml. of chloroform was added to a solution of 51.0 g. (0.160 mole) of 9-chloro-2,3-dimethoxy-6-nitroacridine (II)[6] in 6 l. of chloroform and the mixture was allowed to stand at room temperature for 18 hr. The chloroform solution turned deep red in color. Approximately 4 l. of chloroform were removed *in vacuo* and the residual chloroform solution was washed successively with two 1 l. portions of 10% sodium carbonate solution and 1 l. of water. The chloroform layer was dried over anhydrous potassium carbonate, the drying agent was collected by filtration and platinum foil was added to the filtrate. The chloroform solution was concentrated *in vacuo* to a volume of 500 ml. and cooled. The precipitate was collected by filtration and dried *in vacuo* at 65°; weight, 27.6 g. (51%), m.p. 265° dec. Addition of anhydrous ether to the filtrate gave 4.3 g. of a second crop, m.p. 253° dec.

Anal. Calcd. for $C_{15}H_{11}ClN_2O_5$: C, 53.82; H, 3.31; N, 8.37. Found: C, 53.89; H, 3.47; N, 8.39.

9-(4-Diethylamino-1-methylbutylamino)-2,3-dimethoxy-6-nitroacridine 10-Oxide Dihydrochloride (IVa).—N^1,N^1-Diethyl-1,4-pentanediamine[2] (4.2 g., 0.0266 mole) and 40 g. of phenol were mixed and 8.0 g. (0.0232 mole) of 9-chloro-2,3-dimethoxy-6-nitroacridine 10-oxide (III) was added. The mixture was

(7) Melting points are uncorrected.

(8) H. Gilman and A. H. Blatt, "Organic Syntheses, Collective Volume I," Second Ed., John Wiley and Sons, Inc., New York, N. Y., 1946, p. 431.

stirred and heated on the steam bath for 4 hr., cooled and poured into 3 l. of acetone containing an excess of concd. hydrochloric acid. The precipitate was collected by filtration and dissolved in water containing a few drops of hydrochloric acid. The solution was made basic with ammonium hydroxide and the solid that separated was extracted with chloroform. The combined chloroform extracts were washed successively with dil. sodium hydroxide solution and water, dried over anhydrous potassium carbonate, and the chloroform removed *in vacuo*. The viscous residue was stirred with two portions of petroleum ether (b.p. 80–100°), dissolved in ethanol, treated with excess ethanolic hydrogen chloride, diluted with acetone, and allowed to crystallize. The orange leaflets were collected by filtration, dried *in vacuo* at 50° for 18 hr., and allowed to equilibrate in the air. The product weighed 2.5 g. (22%), m.p. 200° dec.

Anal. Calcd. for $C_{24}H_{32}N_4O_5 \cdot 2HCl \cdot 1.5H_2O$: C, 51.79; H, 6.70; N, 10.07; H_2O, 4.85. Found: C, 52.00; H, 6.75; N, 10.03; H_2O, 5.02.

1-Diethylamino-3-(2,3-dimethoxy-6-nitro-9-acridinylamino)-2-propanol 10-Oxide Dihydrochloride (IVb).—9-Chloro-2,3-dimethoxy-6-nitroacridine 10-oxide (III) (14.0 g., 0.0418 mole) and 80 g. of phenol were heated to 70° on the steam bath and 7.0 g. (0.0478 mole) of 1-amino-3-diethylamino-2-propanol[3] was added dropwise with mechanical stirring. The reaction mixture was subsequently stirred and heated on the steam bath for 1 hr., cooled, and poured slowly with stirring into 1 l. of an ice-water mixture containing an excess of sodium hydroxide. The mixture was extracted with chloroform and the combined chloroform extracts were washed thoroughly with dil. sodium hydroxide solution and water and dried over anhydrous potassium carbonate. The drying agent was collected by filtration and the chloroform was removed *in vacuo*. The residue was dissolved in ethanol, treated with an excess of ethanolic hydrogen chloride and diluted with acetone. Recrystallization from an ethanol–acetone mixture gave 1.0 g. (5%) of orange crystals, m.p. 197° dec. The sample was equilibrated in the air prior to analysis.

Anal. Calcd. for $C_{22}H_{28}N_4O_6 \cdot 2HCl \cdot 0.5H_2O$: C, 50.19; H, 5.94; N, 10.64. Found: C, 50.53; H, 6.05; N, 10.58.

2-[3-(2,3-Dimethoxy-6-nitro-9-acridinylamino)propylamino]ethanol 10-Oxide Dihydrochloride (IVc).—Utilizing the procedure described under IVb, 10.0 g. (0.030 mole) of 9-chloro-2,3-dimethoxy-6-nitroacridine 10-oxide (III) and 4.0 g. (0.034 mole) of 2-(3-aminopropylamino)ethanol[4] gave 3.0 g. (20%) of orange crystals, m.p. 196° dec.

Anal. Calcd. for $C_{20}H_{24}N_4O_6 \cdot 2HCl \cdot 1.5H_2O$: C, 46.52; H, 5.66; N, 10.85; H_2O, 5.23. Found: C, 46.49; H, 5.97; N, 10.95; H_2O, 5.60.

α-Diethylamino-4-(2,3-dimethoxy-6-nitro-9-acridinylamino)-*o*-cresol 10-Oxide Dihydrochloride (V).—A mixture of 10.0 g. (0.03 mole) of 9-chloro-2,3-dimethoxy-6-nitroacridine 10-oxide (III) and 50 g. of phenol was melted and 8.0 g. (0.03 mole) of 4-amino-α-diethylamino-*o*-cresol dihydrochloride[5] subsequently was added. The mixture was heated on the steam bath for 3 hr., a few drops concd. hydrochloric acid added, and the mixture diluted with acetone. The precipitate was collected by filtration and shaken with a mixture of ammonium hydroxide and chloroform. The chloroform layer was washed with sodium hydroxide solution and water, dried over anhydrous potassium carbonate, and evaporated to dryness *in vacuo*. The residue was dissolved in ethanol and the ethanol solution was treated with excess concd. hydrochloric acid, diluted with acetone, and concentrated. The precipitate was collected by filtration and crystal-

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 equllibrate 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

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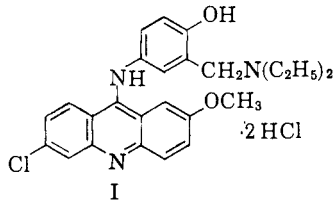
A group of 4-(3-chloro-9-acridinylamino)-α-amino-*o*-cresol 10-oxides has been prepared by the condensation of a 3,9-dichloroacridine 10-oxide with the appropriate 4-amino-α-amino-*o*-cresol hydrochloride in phenol. Several compounds exhibited good activity against *Entamoeba histolytica in vitro* and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



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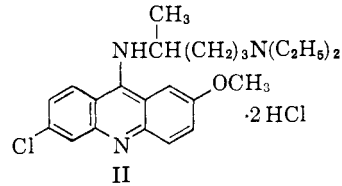

II

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.