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

Synthetic Amebicides. II. 7-Dialkylaminoalkylaminobenz[c]acridines and Other 7-Aminobenz[c]acridines[1,2]

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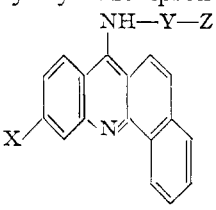
A number of 7-dialkylaminoalkylaminobenz[c]acridines and other 7-aminobenz[c]acridines have been prepared for antiamebic evaluation. These compounds were prepared by the condensation of a 7-chlorobenz[c]acridine with the appropriate amine or by ring closure of an N-(dialkylaminoalkyl)-2-(1-naphthylamino)-benzamide with phosphorus oxychloride. When tested against *Endamoeba histolytica in vitro*, against experimentally induced intestinal amebiasis in rats and against amebic hepatitis in hamsters, these compounds were found to possess good activity.

This communication reports a number of new 7-aminobenz[c]acridines of type Ia through f (where X represents hydrogen or chlorine and Y and R alkyl groups) which were prepared for antiamebic evaluation. When tested for antiamebic activity by Thompson and co-workers[3] of these

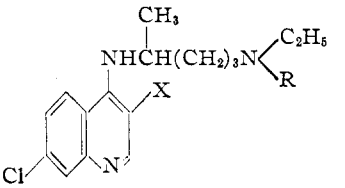


a, Z = -H
b, Z = -OH
c, Z = $-CHOHCH_2OH$
d, Z = $-OCH(CH_3)_2$
e, Z = $-NH_2$
f, Z = $-NR_2$

I

laboratories, many of these compounds were found to possess good activity against *Endamoeba histolytica in vitro*,[4] against amebic hepatitis in hamsters[5] and against intestinal amebiasis in rats.[6]

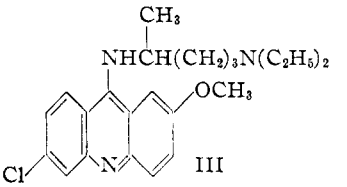
The chemical literature contains several reports of 7-dialkylaminoalkylaminobenz[c]acridines of type If prepared by various workers.[7-10] These earlier compounds were prepared during World War II primarily for antimalarial evaluation, and their synthesis was stimulated by the known antimalarial properties of chloroquine (IIa), quinacrine (III) and related compounds.[11-15] However, the hope that benz[c]acridines of type If might have useful antimalarial properties was not realized, and



IIa, X = -H, R = $-C_2H_5$
b, X = $-CH_3$, R = $-C_2H_5$
c, X = -H, R = $-CH_2CH_2OH$

indeed, available literature[7-10,14,15] indicates that compounds of type If are devoid of antimalarial properties even at high doses.

In addition to their potent antimalarial properties, the compounds chloroquine, quinacrine, sontochin (IIb) and hydroxychloroquine (IIc) are effective against amebic hepatitis in hamsters[5] and



III

in man.[16] If one assumed a positive correlation for structure–activity relationships in amebiasis with those observed in malaria, then based on the known antimalarial data, one would have predicted the benz[c]acridines to be devoid of useful properties in amebiasis. However, the evaluation of compounds of type If in our laboratories[3] against amebiasis demonstrated that these substances are, in fact, more active in amebiasis than the published quinolines and acridines (*e.g.*, IIa through c, III), even though they are devoid of significant antimalarial properties. Therefore, the apparent positive correlation of antimalarial and antiamebic activity among certain quinolines and acridines does not hold for the benz[c]acridines and cannot be assumed to hold for other dialkylaminoalkylaminoheterocyclic compounds.

The 7-aminobenz[c]acridines (Ia through f) were prepared by the condensation of a 7-chlorobenz[c]acridine (VI) with the appropriate amine or by ring-closure of an N-(dialkylaminoalkyl)-2-

(1) Presented before the Division of Medicinal Chemistry at the 131st National A.C.S. Meeting, April, 1957, in Miami, Florida.

(2) For previous paper in this series see E. F. Elslager, E. L. Benton, F. W. Short and F. H. Tendick, THIS JOURNAL, **78**, 3453 (1956).

(3) P. E. Thompson, A. Bayles, D. A. McCarthy and J. W. Reinertson, unpublished results.

(4) 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).

(5) 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. Exper. Biol. and Med.*, **76**, 518 (1951).

(6) 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).

(7) G. B. Bachman and G. M. Picha, THIS JOURNAL, **68**, 1599 (1946).

(8) G. B. Bachman and J. W. Wetzel, *J. Org. Chem.*, **11**, 454 (1946).

(9) J. Dobson, W. C. Hutchison and W. O. Kermack, *J. Chem. Soc.*, 123 (1948).

(10) D. P. Spalding, E. C. Chapin and H. S. Mosher, *J. Org. Chem.*, **19**, 357 (1954).

(11) F. Schönhöfer, "Chemotherapy, FIAT Review of German Science, 1939–1946," PB 85033, U. S. Dept. of Commerce, Office of Technical Services, Washington, D. C., 1948.

(12) A. R. Surrey and H. F. Hammer, THIS JOURNAL, **68**, 113 (1946).

(13) F. Mietzsch and H. Mauss, German Patent 553,072 and 571,449 (1934); U. S. Patent 2,113,357 (1938).

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

(15) G. M. Findlay, "Recent Advances in Chemotherapy," Vol. II. "Malaria," The Blakiston Co., Philadelphia, Penna., 1951, p. 65.

(16) (a) N. J. Conan, Jr., *Am. J. Trop. Med.*, **28**, 107 (1948); (b) R. A. Radke, *Ann. Int. Med.*, **34**, 1482 (1951); (c) N. J. Conan, Jr., *Am. J. Trop. Med.*, **31**, 18 (1951); (d) Dr. Bernardo Sepúlveda, Hospital de Enfermedales, Mexico City, has found hydroxychloroquine to be effective in hepatic amebiasis; paper in press.

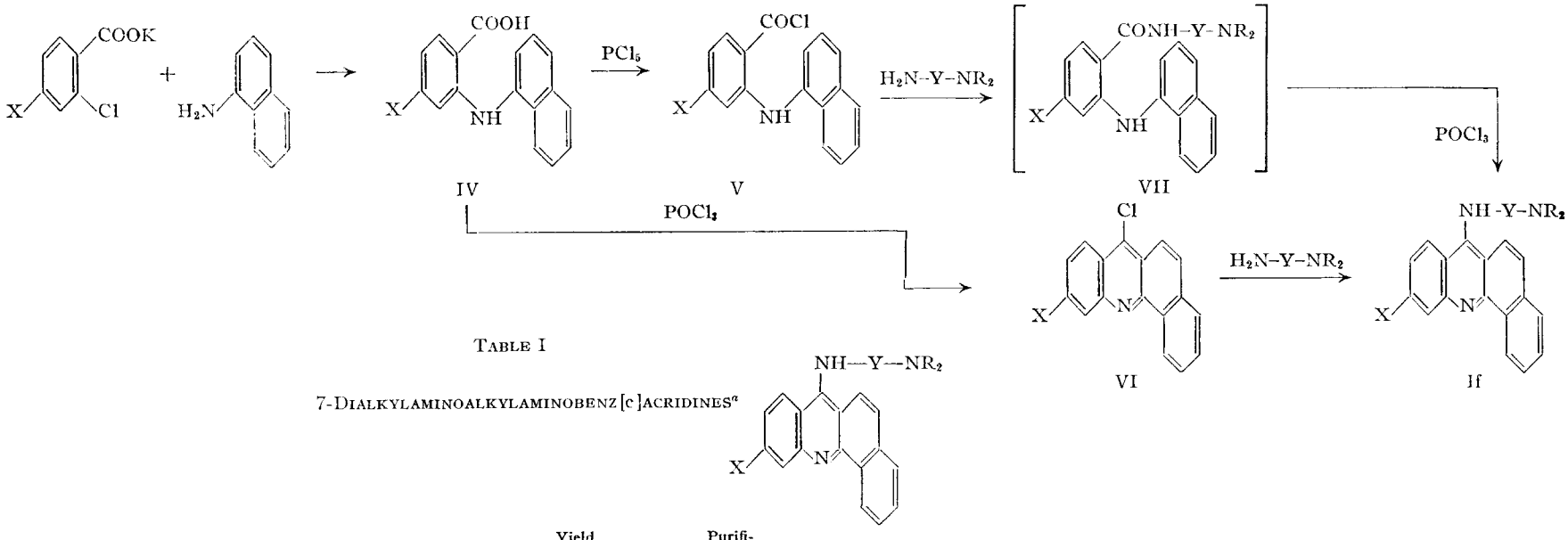


TABLE I

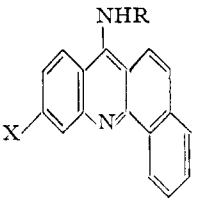
7-DIALKYLAMINOALKYLAMINOBENZ[c]ACRIDINES[a]

X	Y	NR₂	M.p., °C.	Yield purified, %	Procedure	Purification solvent[r]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	$-(CH_2)_3-$	$-N(CH_3)_2$	213 (dec.)	41[b]	IV[d]	D	$C_{22}H_{23}N_3 \cdot 2HCl$	65.66	65.84	6.26	6.51	10.44	10.52
Cl	$-(CH_2)_2-$	$-N(C_2H_5)_2$	260 (dec.)	56	III[d,f]	A	$C_{23}H_{24}ClN_3 \cdot 2HCl$	61.27	61.50	5.81	5.81	9.32	9.31
Cl	$-(CH_2)_3-$	$-N(C_2H_5)_2$	105–106	33	II[d]	F	$C_{24}H_{26}ClN_3$[h]	73.55	73.50	6.68	6.83		
H	$-(CH_2)_3-$	$-N(CH_2)_5$	255–256 d.	73	I[d,e]	G	$C_{26}H_{27}N_3 \cdot 2HCl \cdot 1^1/_3H_2O$[m]	64.37	64.80	6.84	6.71	9.01	9.19
Cl	$-(CH_2)_3-$	$-N(CH_2)_5$	131–133	61	I[d]	B	$C_{25}H_{26}ClN_3$	74.33	74.07	6.49	6.40	10.42	10.42
H	$-(CH_2)_3-$	$-N[(CH_2)_2CH_3]_2$	208–210	71	IV[c]	E	$C_{26}H_{31}N_3 \cdot 2HCl \cdot {}^1/_2H_2O$	66.79	66.61	7.33	7.77	8.99	9.19
H	$-(CH_2)_4-$	$-N(CH_2)_5$	230–240 d.	43	I[f]	C	$C_{26}H_{29}N_3 \cdot 2HCl$	68.41	68.73	6.85	7.09	9.21	9.01
H	$-(CH_2)_5-$	$-N(C_2H_5)_2$	Indefinite	10	I[d]	C	$C_{26}H_{31}N_3 \cdot 2(C_{11}H_8O_3) \cdot {}^1/_2H_2O$[i,n]	74.78	74.74	6.27	6.64	5.45	5.65
Cl	$-CHCH_3(CH_2)_3-$	$-N(C_2H_5)_2$	270	15	III[d,e]	H	$C_{26}H_{30}ClN_3 \cdot 2HCl \cdot 2^1/_4H_2O$[o]	58.54	58.25	6.90	6.95	7.88	8.15
Cl	$-(CH_2)_4-$	$-N(CH_2)_5$	255	25	I[f]	I	$C_{26}H_{28}ClN_3 \cdot 2HCl$	63.61	63.78	6.16	6.17	8.56	8.75
H	$-(CH_2)_5-$	$-N(CH_2)_5$	255–260	78	V[d]	L	$C_{27}H_{31}N_3 \cdot C_{23}H_{16}O_6 \cdot H_2O$[l]	74.63	74.61	6.13	6.20	5.24	5.21
Cl	$-(CH_2)_5-$	$-N(CH_2)_5$	Indefinite	63	I[d,e]	J	$C_{27}H_{30}ClN_3 \cdot 2HCl \cdot 2H_2O$[p]	59.94	59.50	6.71	5.98	7.77	7.79
H	$-(CH_2)_3-$	$-NC_8H_{16}$[k]	150 (eff.)	31	I[j]	K	$C_{28}H_{33}N_3 \cdot 2HCl \cdot 2H_2O$[q]	64.60	64.60	7.55	7.81	8.08	7.93
H	$-(CH_2)_6-$	$-N(CH_2)_5$	245–250	59	I[f]	E	$C_{28}H_{33}N_3 \cdot 2HCl$	69.40	69.69	7.28	7.49	8.67	8.80

[a] All compounds were yellow or yellow-green solids. [b] A substantial quantity of product was accidentally spilled. [c] This compound was purified twice through the free base. [d] Dried *in vacuo* at room temperature for 18 hr. [e] Allowed to equilibrate in the air. [f] Analyzed in "piggy" after drying to constant weight *in vacuo* at 40–80°. [g] A large volume of acetone was added to precipitate the crude product from the reaction mixture. [h] Hydrochloride, m.p. 253–255°, previously reported by G. B. Bachman and G. M. Picha, THIS JOURNAL, 68, 1599 (1946). [i] $C_{11}H_8O_3$ represents 3-hydroxy-2-naphthoic acid. [j] Dried *in vacuo* at 100° for 3 hr., allowed to equilibrate in air. [k] $-NC_8H_{16}$ represents the 5-ethyl-2-methylpiperidinyl radical. [l] $C_{23}H_{16}O_6$ represents 4,4′-methylenebis-(3-hydroxy-2-naphthoic acid). Water determinations (Karl Fischer): [m] calcd. 5.15, found 5.48; [n] calcd. 1.17, found 1.16; [o] calcd. 7.59, found 7.28; [p] calcd. 6.66, found 5.90; [q] calcd. 6.92, found 7.51. [r] A, ethanolic hydrogen chloride; B, ethanol containing a few drops of concentrated ammonium hydroxide solution; C, ethanol–ether; D, ethanol–acetone; E, ethanol–acetone–ether mixture containing a few drops of ethanolic hydrogen chloride; F, ethanol; G, ethanol–methanol; H, dilute hydrochloric acid; I, 2-propanol; J, methanol; K, methanol–ethyl acetate; L, salt extremely insoluble; washed thoroughly with water.

TABLE II

OTHER 7-AMINOBENZ[c]ACRIDINES[a]



X	R	M.p., °C.	Yield purified, %	Procedure	Purification solvent[k]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
H	$-(CH_2)_3CH_3$	243–245 d.	83	VI[b]	A	$C_{21}H_{20}N_2 \cdot HCl$	73.94	73.99	6.51	6.52	8.66	8.54
H	$-(CH_2)_5CH_3$	68	63	VII[b,c]	B	$C_{23}H_{24}N_2$	84.10	83.87	7.36	6.99	8.53	8.68
H	$-(CH_2)_7CH_3$	76	56	VII[b,d]	B,C	$C_{25}H_{28}N_2$	84.22	84.07	7.92	7.84	7.86	8.02
H	$-(CH_2)_2OH$	149–151	53	II[e]	E	$C_{19}H_{16}N_2O$	79.14	78.80	5.59	5.52	9.72	9.55
Cl	$-(CH_2)_2OH$	181–182	78	II[b]	F	$C_{19}H_{15}ClN_2O$	70.76	70.30	4.68	4.76	8.68	8.79
H	$-(CH_2)_4OH$	111–113	70	I[b]	D	$C_{20}H_{18}N_2O$	79.40	79.62	6.00	6.06	9.26	9.36
H	$-CH_2CHOHCH_2OH$	205–210	49	VI[f]	G	$C_{20}H_{18}N_2O_2 \cdot HCl \cdot 1^1/_4H_2O$	63.65	63.82	5.74	5.67	7.43	7.50
H	$-(CH_2)_3OCH(CH_3)_2$	146–147	51	VII[g]	D	$C_{23}H_{24}N_2O \cdot C_7H_6O_3$[j]	74.66	74.77	6.27	6.27	5.81	5.99
H	$-(CH_2)_3NH_2$	180	63	I[e,h]	H	$C_{26}H_{19}N_3 \cdot 2C_7H_6O_3$[j]	70.69	71.01	5.41	5.71	7.28	7.26
H	$-(CH_2)_6NH_2$	230 (dec.)	74	I[h,i]	I	$C_{23}H_{25}N_3 \cdot 2C_7H_6O_3$[j]	71.71	71.49	6.02	6.27	6.78	6.45

[a] All compounds were yellow or yellow-green solids. [b] Air-dried. [c] Exothermic reaction occurred at 130°, temporarily raising reaction temperature to 170°. [d] Hydrochloride, m.p. 170–172° dec. [e] Dried for 1 hr. *in vacuo* at 56°. [f] Allowed to equilibrate in air prior to analysis. [g] Dried for 3 hr. *in vacuo* at 78°. [h] One molar excess of the diamine was used. [i] Dried *in vacuo* over calcium chloride for 72 hr. [j] $C_7H_6O_3$ represents salicylic acid. [k] A, methanol–acetone; B, petroleum ether (b.p. 80–100°)–petroleum ether (b.p. 30–60°); C, ethanol–water; D, absolute ethanol; E, ethyl acetate; F, 2-propanol; G, ethanol–ethyl acetate; H, ethanol–ether; I, sample not recrystallized.

(1-naphthylamino)-benzamide (VII). Condensation of the potassium salt of the appropriate *o*-chlorobenzoic acid with 1-naphthylamine employing modifications of the procedures described by Ullmann[17] and by Bachman and Picha[7] gave the corresponding N-1-naphthylanthranilic acids (IV). These intermediates were subsequently converted to the N-1-naphthanthraniloyl chlorides (V) by the action of phosphorus pentachloride or ring-closed with phosphorus oxychloride to the 7-chlorobenz[c]acridines (VI). A majority of the 7-dialkylaminoalkylaminobenz[c]acridines (If) (Table I) and all of the 7-aminobenz[c]acridines of types Ia through e (Table II) were prepared by heating the appropriate 7-chlorobenz[c]acridine and amine in phenol or excess amine (methods I-III, VI, VII). Alternatively, the acid chloride V was allowed to react with the appropriate dialkylaminoalkylamine in benzene, and the resulting amide VII, which was usually not isolated, was closed to the desired 7-dialkylaminoalkylaminobenz[c]acridine (If) with phosphorus oxychloride (method IV). Most of the intermediate dialkylaminoalkylamines are commercially available[18,19]; others were prepared by base, acid[20,21] or hydrazine hydrolysis of the appropriate N-(dialkylaminoalkyl)-phthalimide or by catalytic reduction of an N-(cyanoethyl)-dialkylamine[22] by the usual methods.

Absorption in the ultraviolet and low-wave length visible range was used to assist in the characterization of many of the 7-aminobenz[c]-acridines described. Figure 1 shows molar absorptivities *vs.* wave length in mμ in 0.1 *N* hydrochloric acid solution which are typical for this series. The solid line represents 7-(3-piperidino-

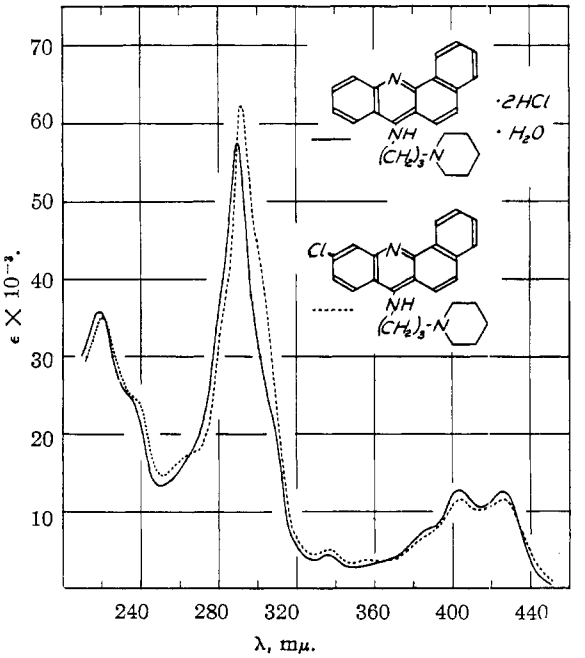


Fig. 1.—Absorption in 0.1 *N* HCl solution, taken on a Beckman model DU spectrophotometer.

(17) F. Ullmann, *Ann.*, **355**, 347 (1907).

(18) The authors are indebted to Dr. Franklin Johnston and Dr. G. W. Fowler of the Union Carbide Chemicals Co. for the sample of 1-(3-aminopropyl)-2-methyl-5-ethylpiperidine.

(19) N,N-Dimethyl-, N,N-diethyl- and N,N-di-*n*-propyl-1,3-propanediamine were obtained through the courtesy of the American Cyanamid Co., New York 20, N. Y.; N',N'-diethyl-1,4-pentanediamine was purchased from the Winthrop Laboratories, New York 18, N. Y.; N,N-diethyl-1,5-pentanediamine was purchased from the Sapon Laboratories, Valley Stream, N. Y.; 1-(3-aminopropyl)-piperidine and 1-(5-aminopentyl)-piperidine were purchased from the Organic Preparations Stocks, University of Illinois, Urbana, Ill.

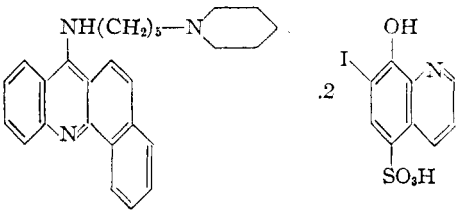
(20) O. Y. Magidson, A. M. Grigorovskii and E. P. Gal'perin, *J. Gen. Chem.* (*U.S.S.R.*), **8**, 56 (1938); *C. A.*, **32**, 5406 (1938).

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

(22) F. C. Whitmore, H. S. Mosher, R. R. Adams, R. B. Taylor, E. C. Chapin, E. Weisel and W. Yanko, *ibid.*, **66**, 725 (1944).

propylamino) - benz[c]acridine dihydrochloride monohydrate and the broken line, 10-chloro-(3-piperidinopropylamino)-benz[c]acridine. Both have three major bands in varying degrees of resolution, one at the low edge of the visible and two in the ultraviolet. The most pronounced characteristic is a very intense band around 290 mμ. Substitution with chlorine in the 10-position produces little change in the spectrum of a 7-aminobenz[c]-acridine, although there is generally a small shift to longer wave lengths. In the case of the most intense band, this shift is about 2 mμ.

Recently, the 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline salt with two formula weights of 8-hydroxy-7-iodo-5-quinolinesulfonic acid has been reported[23] to be clinically effective in both intestinal and extra-intestinal amebiasis. We have observed[3] that 8-hydroxy-7-iodo-5-quinolinesulfonic acid salts of the 7-dialkylaminoalkylaminobenz[c]acridines, such as the 7-(5-piperidinopentylamino)-benz[c]acridine salt with two formula weights of 8-hydroxy-7-iodo-5-quinolinesulfonic acid (VIII), also possess interesting antiamebic properties, as do salts with benzylpenicillin. These salts are conveniently prepared by combining aqueous solutions of the sodium or potassium salts of the acids with the appropriate 7-dialkylaminoalkylaminobenz[c]acridine hydrochlorides.



VIII

A second group of 7-dialkylaminoalkylaminobenz[c]acridines have been prepared in the Parke, Davis Research Laboratories in Hounslow, England. These compounds will be the subject of a separate communication.[24]

Acknowledgment.—The authors take this opportunity to thank Dr. Loren M. Long and Dr. George Rieveschl, Jr., for advice and encouragement, Dr. Paul E. Thompson, Miss Anita Bayles, Mr. D. A. McCarthy and Mr. J. W. Reinertson for biological testing, and Dr. H. S. Mosher of Stanford University for making various aminobenz[c]acridine samples available to us. We also are indebted to Mr. Charles E. Childs and associates for the microanalyses and to Dr. J. M. Vandenbelt and co-workers for the determination and interpretation of the infrared and ultraviolet spectra.

Experimental[25]

N-(6-Bromohexyl)-phthalimide.—A modification of the procedures described by Salzberg and Supniewski[26] and Sheehan and Bolhofer[27] for the condensation of potassium phthalimide with organic halides was employed.

In a 5-l. round-bottom flask were mixed 138 g. (0.75 mole) of potassium phthalimide, 367 g. (1.5 moles) of 1,6-dibromohexane and 1.5 l. of dimethylformamide. A slightly exothermic reaction occurred, the temperature rising to 50°. The mixture was stirred at room temperature for 18 hr., the potassium bromide which separated was collected by filtration and the excess dibromide and dimethylformamide were removed *in vacuo*. The semi-solid residue crystallized upon trituration with petroleum ether (b.p. 30–60°) and was collected by filtration. Crystallization from methanol gave 120 g. (52%) of colorless crystals, m.p. 120°.

Anal. Calcd. for $C_{14}H_{16}BrNO_2$: C, 54.23; H, 5.20. Found: C, 54.60; H, 5.38.

1-(6-Aminohexyl)-piperidine.—Condensation of 120 g. (0.39 mole) of N-(6-bromohexyl)-phthalimide and 170 g. (2 moles) of piperidine in boiling xylene followed by sodium hydroxide and hydrochloric acid hydrolysis of the crude N-(6-piperidinohexyl)-phthalimide according to the method of Blicke, *et al.*,[21] gave 19.4 g. (27%) of 1-(6-aminohexyl)-piperidine, b.p. 84–87° (0.6 mm.).

Anal. Calcd. for $C_{11}H_{24}N_2$: N, 15.20. Found: N, 15.17.

1-(4-Aminobutyl)-piperidine.—Utilizing the above procedure, 282 g. (1 mole) of N-(4-bromobutyl)-phthalimide yielded 99 g. (63%) of 1-(4-aminobutyl)-piperidine, b.p. 55° (0.5 mm.) (lit.[22] reports b.p. 120–122° (25 mm.)).

N-1-Naphthylanthranilic Acid.—A modification of the procedures described by Ullmann[17] and by Bachman and Picha[7] was employed: in a 12-l. 3-necked flask fitted with a Barrett distilling receiver was placed 7 l. of 3-methyl-1-butanol, which was dried by boiling under reflux until no more water distilled. While reflux was maintained, 626 g. (4 moles) of *o*-chlorobenzoic acid was added, followed by the cautious addition of 276 g. (2 moles) of powdered anhydrous potassium carbonate. When all of the water evolved in the formation of the potassium salt had been removed, 2 l. of dry 3-methyl-1-butanol was collected by distillation and 573 g. (4 moles) of 1-naphthylamine was dissolved in the dry solvent. While stirring and heating were maintained, 4 g. of copper powder was added, followed by the slow addition of the dry 1-naphthylamine solution over a period of 1 hr. The mixture was boiled under reflux with stirring for 24 hr., cooled and filtered. The filter cake was washed with several portions of warm 3-methyl-1-butanol. The combined filtrates were evaporated to dryness *in vacuo*, the residue was triturated with cold 95% ethanol followed by petroleum ether (b.p. 35–50°) and dried *in vacuo* at 60°. The crude acid weighed 623 g. (59%), m.p. 180–185°, and was of sufficient purity to use directly in the ring closure.

4-Chloro-N-(1-naphthyl)-anthranilic Acid.—To a solution of 191 g. (1 mole) of 2,4-dichlorobenzoic acid in 1200 ml. of dimethylformamide was added 69 g. (0.5 mole) of anhydrous potassium carbonate with vigorous mechanical stirring. Subsequently, 143 g. (1 mole) of 1-naphthylamine and 1 g. of copper powder were added, and the mixture was boiled under reflux for 8 hr. The mixture was diluted with 8 l. of water, adjusted to *p*H 11 with sodium hydroxide solution, treated with decolorizing charcoal and filtered. The filtrate was made acid with glacial acetic acid and the precipitate collected by filtration and crystallized from an ethanol–acetone mixture; yield 115 g. (39%), m.p. 238–240° (lit.[7] reports m.p. 236–237.5°).

N-1-Naphthylanthraniloyl Chloride.—To a suspension of 26.3 g. (0.1 mole) of N-1-naphthylanthranilic acid in 500 ml. of dry petroleum ether (b.p. 80–110°) was added 22.9 g. (0.11 mole) of phosphorus pentachloride, and the mixture was warmed gradually to boiling. The mixture was boiled under reflux for 20 minutes, filtered through a sintered glass funnel and the filtrate chilled. The precipitate which separated was collected by filtration and crystallized from petroleum ether (b.p. 80–110°) (decolorizing charcoal) to give 17.8 g. (63%) of colorless crystals, m.p. 112–114°, becoming turbid at 118°.

Anal. Calcd. for $C_{17}H_{12}ClNO$: C, 72.47; H, 4.29; N, 4.97. Found: C, 72.47; H, 4.32; N, 5.10.

7-Chlorobenz[c]acridines.—Utilizing the procedures described by Bachman and Picha,[7] 7-chlorobenz[c]acridine

(23) (a) L. Pfannemueller, *Lancet*, **1**, 934 (1956), and references cited therein; (b) Farbenfabriken Bayer, British Patent 692,460, June 3, 1953.

(24) M. J. Dean, E. N. Morgan and D. J. Tivey, *J. Chem. Soc.*, in press.

(25) Melting points are uncorrected.

(26) P. L. Salzberg and J. V. Supniewski, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 119.

(27) J. C. Sheehan and W. A. Bolhofer, THIS JOURNAL, **72**, 2786 (1950).

was prepared from N-1-naphthylanthranilic acid and phosphorus oxychloride in 73% yield, m.p. 144–145° (lit.[7] reports m.p. 144–145°). 7,10-Dichlorobenz[c]acridine was prepared from 4-chloro-N-(1-naphthyl)-anthranilic acid and phosphorus oxychloride in 85% yield, m.p. 200–201° (lit.[7] reports m.p. 201–202°).

7-Phenoxybenz[c]acridine Hydrochloride.—A mixture of 10 g. (0.038 mole) of 7-chlorobenz[c]acridine and 40 g. of phenol was stirred and heated on a steam-bath for 2 hr., allowed to cool and dissolved in 500 ml. of acetone. The product separated as gold-colored crystals which were collected by filtration, washed with acetone and dried; yield 12.9 g. (95%), m.p. 194–195°. This material was dissolved in warm methanol and reprecipitated with ether to give 8.9 g. of a yellow product which softened at 190°, then resolidified and remained unmelted at 300°.

Anal. Calcd. for $C_{23}H_{15}NO\cdot HCl$: C, 77.20; H, 4.51; N, 3.92. Found: C, 77.21; H, 4.89; N, 4.29.

General Methods for Preparing 7-Aminobenz[c]acridines (Tables I–II). Method I.—A mixture of 24 to 80 g. of phenol and 0.03 to 0.4 mole of the 7-chlorobenz[c]acridine was stirred and heated at 100° for 15 minutes; 0.035 to 0.425 mole of the appropriate amine was added, and stirring and heating was continued for 2 to 3 hr. Upon cooling, the mixture was poured into an excess of cold sodium or potassium hydroxide solution. The base was extracted with ether or chloroform, the extracts washed with water and dried over anhydrous potassium carbonate. Free bases were prepared by evaporating the dry ether or chloroform solutions and crystallizing the residue from the appropriate solvents. Salts were prepared by adding an ether solution of the desired acid to the dry ether or chloroform solution and recrystallizing the crude salt from the solvent indicated.

Method II.—A mixture of 0.05 to 0.19 mole of the 7-chlorobenz[c]acridine and 75 to 150 ml. of the appropriate amine was stirred and heated at 100 to 140° for 4 to 24 hr. The reaction was protected from moisture by a calcium chloride tube. After refrigeration, the product was collected by filtration, the precipitate washed with cold absolute ethanol or acetone and dried for 18 hr. *in vacuo* at room temperature. Recrystallization from the appropriate solvent yielded the pure base.

Method III.—A mixture of 0.068 mole of the 7-chlorobenz[c]acridine and 50 ml. of the appropriate amine was stirred and heated at 130° for 3 hr. The reaction mixture was cooled, poured into 3 l. of water and the base extracted with ether. The combined ether extracts were washed thoroughly with water and dried over anhydrous potassium carbonate. The drying agent was collected by filtration, and the dry ether extracts were treated with anhydrous hydrogen chloride. The crude hydrochloride was collected by filtration, crystallized from dilute hydrochloric acid and washed with acetone. Recrystallization from ethanolic hydrogen chloride yielded the pure hydrochlorides.

Method IV.—To a solution of 0.045 to 0.063 mole of N-1-naphthylanthraniloyl chloride in 100 to 250 ml. of dry benzene was added a solution of 0.049 to 0.068 mole of the appropriate diamine in 100 ml. of dry benzene, and the mixture was stirred and boiled under reflux for 30 minutes. Subsequently, four equivalents (16.4 to 23.1 ml.) of phosphorus oxychloride was added dropwise and the mixture stirred and boiled under reflux for 7 hr. Upon cooling, the benzene was decanted, the residue was dissolved in water and the aqueous solution of the hydrochloride treated with decolorizing charcoal and filtered. The filtrate was made strongly alkaline with ammonium hydroxide and the base extracted with chloroform or ether. The chloroform or ether extracts were washed with water and dried over anhydrous potassium carbonate. The drying agent was collected by filtration, the solvents removed *in vacuo* on the steam-bath and the residue dissolved in absolute ethanol and treated with ethanolic hydrogen chloride. Acetone was added to the ethanol solution to precipitate the crude hydrochloride, which was collected by filtration and washed with acetone. The yellow salts were recrystallized from the indicated solvents, dried *in vacuo* at room temperature for 20 hr. and allowed to stabilize in the air.

Method V.—When aqueous solutions of 0.98 g. (0.002 mole) of 7-(5-piperidinopentylamino)-benz[c]acridine dihydrochloride monohydrate and 0.86 g. (0.002 mole) of 4,4′-methylene-bis-(3-hydroxy-2-naphthoic acid), disodium salt were mixed a very insoluble salt precipitated which slowly solidified. The salt was collected by filtration and washed thoroughly with water.

Method VI.—A mixture of 0.042 to 0.2 mole of the appropriate amine, 40 to 70 g. of phenol and 0.038 to 0.12 mole of the 7-chlorobenz[c]acridine was stirred and heated at 100–140° for 2 hr., cooled and poured with stirring into a mixture of 125 to 500 ml. of acetone and 5 to 25 ml. of concentrated hydrochloric acid. Upon standing for 20 to 48 hr., a yellow precipitate formed, which was collected by filtration, washed with acetone and dried. Recrystallization (decolorizing charcoal) from the appropriate solvent yielded the desired amine hydrochloride.

Method VII.—A mixture of 0.042 to 0.2 mole of the appropriate amine, 40 to 80 g. of phenol and 0.038 to 0.15 mole of the 7-chlorobenz[c]acridine was stirred and heated at 100–155° for 2 to 3 hr. Upon cooling, the mixture was stirred into a solution of 10 to 20 ml. of concentrated hydrochloric acid in 150 to 300 ml. of acetone. No precipitate formed. The mixture was evaporated to a small volume and triturated twice with 500-ml. portions of dry ether. The residue was made strongly alkaline with ammonium hydroxide or potassium hydroxide solution, the base extracted with ether and the combined ether extracts washed successively with 10% sodium hydroxide and water. The free bases were prepared as follows: the ether solution was filtered, evaporated to an oily residue and the residue dissolved in boiling petroleum ether (b.p. 80–110°) (charcoal). Dilution with petroleum ether (b.p. 30–60°) yielded the crude 7-aminobenz[c]acridines which were subsequently recrystallized from the appropriate solvent. The salts were prepared by adding the desired acid to a dry ether solution of the base and recrystallizing the precipitated salt from the indicated solvent.

7-(5-Piperidinopentylamino)-benz[c]acridine Salt with Two Formula Weights of 8-Hydroxy-7-iodo-5-quinolinesulfonic Acid.—To a filtered solution of 9.4 g. (0.02 mole) of 7-(5-piperidinopentylamino)-benz[c]acridine dihydrochloride in 100 ml. of water was added slowly with vigorous stirring a warm filtered solution of 15.0 g. (0.0415 mole) of 8-hydroxy-7-iodo-5-quinolinesulfonic acid and 1.7 g. (0.042 mole) of sodium hydroxide in 500 ml. of water. The orange-red oil which deposited solidified upon cooling and scratching and was collected by filtration. The solid was pulverized in ice-water, collected by filtration, washed thoroughly with water and dried *in vacuo* at 40° for 24 hr. Crystallization from an ethanol–acetone mixture gave 8.5 g. (40%) of the mustard colored salt, softening at 113°, m.p. 176–178° dec.

Anal. Calcd. for $C_{27}H_{31}N_3\cdot 2C_9H_6INO_4S$: N, 6.37. Found: N, 6.33.

7-(5-Piperidinopentylamino)-benz[c]acridine Salt with Two Formula Weights of Penicillin G.—Cold filtered solutions of 20.0 g. (0.041 mole) of 7-(5-piperidinopentylamino)-benz[c]acridine dihydrochloride monohydrate in 50 ml. of water and 31.0 g. (0.083 mole) of potassium benzyl penicillin in 200 ml. of water were mixed in an ice-bath, and the yellow oil which separated was cooled and scratched in ice water until it solidified. The salt was collected by filtration, washed with ice-water and dried *in vacuo* at 40° for 24 hr. Purification by dissolving the salt in absolute ethanol and reprecipitating with anhydrous ether gave 22 g. (49%) of a hygroscopic yellow salt, m.p. indefinite from 85–105° dec. For analysis, the salt was dried *in vacuo* at 45° for 24 hr.

Anal. Calcd. for $C_{27}H_{31}N_3\cdot 2C_{16}H_{18}N_2O_4S$: C, 66.45; H, 6.33; N, 9.20; S, 6.01. Found: C, 66.33; H, 6.46; N, 9.21; S, 6.16; 6.12.

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