of phenylglyoxylic acid, although the quantity must have been very small since no precipitate was obtained when an ethanolic solution of the acid material was treated with Brady reagent. A trial experiment showed that even a very dilute solution of phenylglyoxylic acid produced a strong positive Brady test.

Acknowledgment.—We are indebted to the National Science Foundation for financial support, and the New York Quinine and Chemical Works for a generous gift of thebaine.

LOS ANGELES 7, CALIFORNIA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS & CO.]

Synthetic Amebicides. IV. [(Benz[c]acridin-7-ylamino)-alkylamino]-alkanols and their Esters[1]

BY EDWARD F. ELSLAGER, FRANKLIN W. SHORT, MARIE JO SULLIVAN AND FRANK H. TENDICK

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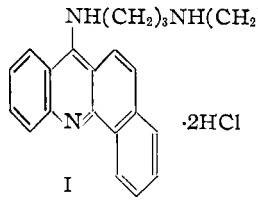
A group of [(benz[c]acridin-7-ylamino)-alkylamino]-alkanols have been prepared by allowing 7-chlorobenz[c]acridine to react with the appropriate aminoalkylaminoalkanol. Condensation of various [(benz[c]acridin-7-ylamino)-alkylamino]-alkanols with aliphatic acid chlorides or succinic anhydride yielded the corresponding [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol esters. Many of these heterocyclic alkanols and esters were highly active against *Endamoeba histolytica in vitro*, against experimentally-induced intestinal amebiasis in rats and dogs, and against amebic hepatitis in hamsters.

In previous communications,[1,2] it was reported that 7-(3-octylaminopropylamino)-benz[c]acridine dihydrochloride (PAA-2056) (I) and certain other 7-aminobenz[c]acridines are highly effective against *Endamoeba histolytica in vitro*, against intestinal amebiasis in rats and dogs, and against amebic hepatitis in hamsters. The present communication describes the synthesis of various [(benz[c]-



I

acridin-7-ylamino)-alkylamino]-alkanols and their esters, whose structures are indicated by formulas IV through VIII, where X and Y represent divalent alkyl groups, R a hydrogen, alkyl or hydroxyalkyl substituent and R′ an alkyl radical.

The [(benz[c]acridin-7-ylamino)-alkylamino]-alkanols of type V (Table I) were synthesized by heating a mixture of the appropriate aminoalkylaminoalkanol, 7-chlorobenz[c]acridine[1] and phenol at 80 to 130° for 2 to 3 hours. Procedures employed in these laboratories for the preparation of 2-[2-(benz[c]acridin-7-ylamino)-ethylamino]-ethanol and 2-[3-(benz[c]acridin-7-ylamino)-propylamino]-ethanol have been reported previously.[3] A benz[c]acridine analog (II) of the anthelmintic and antiprotozoan drug Acranil[4] (IIIa) and the antibacterial and antirickettsial agent Entozon[5] (IIIb) was prepared in a similar manner from 7-chlorobenz[c]acridine and 1-amino-3-diethylamino-2-propanol.[6] Many of the intermediate aminoalkylaminoalkanols are commercially available or were generously supplied by other laboratories.[7-9] 2-[(5-Aminopentyl)-ethylamino]-ethanol was prepared from N-(5-bromopentyl)-phthalimide[10] by acid hydrolysis of the intermediate N-{5-[ethyl-(2-hydroxyethyl)-amino]-pentyl}-phthalimide. 2-[(3-Aminopropyl)-ethylamino]-ethanol,[11] 2-[(3-aminopropyl)-pentylamino]-ethanol and 1-(3-aminopropyl)-3-piperidinol were prepared by catalytic hydrogenation of the corresponding nitriles in the presence of Raney nickel or Raney cobalt catalyst.

[(Benz[c]acridin-7-ylamino)-alkylamino]-alkanol esters of type IV (Table II) and [(benz[c]-acridin-7-ylamino)-alkylimino]-dialkanol esters of structure VII (Table II) were prepared by stirring a suspension of the anhydrous [(benz[c]-acridin-7-ylamino)-alkylamino]-alkanol dihydrochloride or [(benz[c]acridin-7-ylamino)-alkylimino]-dialkanol dihydrochloride with an excess of the appropriate acid chloride on the steam-bath for 7 to 24 hours. The synthesis of the [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol monosuccinate esters (VI) (Table II) was accomplished by heating approximately molar equivalents of the anhydrous [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol dihydrochloride and succinic anhydride at 100–150° for 20 to 24 hours. The 2-{[3-(benz[c]-acridin-7-ylamino)-propyl]-ethylamino}-ethanol, diester with succinic acid, tetrahydro-

(1) For previous paper in this series, see F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan and F. H. Tendick, THIS JOURNAL, **80**, 223 (1957).

(2) (a) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan and F. H. Tendick, *ibid.*, **79**, 4699 (1957); (b) P. E. Thompson, D. A. McCarthy, J. W. Reinertson, A. Bayles and H. Najarian, *Antibiotics and Chemotherapy*, **7**, in press (1957).

(3) E. F. Elslager, E. L. Benton, F. W. Short and F. H. Tendick, THIS JOURNAL, **78**, 3453 (1956).

(4) F. Mietzsch and H. Mauss, German Patent 553,072 (1930) and U. S. Patent 2,113,357 (1938).

(5) Final Report 766, British Intelligence Objectives Sub-Committee (1946), H. M. Stationery Office, London.

(6) Purchased from the Eastman Kodak Co., Rochester 3, N. Y.

(7) 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, 2-(2-amino-1-methylethylamino)-ethanol and 4-(3-aminopropylamino)-2-butanol.

(8) 2,2-(3-Aminopropylimino)-diethanol was obtained from the American Cyanamid Co., New York 20, N. Y.

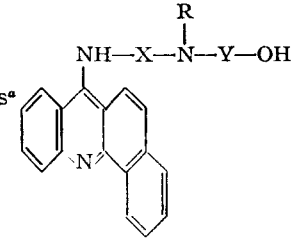
(9) 2-[(4-Aminopentyl)-ethylamino]-ethanol and 2,2′-(4-aminopentylimino)-diethanol were obtained through the courtesy of Dr. C. M. Suter and Mr. B. F. Tullar of the Sterling-Winthrop Research Institute, Rensselaer, N. Y.

(10) W. Dirscherl and F. W. Weingarten, *Ann.*, **574**, 131 (1951).

(11) (a) J. H. Burckhalter, E. M. Jones, W. F. Holcomb and L. A. Sweet, THIS JOURNAL, **65**, 2012 (1943); (b) A. R. Surrey and H. F. Hammer, *ibid.*, **72**, 1814 (1950).

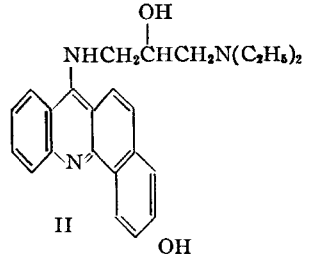
TABLE I

[(BENZ[c]ACRIDIN-7-YLAMINO)-ALKYLAMINO]-ALKANOLS[a]

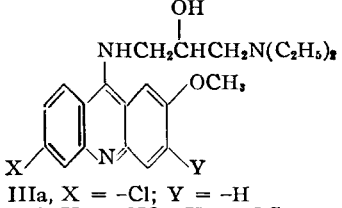


X	Y	R	M.p., °C.	Yield purified, %	Procedure	Purification solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-(CH_2)_2-$	$-(CH_2)_2-$	H	147 d.	38	I	C	$C_{21}H_{21}N_3O\cdot 2HCl$[b,d]	62.38	62.76	5.73	6.07	10.39	10.55
$-CH_2CHCH_3$	$-(CH_2)_2-$	H	s. 85[h]	80	I	E	$C_{22}H_{23}N_3O\cdot 2HCl\cdot 2H_2O$[c]	58.15	58.40	6.43	6.56	9.23	9.70
$-(CH_2)_3-$	$-(CH_2)_2-$	H	215–220				$C_{22}H_{23}N_3O\cdot 2HCl\cdot H_2O$[e]						
$-(CH_2)_3-$	$-(CH_2)_2CHCH_3$	H	s. 70[h]	53	II	A	$C_{24}H_{27}N_3O\cdot 2HCl\cdot {}^1/_4H_2O$[c]	63.92	63.83	6.59	7.12	9.32	8.95
$-(CH_2)_3-$	$-(CH_2)_2-$	C_2H_5	223–225 d.	52	I	D	$C_{24}H_{27}N_3O\cdot 2HCl$[b]	64.57	64.57	6.55	7.04	9.41	9.30
				57	II	B							
$-(CH_2)_3-$	$-(CH_2)_2-$	C_2H_5	80–82 d.	87	VI	B	$C_{24}H_{27}N_3O$	77.18	77.17	7.29	7.81	11.25	11.58
$-(CH_2)_3-$	$-(CH_2)_2-$	$(CH_2)_4CH_3$	150	60	I	E	$C_{27}H_{33}N_3O\cdot 2HCl\cdot 2{}^1/_4H_2O$[c]	61.30	61.20	7.53	7.38	7.94	7.97
$-(CH_2)_5-$	$-(CH_2)_2-$	C_2H_5	133–135 d.	63	II	B	$C_{26}H_{31}N_3O\cdot 2C_7H_6O_3\cdot {}^1/_4H_2O$[c,f]	70.41	70.20	6.43	6.64	6.16	6.52
$-CHCH_3(CH_2)_3-$	$-(CH_2)_2-$	C_2H_5	135–140	45	IV	A	$C_{26}H_{31}N_3O\cdot 2HCl\cdot {}^1/_2H_2O$[c]	64.59	64.72	7.09	7.37	8.69	8.75
$-(CH_2)_3-$	$-(CH_2)_2-$	$(CH_2)_2OH$	220–230	91	I	B	$C_{24}H_{27}N_3O_2\cdot 2HCl$[b]	62.34	62.51	6.32	6.84	9.09	9.39
				43	III	B							
$-CHCH_3(CH_2)_3-$	$-(CH_2)_2-$	$(CH_2)_2OH$	s. 80[h]	37	V	F	$C_{26}H_{31}N_3O_2\cdot 2HCl\cdot {}^3/_4H_2O$[c]	61.96	61.92	6.90	7.21	8.34	8.30

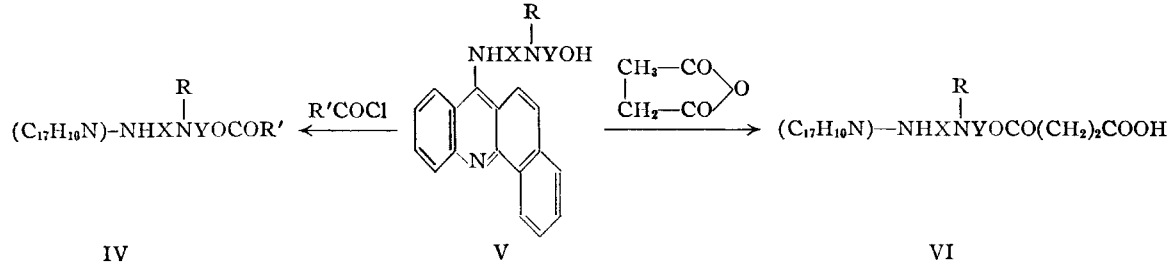
[a] All compounds were yellow solids. [b] Dried to constant weight; analyzed in a "piggy" or by quick weight. [c] Allowed to equilibrate in the air, analyzed as a hydrate. [d] Free base previously described.[3] [e] Described previously.[3] [f] $C_7H_6O_3$ represents salicylic acid. [g] A, attempts to recrystallize the compound from a variety of organic solvents failed; B, methanol; C, methanol–ether; D, methanol–acetone; E, ethanol–ethyl acetate; F, ethanol. [h] Indefinite.



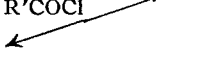
II

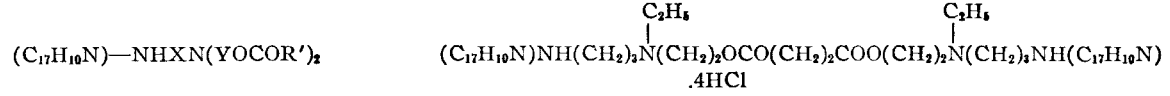


IIIa, X = -Cl; Y = -H
b, X = $-NO_2$; Y = $-OCH_3$



IV V VI





VII VIII

TABLE II

[(BENZ[c]ACRIDIN-7-YLAMINO)-ALKYLAMINO]-ALKANOL ESTERS[a]

X	R	R'	M.p., °C.	Yield purified, %	Procedure	Purification[c] solvent	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Infrared ester absorption, μ
$-(CH_2)_2-$	$-H$	$-CH_3$	135–145	100	I	A	$C_{23}H_{23}N_3O_2 \cdot 2HCl \cdot 1/2H_2O$	60.66	60.60	5.75	5.74	9.23	9.25	5.73
$-(CH_2)_2-$	$-H$	$-(CH_2)_{14}CH_3$	170–180	67	I	B	$C_{37}H_{51}N_3O_2 \cdot 2HCl \cdot H_2O$	67.25	67.47	8.39	8.94	6.36	5.76	5.73
$-(CH_2)_2-$	$-H$	$-(CH_2)_2COOH$	80 d.	77	II	A	$C_{25}H_{25}N_3O_4 \cdot 2HCl \cdot 1/2H_2O^c$	58.48	58.50	5.50	5.82	8.18	8.76	5.77
$-(CH_2)_2-$	$-C_2H_5$	$-CH_3$	174–176	93	I	A	$C_{26}H_{29}N_3O_2 \cdot 2HCl \cdot H_2O$	61.66	61.49	6.57	6.65	8.30	8.67	5.80
$-(CH_2)_2-$	$-C_2H_5$	$-(CH_2)_5CH_3$	147–149	80	I	A	$C_{31}H_{39}N_3O_2 \cdot 2HCl \cdot 2H_2O$	62.61	62.99	7.63	7.47	7.07	6.91	5.75
$-(CH_2)_2-$	$-C_2H_5$	$-(CH_2)_{14}CH_3$	168–171	92	I	A	$C_{40}H_{67}N_3O_2 \cdot 2HCl \cdot 3H_2O$	65.02	64.86	8.87	9.11	5.69	5.87	5.81
$-(CH_2)_2-$	$-C_2H_5$	$-(CH_2)_2COOH$	120	73	II[b]	C	$C_{28}H_{31}N_3O_4 \cdot 2HCl \cdot H_2O^d$	59.57	59.48	6.25	6.60	7.44	7.65	5.76
$-(CH_2)_2-$	$-(CH_2)_2OH$	$-(CH_2)_2COOH$	80 d.	90	II	A	$C_{28}H_{31}N_3O_5 \cdot 2HCl \cdot 1/4H_2O^e$	59.31	59.22	5.95	6.28	7.41	8.08	5.78
$-(CH_2)_2-$	$-(CH_2)_2OCO(CH_2)_{14}CH_3$	$-(CH_2)_{14}CH_3$	185–186	85	I	B	$C_{46}H_{87}N_3O_4 \cdot 2HCl \cdot 2^1/_2H_2O$	68.33	68.52	9.63	9.64	4.27	4.53	5.74

[a] All esters were yellow solids. [b] Under nitrogen. [c] *Anal.* Calcd.: Cl, 13.81. Found: Cl, 13.43. [d] *Anal.* Calcd.: Cl, 12.56. Found: Cl, 12.29. [e] *Anal.* Calcd.: Cl, 12.51. Found: Cl, 12.65; 12.20. [f] Nujol mull. [g] A, attempts to recrystallize these hygroscopic esters from a variety of organic solvents were unsuccessful; B, methanol; C, dimethylformamide–ether.

chloride (VIII) was obtained when a dry ether solution of two molar equivalents of 2-{[3-benz[c]acridin-7-ylamino)-propyl]-ethylamino}-ethanol was treated with one molar equivalent of succinyl chloride, followed by the addition of dry hydrogen chloride.

As in previous work,[1,2] absorption in the ultraviolet, low-wave length visible and infrared was frequently used to assist in the characterization of the 7-aminobenz[c]acridines prepared. Typical ultraviolet absorption spectra already have been described.[1] The esters reported here showed characteristic ester carbonyl absorption in the 5.7–5.8 μ region (Table II).

The [(benz[c]acridin-7-ylamino)-alkylamino]-alkanols and [(benz-[c]-acridin-7-ylamino)-alkylamino]-alkanol esters described herein were tested by Thompson and co-workers[12] of these laboratories against *Endamoeba histolytica in vitro*[13] and when indicated against experimentally induced *E. histolytica* infections in rats,[14] hamsters[15] and dogs.[16] Although details of these tests results will be published elsewhere, it is of interest to note that nineteen of the compounds described were amebicidal *in vitro* at concentrations of 2–200 μg./ml., and all of them were active against intestinal amebiasis in rats. Several compounds were also active against amebic colitis in dogs and amebic hepatitis in hamsters.

Acknowledgment.—The authors are indebted to Dr. Loren M. Long, Dr. Alexander M. Moore and Dr. George Rieveschl, Jr., for advice and encouragement in this investigation, to Dr. Paul E. Thompson, Mr. D. A. McCarthy, Mr. J. W. Reinertson, Miss Anita Bayles and Dr. Haig Najarian for the antiamebic testing, and to Mr. Donald F. Worth for the synthesis of several of the compounds described herein. We also thank Mr. Charles E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and associates for the determination and interpretation of the infrared and ultraviolet absorption spectra, and Mr. William Pearlman for carrying out several of the catalytic hydrogenations described herein.

Experimental[17]

2-[(5-Aminopentyl)-ethylamino]-ethanol.—A modification of the procedure described by Blicke, *et al.*,[18] for the preparation of 1-(3-aminopropyl)-piperidine was employed: A mixture of 220 g. (0.74 mole) of N-(5-bromopentyl)-phthalimide, 480 g. (30 moles) of 2-ethylaminoethanol and 2 l. of xylene was boiled under reflux for 18 hr. Upon cooling, the 2-ethylaminoethanol hydrobromide did not separate, but dilution of a small sample of the reaction mixture with ether precipitated the salt, indicating that the reaction had taken place. One mole of anhydrous potassium carbonate

(12) P. E. Thompson, D. A. McCarthy, J. W. Reinertson, A. Bayles and H. Najarian, unpublished reports.

(13) 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).

(14) 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).

(15) For a description of test methods, see P. E. Thompson and J. W. Reinertson, *ibid.*, **31**, 707 (1951).

(16) For a description of test methods, see P. E. Thompson and B. L. Lilligren, *ibid.*, **29**, 323 (1949).

(17) Melting points are uncorrected.

(18) F. F. Blicke, H. C. Parke and E. L. Jenner, THIS JOURNAL, **62**, 3316 (1940).

was added and the mixture was distilled *in vacuo* to remove excess amine and xylene. The residue was extracted with methylene chloride and the solvent removed *in vacuo* leaving the crude N-{5-[ethyl-(2-hydroxyethyl)-amino]-pentyl}-phthalimide as a thick oil. This crude product was cautiously treated with a mixture of 200 ml. of concentrated hydrochloric acid and 200 ml. of water with cooling and the resulting mixture boiled under reflux for 4 hr. Upon cooling, the phthalic acid was collected by filtration, washed with 25 ml. of water and discarded. The combined filtrates were made strongly alkaline by the addition of saturated potassium hydroxide and the product salted out by saturating the solution with solid potassium hydroxide. The oily layer which separated was dried over solid potassium hydroxide and distilled through a seven-inch Vigreux column to give 45 g. (35%) of a colorless oil, b.p. 103–104° (1 mm.), $n^{25}D$ 1.4870.

Anal. Calcd. for $C_9H_{22}N_2O$: N, 16.08. Found: N, 16.28.

2-[(3-Aminopropyl)-pentylamino]-ethanol.—To 52.6 g. (0.40 mole) of 2-pentylaminoethanol was added below 30° with stirring 23.4 g. (0.44 mole) of acrylonitrile over a period of 7 minutes. A mild exothermic reaction occurred. The solution was stirred for 2 hr. at room temperature, heated at 80° for 1 hr., allowed to stand for 18 hr. at room temperature and subsequently stirred *in vacuo* for 2 hr. The residual crude nitrile (72 g., 0.39 mole) was dissolved in 300 ml. of ethanol saturated with ammonia and hydrogenated at 1100 p.s.i.g. and 100° in 1.5 hr. using Davison Raney nickel catalyst. The catalyst was collected by filtration and the ethanol removed *in vacuo*. Distillation of the residue yielded 54.5 g. (72% over-all) of a colorless oil, b.p. 162–165° (16 mm.), $n^{25}D$ 1.4664.

Anal. Calcd. for $C_8H_{24}N_2O$: N, 14.88. Found: N, 14.58.

1-(3-Aminopropyl)-3-piperidinol.—Acrylonitrile (106 g., 2 moles) was added dropwise with stirring to 200 g. (2 moles) of 3-piperidinol (Aldrich Chemical Co.), which had previously been liquified on the steam-bath and cooled to 35°. An exothermic reaction occurred and the reaction temperature was maintained at 30–40° by external cooling. After the addition was complete, the reaction mixture was allowed to stand at room temperature for 18 hr. and subsequently heated on the steam-bath for 2 hr., the last hour *in vacuo*. The resulting 3-hydroxy-1-piperidinepropionitrile was reduced catalytically without further purification by the following procedure[19]: 90 g. of moist Raney cobalt[20] was washed successively with five 100-ml. portions of absolute ethanol and three 100-ml. portions of cyclohexane and placed in a 1600-ml. Aminco bomb together with the crude 3-hydroxy-1-piperidinepropionitrile and 90 ml. of triethylamine. The bomb was pressurized to 1775 p.s.i.g. with hydrogen and heated rapidly to 102°. The reaction began at approximately 70°, the pressure dropping to 600 p.s.i.g. within 15 minutes. No additional absorption of hydrogen was noted, although the mixture was heated for an additional 25 minutes during which time the hydrogen pressure was increased to 1750 p.s.i.g. The reaction mixture was flushed out of the bomb with ethanol and cyclohexane and the volatile materials were removed *in vacuo* on the steam-bath. The residue was fractionally distilled *in vacuo* through a 7-inch Vigreux column to give 234 g. (74%) of a colorless liquid, b.p. 79–80° (0.07 mm.), $n^{25}D$ 1.5022.

Anal. Calcd. for $C_8H_{18}N_2O$: C, 60.72; H, 11.46; N, 17.71. Found: C, 60.54; H, 11.50; N, 17.77.

Methods for Preparing [(Benz[c]acridin-7-ylamino)-alkylamino]-alkanols (Table I). Method I.—A mixture of 0.038 to 0.080 mole of 7-chlorobenz[c]acridine,[1] 0.042 to 0.085 mole of the appropriate aminoalkylaminoalkanol and 40 to 60 g. of phenol was stirred and heated on a steam-bath for 3 to 4 hr. The cooled reaction mixture was poured into a solution of 10 to 20 ml. of concentrated hydrochloric acid in 125 to 200 ml. of acetone. The mixture was cooled and diluted with 200 to 400 ml. of acetone or ether; upon scratching, the product solidified. The crude hydrochloride was collected by filtration, washed with acetone and dried. Recrystallization from the appropriate solvent yielded the corresponding [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol dihydrochlorides.

Method II.—A mixture of 0.030 to 0.038 mole of 7-chlorobenz[c]acridine[1] and 25 to 40 g. of phenol was heated to 120° with mechanical stirring and cooled to 80°. The appropriate diamine (0.035 to 0.042 mole) was then added, and heating and stirring at 80° to 110° was continued for 3 hr. The reaction mixture was poured into a solution of 5 to 90 g. of potassium hydroxide in 300 to 400 ml. of water. The product was extracted with three 100- to 300-ml. portions of ether or chloroform, the combined organic extracts were dried over anhydrous potassium carbonate and the drying agent was collected by filtration. After treatment with decolorizing charcoal, dry hydrogen chloride or an ether solution of the appropriate acid was added; the product which separated was triturated with ether or acetone, collected by filtration, dried *in vacuo* and recrystallized from the solvent indicated.

Method III.—To a mixture of 0.030 mole of 7-chlorobenz[c]acridine[1] and 26 g. of phenol, previously heated together at 80°, was slowly added 0.035 mole of 2,2′-(3-aminopropylimino)-diethanol[8]; stirring and heating at 100° were continued for 3 hr. The reaction mixture was cooled and slowly poured into a solution of 90 g. of potassium hydroxide in 300 ml. of water. The water layer was decanted from the gummy base, the product extracted with dilute hydrochloric acid and the base reprecipitated with ammonium hydroxide. The base was collected by filtration, dissolved in acetone (charcoal) and the acetone solution dried over anhydrous potassium carbonate. The addition of dry hydrogen chloride to the dry acetone solution precipitated the desired dihydrochloride salt which was collected by filtration and dried to constant weight.

Method IV.—A mixture of 0.100 mole of 7-chlorobenz[c]acridine,[1] 0.105 mole of [(4-aminopentyl)-ethylamino]-ethanol[9] and 60 g. of phenol was stirred and heated at 120–130° for 2 hr. Upon cooling, the reaction mixture was stirred into 20% sodium hydroxide solution and the product extracted with chloroform. The chloroform extracts were washed with several portions of 10% sodium hydroxide and water and treated with decolorizing charcoal. The chloroform solution was evaporated to an oil, which was dissolved in ethanol and made strongly acid with ethanolic hydrogen chloride. Upon dilution with an acetone–ether mixture, a dark tarry precipitate was obtained which could not be crystallized. The solvents were evaporated, and the residue made alkaline with excess ammonium hydroxide and extracted with ether. The ether solution was washed with water and subsequently extracted with 10% acetic acid until the extracts gave no precipitate with ammonium hydroxide. The acetic acid solution was treated with decolorizing charcoal, filtered, made alkaline with 20% sodium hydroxide solution and again extracted with ether; the ether extracts were washed with water, and dried for 18 hr. over anhydrous potassium carbonate. Upon treatment with excess ethanolic hydrogen chloride, an orange waxy material precipitated. Attempts to crystallize the compound from various mixtures of methanol, ethanol, acetone and ether failed. The material was dissolved in methanol, the solvent evaporated, and the residue powdered in a mortar and allowed to dry at room temperature for 24 hr.

Method V.—A mixture of 55.5 g. (0.21 mole) of 7-chlorobenz[c]acridine,[1] 40 g. (0.21 mole) of 2,2′-(4-aminopentylimino)-diethanol[9] and 250 g. of phenol was stirred and heated on the steam-bath for 4 hr. The cooled reaction mixture was poured into 2 l. of acetone containing an excess of concentrated hydrochloric acid. An orange-red tar precipitated which solidified upon trituration with acetone and ether. The crude dihydrochloride was recrystallized twice from ethanol (decolorizing charcoal) to give a dull yellow solid. This material was dissolved in water, the solution was poured into an excess of ammonium hydroxide, the base extracted with chloroform and the combined chloroform extracts dried over anhydrous potassium carbonate. The drying agent was collected by filtration, the chloroform extracts evaporated *in vacuo* to 100 ml., and the chloroform concentrate diluted with 1.5 l. of anhydrous ether. Treatment of the chloroform–ether solution with excess hydrogen

(19) The authors are indebted to Mr. William Pearlman of the Parke, Davis High Pressure Laboratory who developed the Raney cobalt procedure described herein and carried out the hydrogenation. An extension of this work will be described in a forthcoming publication.

(20) The Raney cobalt was prepared according to the method described by H. Adkins and H. R. Billica, THIS JOURNAL, **70**, 695 (1948), for the preparation of W-6 Raney nickel with the exception that the catalyst was stored under water instead of ethanol.

chloride yielded 38 g. (37%) of a bright yellow solid which was collected by filtration, washed with acetone and ether and dried *in vacuo* over calcium chloride. The hygroscopic product was allowed to equilibrate in the air prior to analysis.

Method VI.—An aqueous solution of 40 g. of 2-{[3-(benz[c]-acridin-7-ylamino)-propyl]-ethylamino}-ethanol dihydrochloride monohydrate was treated with decolorizing charcoal, filtered, and the base liberated as a yellow taffy-like material by the addition of ammonium hydroxide. The aqueous solution was decanted and ether added to the residue, whereupon the gum crystallized. The ether was evaporated and the base crystallized from methanol; yield 28 g.

(Benz[c]acridin-7-ylamino)-3-diethylamino-2-propanol, Dihydrochloride.—A mixture of 20 g. (0.076 mole) of 7-chlorobenz[c]acridine,[1] 12.7 g. (0.087 mole) of 1-amino-3-diethylamino-2-propanol[6] and 75 g. of phenol was stirred and heated at 110° for 2 hr. and allowed to stand at room temperature for 16 hr. The dark red melt was poured with stirring into a solution of 175 g. of potassium hydroxide in 1 l. of water containing 500 g. of ice. The viscous oil which separated was extracted with several portions of ether, and the combined ether extracts were washed successively with two portions of 5% potassium hydroxide solution and water. The ether extracts were treated with decolorizing charcoal and dried over anhydrous potassium carbonate. The drying agent was collected by filtration and the filtrate treated with anhydrous hydrogen chloride. The hygroscopic yellow solid was collected by filtration, washed quickly with successive portions of anhydrous ether and acetone, and dried *in vacuo* at 40° for 24 hr. Purification from an ethanol–ether mixture yielded 14.2 g. (42%) of a hygroscopic yellow powder, m.p. indefinite beginning at 100°. For analysis, the compound was dried in a "piggy" at 60° for 24 hr.

Anal. Calcd. for $C_{24}H_{27}N_3O\cdot 2HCl$: C, 64.57; H, 6.54. Found: C, 64.15; H, 6.95.

1-[3-(Benz[c]acridin-7-ylamino)-propyl]-3-piperidinol, Dihydrochloride.—A mixture of 26.3 g. (0.100 mole) of 7-chlorobenz[c]acridine,[1] 16.6 g. (0.105 mole) of 1-(3-aminopropyl)-3-piperidinol and 50 g. of phenol was stirred and heated on the steam-bath for 3 hr. The cooled reaction mixture was treated with an excess of ethanolic hydrogen chloride and diluted with 1 l. of dry acetone. The waxy yellow precipitate which separated quickly solidified and was chilled, collected by filtration and washed with dry acetone. The crude hydrochloride was added to an excess of ammonium hydroxide, the base was extracted with chloroform, and the combined chloroform extracts were washed successively with two portions of 5% sodium hydroxide solution and water. The chloroform extracts were treated with decolorizing charcoal and evaporated to dryness *in vacuo*. The oily residue was dissolved in absolute ethanol and an excess of ethanolic hydrogen chloride was added, whereupon the yellow dihydrochloride crystallized. The mixture was stirred and warmed with methanol, dry acetone was added, and the mixture chilled. The product was collected by filtration, washed with acetone and dried *in vacuo* at 60°. After exposure to the air for 24 hr., the dihydrochloride monohydrate was obtained; yield 42.5 g. (89%), m.p. 262°.

Anal. Calcd. for $C_{25}H_{27}N_3O\cdot 2HCl\cdot H_2O$: C, 63.02; H, 6.56; N, 8.82. Found: C, 63.22; H, 6.73; N, 9.11.

Methods for Preparing [(Benz[c]acridin-7-ylamino)-alkylamino]-alkanol Esters (Table II). Method I.—A suspension of 0.009 to 0.076 mole of the [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol dihydrochloride, which had previously been dried *in vacuo* for 18 to 48 hr. at 35 to 100°, in 40 to 500 ml. of the appropriate acid chloride was stirred and heated on the steam-bath for 7 to 24 hr. The reaction was protected from moisture by a calcium chloride tube. After standing at room temperature for 1 to 16 hr., the reaction mixture was diluted with anhydrous ether, and the solid which precipitated collected by filtration and washed with anhydrous ether. The solid was pulverized under anhydrous ether, collected by filtration and dried *in vacuo* at room temperature for 5 to 18 hr. When feasible, the esters were recrystallized from the solvents indicated and dried *in vacuo* at room temperature.

Method II.—A mixture of 0.011 to 0.034 mole of the appropriate [(benz[c]acridin-7-ylamino)-alkylamino]-alkanol dihydrochloride, previously dried *in vacuo* at 35 to 100° for 18 hr. and 0.011 to 0.040 mole of succinic anhydride was heated at 100–150° for 20 to 24 hr. Dry nitrogen or a calcium chloride tube was used to protect the reaction from moisture. Subsequently, the reaction mixture was dissolved in boiling absolute ethanol and the ester reprecipitated with petroleum ether (b.p. 30–60°). After trituration with several portions of dry ether, the yellow solid was collected by filtration, washed with ether and dried *in vacuo* over calcium chloride for 20 to 60 hr. at room temperature.

2-{[3-(Benz[c]acridin-7-ylamino)-propyl]-ethylamino}-ethanol, Diester with Succinic Acid, Tetrahydrochloride, Trihydrate.—A mixture of 10 g. (0.038 mole) of 7-chlorobenz[c]acridine[1] and 40 g. of phenol was stirred and heated on the steam-bath for 15 minutes; 6.1 g. (0.042 mole) of 2-[(3-aminopropyl)-ethylamino]-ethanol[11] was added, the mixture stirred and heated on the steam-bath for 2 hr. and poured into 500 g. of 10% sodium hydroxide solution. The 2-{[3-(benz[c]acridin-7-ylamino)-propyl]-ethylamino}-ethanol was extracted with ether, the ether extracts washed with water until nearly neutral and dried over anhydrous potassium carbonate. The dry ether solution was treated dropwise with 2.9 g. (0.019 mole) of succinyl chloride with shaking. After standing at room temperature for 1 hr., dry hydrogen chloride was bubbled through the suspension for several minutes and the yellow-brown solid collected by filtration, washed with anhydrous ether and dried *in vacuo* at room temperature for 18 hr.; yield 16 g. (82%), s. 80°, m.p. 130–135°. Attempts to recrystallize the ester from a variety of organic solvents failed. The infrared spectrum showed a characteristic ester carbonyl absorption at 5.76 μ.

Anal. Calcd. for $C_{52}H_{56}N_6O_4\cdot 4HCl\cdot 3H_2O$: C, 60.70; H, 6.47; Cl, 13.78; N, 8.17. Found: C, 60.65; H, 6.15; Cl, 13.34; N, 7.53, 7.63.

DETROIT, MICHIGAN