Synthetic Amebicides. V. 6-(Mono- and Dialkylaminoalkylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)diones[1]

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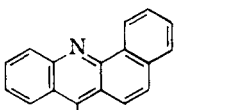
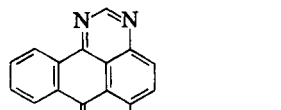
Received August 4, 1960

A variety of amine derivatives of nitrogen heterocyclic compounds has been reported to possess activity against *Entamoeba histolytica*, the causative agent of amebiasis.[2] Among these, striking activity has been observed with polycyclic amines such as 7-aminobenz[c]acridines of general formula I[1,3] and 6-aminoanthrapyrimidines of structure II,[4] where Y represents an alkylene

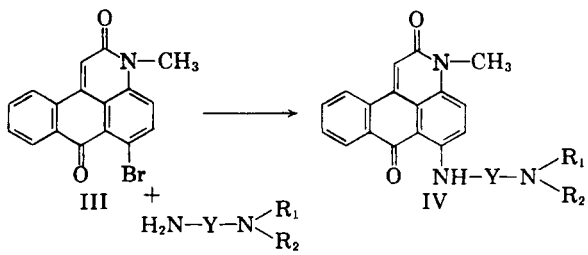


I



II

radical. In a search for polycyclic amines with antiamebic activity, we have synthesized a series of 6-(mono- and dialkylaminoalkylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)diones (IV) (Table I) for biological evaluation. These compounds were prepared by the condensation



III + $H_2N-Y-N(R_1)(R_2)$ → IV

of the commercially available[5] 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione (III) with the appropriate *N*-monoalkyl-or *N,N*-dialkylalkylenediamine utilizing xylene, pyridine or excess

(1) For previous paper in this series, see E. F. Elslager, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 451 (1958).

(2) For a summary of these studies, see E. F. Elslager in *Medicinal Chemistry*, A. Burger, ed., Interscience, New York, 1960, pp. 862–864.

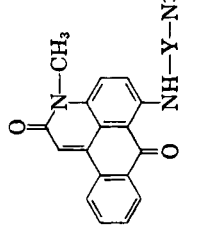
(3) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **79**, 4699 (1957); F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 223 (1958); P. E. Thompson, D. A. McCarthy, J. W. Reinertson, A. Bayles, and H. Najarian, *Antibiotics & Chemotherapy*, **8**, 37 (1958).

(4) W. R. Jones, J. K. Landquist, and N. Senior, *Brit. J. Pharmacol.*, **7**, 486 (1952).

(5) The authors express their appreciation to the Antara Chemicals Division of General Dyestuff Corp., New York for the generous supply of the 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione used in this work.

TABLE I

6-(MONO- AND DIALKYLAMINOALKYLAMINO)-3-METHYL-7H-DIBENZ[f,ij]ISOQUINOLINE-2,7(3H)DIONES[a]

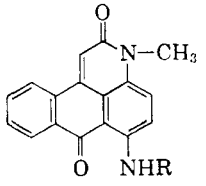


Y	NR_1R_2	M.P.	Yield purified, %	Procedure	Purification Solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
—$(CH_2)_2$—	$N(C_2H_5)_2$	195–197	35	I[d]	A	$C_{24}H_{23}N_3O_2$	73.57	73.66	6.72	6.78	11.18	11.41
—$(CH_2)_2$—	$NHCH(CH_3)_2$	157–158 (s. 153)	43	I	A, B	$C_{25}H_{25}N_3O_2$	73.57	73.59	6.72	6.68	11.18	10.98
—$(CH_2)_3$—	$N(CH_3)_2$	168–170	76	II	B	$C_{22}H_{21}N_3O_2 \cdot H_2O$[c]	69.63	69.58	6.64	6.66	11.07	11.15
—$(CH_2)_3$—	$N(C_2H_5)_2$	175–176	42	I[d]	B	$C_{24}H_{27}N_3O_2$	74.01	73.83	6.99	7.16	10.79	10.63
—$(CH_2)_3$—	$N[(CH_2)_2]_2O$	204–205	30	I[d]	A	$C_{24}H_{25}N_3O_3$	71.44	71.17	6.25	6.22	10.41	10.84
—$(CH_2)_5$—	$N(CH_3)_2$	183–185 (s. 178)	22	III	B	$C_{27}H_{31}N_3O_2$	75.49	75.48	7.28	7.20	9.78	9.84
—$CH_2CHOHCH_2$—	$N(C_2H_5)_2$	189–191 (s. 185)	53	II	B	$C_{24}H_{27}N_3O_3$	71.09	70.54	6.71	6.76	10.36	10.48

[a] All compounds were orange-red or red solids. [b] A, Benzene; B, acetone. [c] Water determination (Karl Fischer): Calcd. 4.75, Found: 4.89. [d] A trace of cuprous chloride was added.

amine as the solvent. The *N*-monoalkyl- and *N,N*-dialkylalkylenediamines have been described previously.[3]

The 6-(mono- and dialkylaminoalkylamino)-3-methyl - 7H - dibenz[f,ij]isoquinoline-2,7(3H)-diones described in the present communication were tested by P. E. Thompson and co-workers of these laboratories against *E. histolytica in vitro*,[6] and when indicated, against acute intestinal amebiasis in rats,[7] amebic colitis in dogs[8] and amebic hepatitis in hamsters.[9] Although details of these test results will be presented elsewhere,[10] the following highlights might be mentioned here. The dibenzisoquinolinediones listed in Table I were amebicidal *in vitro* at concentrations of 2 to 67 μg./ml. and each was active against intestinal amebiasis in the rat. Five compounds were tested against amebic dysentery in dogs and all were active. One compound (Va) was tested against amebic hepatitis in hamsters and was found to be approximately as active as chloroquine. Compound Vb,[11] which lacks the basic side chain, was inactive *in vitro* at 2000 μg./ml. and was ineffective against intestinal amebiasis in the rat at the M.T.D.



Va, R = $-(CH_2)_3N(CH_2)_5$
b, R = $-CH_3$

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

(7) For a description of test methods, see P. E. Thompson, M. C. Dunn, A. Bayles, and J. W. Reinertson, *Am. J. Trop. Med.*, 30, 203 (1950).

(8) For a description of test methods, see P. E. Thompson and B. L. Lilligren, *Am. J. Trop. Med.*, 29, 323 (1949).

(9) For a description of test methods, see (a) P. E. Thompson and J. W. Reinertson, *Am. J. Trop. Med.*, 31, 707 (1951); (b) J. W. Reinertson and P. E. Thompson, *Proc. Soc. Exp. Biol. Med.*, 76, 518 (1951).

(10) P. E. Thompson, to be published.

(11) Farbenfabriken Bayer Aktiengesellschaft, Brit. Pat. 486/1908 (Nov. 12, 1908).

EXPERIMENTAL[12]

Methods for preparing 6-(mono- and dialkylaminoalkylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)diones (Table I). Procedure I. *6-(3-Isopropylaminopropylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione.* A mixture of 68 g. (0.2 mole) of 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione and 130 g. (1.6 mole) of *N*-isopropylpropylenediamine was stirred and heated at approximately 120° for 24 hr. The red solution was cooled and poured into a mixture of 200 ml. of water and 40 g. of sodium hydroxide. Excess starting amine was removed by steam distillation, the residue was cooled, and the alkaline solution decanted from the gummy red solid. The crude product was extracted with warm 10% acetic acid, the extract was treated with decolorizing charcoal, filtered, and the red filtrate was made strongly alkaline with 20% sodium hydroxide solution. The alkaline solution was decanted and the residue crystallized from acetone or benzene.

Procedure II. *6-(3-Dimethylaminopropylamino)-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione.* A mixture of 68 g. (0.2 mole) of 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione, 40.8 g. (0.4 mole) of *N,N*-dimethylpropylenediamine and 350 ml. of xylene was heated under reflux for 24 hr. The red solid that separated was collected by filtration and dried *in vacuo* at 50° for 18 hr. The product was purified by extraction with 10% acetic acid and crystallization from acetone as outlined under procedure I above.

Procedure III. *3-Methyl-6-[5-(1-piperidyl)-amylamino]-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione.* A mixture of 34 g. (0.1 mole) of 6-bromo-3-methyl-7H-dibenz[f,ij]isoquinoline-2,7(3H)dione, 34 g. (0.2 mole) of 1-(5-aminopentyl)piperidine, and 60 g. of dry pyridine was heated under reflux for 18 hr. The red reaction mixture was cooled, poured into a 5-l. three-neck flask containing 200 ml. of 2*N* sodium hydroxide solution, and steam distilled for 3 hr. Upon cooling, the alkaline supernatant liquid was decanted and the dark red oily residue extracted with 10% acetic acid. The deep red acid extract was treated with decolorizing charcoal, filtered, and made strongly alkaline with 20% sodium hydroxide solution. The aqueous supernatant layer was decanted from the dark red gum which separated and the gum slowly solidified. The crude product was crystallized from acetone.

Acknowledgment. The authors thank Dr. Loren M. Long and Dr. George Rieveschl, Jr., for advice and encouragement, Dr. Paul E. Thompson, Miss Anita Bayles, Dr. D. A. McCarthy and Miss B. Olszewski for the biological testing, Mr. Charles E. Childs and associates for the microanalyses, and Dr. J. M. Vandenbelt and associates for determination of the infrared and ultraviolet absorption spectra.

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(12) All melting points are uncorrected.