Ether, Dioxane, Methanol and Acetic Acid.—When solutions of I in the preceding solvents were refluxed for 3 hours and the solvents evaporated, there remained orange-colored oils from which only PCP was isolated; PCP was obtained in yields of 57, 64 and 68%, respectively.

CHINA LAKE, CALIF.

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

Synthetic Amebicides. III. 7-(3-Octylaminopropylamino)-benz[c]acridine (PAA-2056) and Related 7-(Alkyl- and Aralkylaminoalkylamino)-benz[c]acridines[1,2]

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

RECEIVED JULY 26, 1957

A series of new 7-(alkyl- and aralkylaminoalkylamino)-benz[c]acridines have been prepared by the condensation of a 7-chlorobenz[c]acridine with the appropriate N-(alkyl or aralkyl)-diaminoalkane, by the action of an alkylamine on a 7-haloalkylaminobenz[c]acridine, or by ring-closure of an N-(alkylaminoalkyl)-2-(1-naphthylamino)-benzamide with phosphorus oxychloride. Acylation of 7-(3-hexyl- and heptylaminopropylamino)-benz[c]acridines with acetic anhydride gave the corresponding N-[3-(benz[c]acridin-7-ylamino)-propyl]-N-hexyl- and heptylacetamides. The 7-(alkyl and aralkylaminoalkylamino)-benz[c]acridines were highly active when tested against *Endamoeba histolytica in vitro*, acute intestinal amebiasis in rats, amebic colitis in dogs and amebic hepatitis in hamsters.

In a previous communication,[2] we reported the preparation of a number of 7-dialkylaminoalkylaminobenz[c]acridines which possessed good antiamebic activity against *Endamoeba histolytica in vitro*, against intestinal amebiasis in rats and against amebic hepatitis in hamsters. During the course of continuing efforts in these laboratories to develop new antiamebic drugs, we have synthesized a group of 7-(alkyl and aralkylaminoalkylamino)-benz[c]acridines (V). In structure V, X represents hydrogen or chlorine, Y a divalent alkyl group and R an alkyl or aralkyl radical.

TABLE I

N-(ALKYL- AND ARALKYL)-1,3-DIAMINOPROPANES, $H_2N(CH_2)_3NHR$

R	B.p., °C.	Mm.	$n^{25}D$	Yield, %	Procedure	Formula	Nitrogen, % Calcd.	Found
Bases[a]								
$-(CH_2)_6CH_3$	110–120	7.5–8.0	1.4512	45	I	$C_{10}H_{24}N_2$	16.26	16.38
$-CHC_2H_5(CH_2)_3CH_3$	64–68	0.9	1.4487	54	II	$C_{10}H_{24}N_2$	16.26	16.47
$-(CH_2)_2C_6H_5$	110–115	1.5	1.5268	34	III	$C_{11}H_{18}N_2$	15.72	15.87
$-CH[(CH_2)_2CH_3](CH_2)_3CH_3$	72–77	0.7	1.4488	22	III	$C_{11}H_{26}N_2$	15.04	15.01
$-CH_2CHC_2H_5(CH_2)_3CH_3$	75–80	0.6	1.4518	73	III	$C_{11}H_{26}N_2$	15.04	15.19
$-CHCH_3(CH_2)_5CH_3$	90–95	2.0	1.4506	51	II	$C_{11}H_{26}N_2$	15.04	15.51[c]
$-(CH_2)_3C_6H_5$	120–126	1.5	1.5213	57	III	$C_{12}N_{20}N_2$[d]	14.57	13.96

Dihydrochlorides[b]

R	M.p., °C.	Yield, %	Procedure	Formula	Nitrogen, % Calcd.	Found
$-(CH_2)_8CH_3$	290–292 dec.[e]	79[f]	II	$C_{12}H_{28}N_2 \cdot 2HCl$	10.25	9.58[g]
$-(CH_2)_9CH_3$	293–295 dec.[e]	86[f]	II	$C_{13}H_{30}N_2 \cdot 2HCl$	9.75	9.38[h]
$-(CH_2)_{15}CH_3$	275–278[e]	70[f]	II	$C_{19}H_{42}N_2 \cdot 2HCl$	7.54	7.35

[a] The bases were obtained as colorless liquids. [b] The dihydrochlorides were isolated as colorless solids. [c] *Anal.* Calcd.: C, 70.90; H, 14.07. Found: C, 70.86; H, 14.13. [d] Dihydrochloride crystallized from aqueous 2-propanol, m.p. 272–273°. *Anal.* Calcd.: N, 10.56. Found: N, 10.80. [e] Crystallized from ethanol. [f] Crude. [g] *Anal.* Calcd.: C, 52.73; H, 11.07. Found: C, 53.01; H, 10.81. [h] *Anal.* Calcd.: C, 54.34; H, 11.23. Found: C, 54.40; H, 11.29.

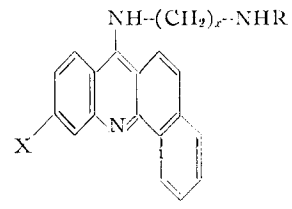
The synthesis of the 7-(alkyl- and aralkylaminoalkylamino)-benz[c]acridines (Table II) was achieved by three routes as illustrated by formulas I through VI. The method most extensively employed was the condensation of a 7-chlorobenz[c]acridine (II) with the appropriate N-(alkyl or aralkyl)-diaminoalkane in phenol. The 7-chlorobenz[c]acridines were prepared by ring-closure of an N-1-naphthylanthranilic acid (I) with phosphorus oxychloride as described previously.[2] Alternatively, the N-1-naphthylanthranilic acid was converted to the N-1-naphthanthraniloyl chloride by the action of phosphorus pentachloride in boiling benzene. Treatment of an N-alkyldiaminoalkane with the acid chloride yielded the corresponding amide IV which was not isolated but was ring-closed *in situ* with phosphorus oxychloride to the desired aminobenz[c]acridine. A third route involved the condensation of a 7-chlorobenz[c]-acridine with an aminoalkanol to give a benz[c]-acridin-7-ylaminoalkanol (III),[2] which upon treatment with thionyl chloride or a constant boiling hydrobromic acid–sulfuric acid mixture yielded the 7-haloalkylaminobenz[c]acridine (VI, where Hal represents Cl or Br). The condensation of a 7-haloalkylaminobenz[c]acridine with an alkyl amine in 1-pentanol at 100° gave the desired 7-alkylaminoalkylaminobenz[c]acridine (V). However, in one

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

(2) For previous paper in this series see E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan and F. H. Tendick, THIS JOURNAL, 79, 4699 (1957).

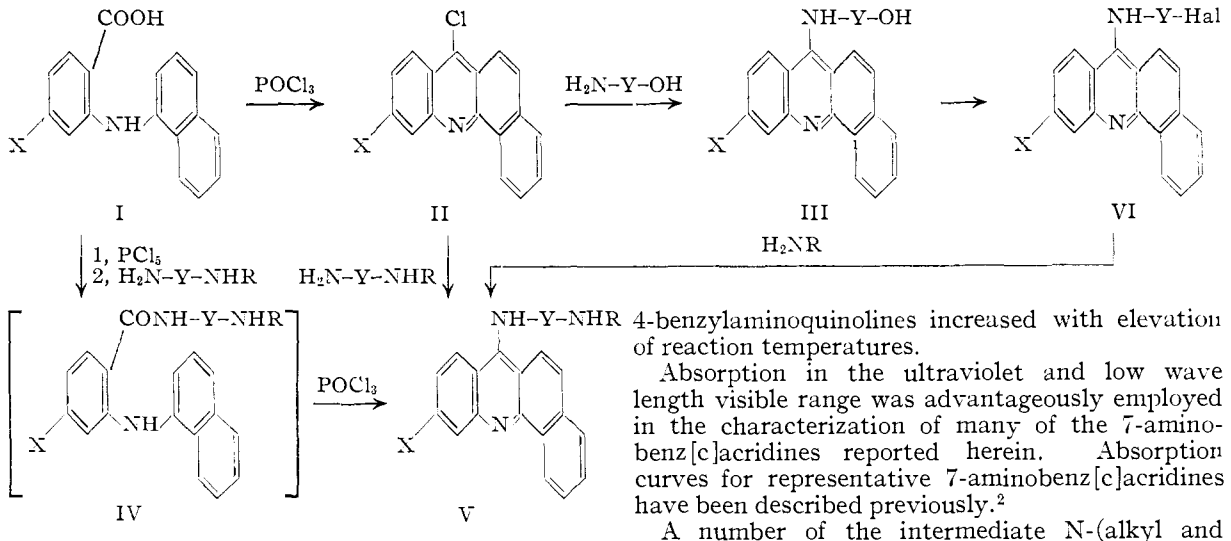
TABLE II

7 (ALKYL- AND ARALKYLAMINOALKYLAMINO)-BENZ[c]ACRIDINES[a]

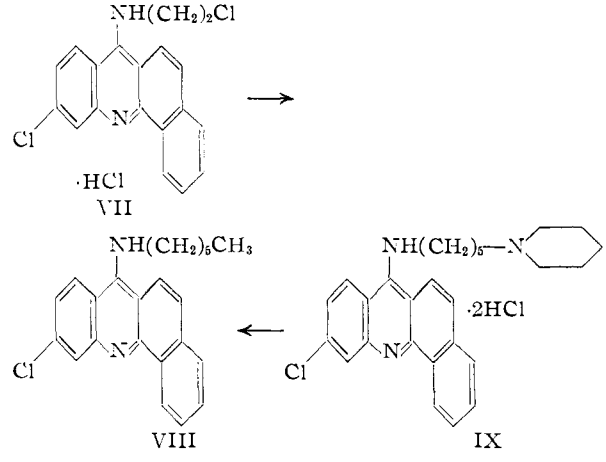


X	x	R	M.p., °C.	Yield purified, %	Procedure	Purifcn. solvent[c]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Water, % Calcd.	Water, % Found[c]
H	3	$-C_2H_5$	230 (eff.)	90	II	E	$C_{22}H_{23}N_3 \cdot 2HCl \cdot 1^1/_4H_2O$	62.19	62.27	6.52	6.77	9.89	9.75	5.30	5.85
H	3	$-CH(CH_3)_2$	261–264	68	I	A	$C_{23}H_{25}N_3 \cdot 2HCl \cdot H_2O$	63.59	63.18	6.73	6.74	9.67	9.55	4.15	4.53
H	3	$-(CH_2)_3CH_3$	277–278	63	I	B	$C_{24}H_{27}N_3 \cdot 2HCl \cdot {}^1/_4H_2O$	66.28	66.54	6.84	7.04	9.66	9.48	1.04	0.95
H	3	$-(CH_2)_5CH_3$	283–284	79	I	C	$C_{26}H_{31}N_3 \cdot 2HCl \cdot H_2O$	65.53	65.42	7.40	7.40	8.82	8.31	3.78	4.46
Cl	3	$-(CH_2)_5CH_3$	260–265	57	IV	E	$C_{26}H_{30}ClN_3 \cdot 2HCl \cdot 2^3/_4H_2O$	57.57	57.42	6.96	7.02	7.74	8.01	9.13	9.05
H	3	$-(CH_2)_6CH_3$	281–282	54	I	D	$C_{27}H_{33}N_3 \cdot 2HCl \cdot 2^1/_2H_2O$	62.66	63.05	7.79	7.82	8.12	7.74	8.70	8.57
H	3	$-CHC_2H_5(CH_2)_3CH_3$	169–171	56	I	D	$C_{27}H_{33}N_3 \cdot 2HCl \cdot 2H_2O$	63.77	63.48	7.73	7.93	8.26	8.51	7.09	8.19
H	3	$-(CH_2)_2C_6H_5$	273–275	74	I	B	$C_{28}H_{27}N_3 \cdot 2HCl \cdot H_2O$	67.74	67.65	6.30	6.33	8.46	8.25	3.63	2.24
H	3	$-(CH_2)_2CH(CH_2)_5$	272–274	45	I	B,D	$C_{28}H_{33}N_3 \cdot 2HCl \cdot 2^1/_2H_2O$	63.51	63.40	7.61	7.65	7.94	7.97	8.51	9.82
H	3	$-CH[(CH_2)_2CH_3](CH_2)_3CH_3$	165–171	44	I	D	$C_{28}H_{35}N_3 \cdot 2HCl \cdot 2H_2O$	64.35	64.49	7.91	7.71	8.04	8.48	6.90	7.42
H	3	$-CH_2CHC_2H_5(CH_2)_3CH_3$	169–170, 235–240	51	I	D	$C_{28}H_{35}N_3 \cdot 2HCl \cdot 2^1/_2H_2O$	63.26	63.38	7.97	8.03	7.90	7.68	8.47	8.30
H	3	$-CHCH_3(CH_2)_5CH_3$	188–190	40	I	B	$C_{28}H_{35}N_3 \cdot 2HCl \cdot 2^1/_2H_2O$	63.26	62.87	7.97	7.98	7.90	8.22	8.47	8.42
H	3	$-(CH_2)_7CH_3$	254–255	65	I	D	$C_{28}H_{35}N_3 \cdot 2HCl \cdot H_2O$	66.65	66.65	7.79	7.92	8.33	8.01	3.58	3.80
				44	III										
Cl	3	$-(CH_2)_7CH_3$	280	73	II	E	$C_{28}H_{34}ClN_3 \cdot 2HCl \cdot 2H_2O$	60.37	60.45	7.24	7.30	7.54	7.41	6.47	6.51
H	3	$-(CH_2)_3C_6H_5$	260–262	44	I	D	$C_{29}H_{29}N_3 \cdot 2HCl \cdot 2H_2O$	65.90	65.73	6.68	6.73	7.95	8.14	6.82	7.21
H	3	$-(CH_2)_8CH_3$	259–261	60	I	B	$C_{29}H_{37}N_3 \cdot 2HCl \cdot 2H_2O$	64.91	65.33	8.08	8.17	7.83	7.80	6.72	6.48
H	5	$-(CH_2)_7CH_3$	225	56	I	B	$C_{30}H_{39}N_3 \cdot 2HCl \cdot 1^1/_2H_2O$	66.53	66.19	8.19	8.57	7.76	7.56	4.99	5.02
H	3	$-(CH_2)_9CH_3$	264–266	58	I	B	$C_{30}H_{39}N_3 \cdot 2HCl \cdot 2^1/_2H_2O$	64.38	64.53	8.28	8.76	7.51	7.82	8.05	7.65
H	3	$-(CH_2)_{10}CH_3$	260–262	66	I	B	$C_{31}H_{41}N_3 \cdot 2HCl \cdot 3H_2O$	63.90	64.15	8.48	8.86	7.21	7.19		
H	3	$-(CH_2)_{11}CH_3$	251–254	63	I	B	$C_{32}H_{43}N_3 \cdot 2HCl \cdot 2^1/_2H_2O$	65.40	65.43	8.58	9.25	7.15	7.00	7.66	7.36
H	3	$-(CH_2)_{15}CH_3$	220–222	72	I	B	$C_{36}H_{51}N_3 \cdot 2HCl \cdot 2H_2O$	68.12	68.05	9.05	9.25	6.62	6.41	5.68	5.80
H	3	$-C_{20}H_{29}$[b]	239–241	56	I	B	$C_{40}H_{47}N_3 \cdot 2HCl \cdot 2H_2O$	70.78	70.63	7.87	8.14	6.19	6.51	5.31	5.20[d]

[a] All compounds were yellow or yellow-green solids. Samples for analysis were dried at 40 to 100° *in vacuo* over P_2O_5, then allowed to stabilize as hydrates by exposure to the air for several hours. [b] $C_{20}H_{29}$ represents the 1,2,3,4,4A,9,10,10A-octahydro-7-isopropyl-1,4A-dimethyl-1-phenanthrylmethyl group. [c] Karl Fischer method. [d] Volatile loss at 100°. [e] A, ethanol–ethyl acetate; B, methanol–ethyl acetate; C, water containing a little hydrochloric acid; D, water; E, ethanol–acetone.



case in which a large excess of the boiling amine was employed as solvent, a side reaction involving displacement of the 7-haloalkylamino group occurred with the formation of the 7-alkylaminobenz[c]acridine. Thus, when 10-chloro-7-(2-chloroethylamino)-benz[c]acridine hydrochloride (VII) was boiled under reflux for four hours with a large excess of hexylamine, 10-chloro-7-hexylaminobenz-[c]acridine (VIII) was isolated in 77% yield. Under similar conditions, VIII was obtained in 82% yield from 10-chloro-7-[5-(1-piperidinyl)-pentylamino]-benz[c]acridine dihydrochloride (IX)[2] and hexylamine; the melting point of a mixture of either sample with an authentic sample of VIII

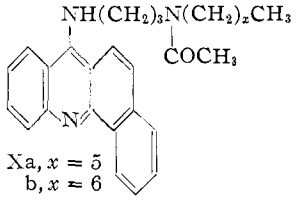


prepared from 7,10-dichlorobenz[c]acridine[2] and hexylamine was not depressed. An analogous displacement reaction involving the quinoline nucleus has been reported by Fulton and co-workers[3]; 4-methylaminoquinaldine and 4-(2-methylaminoethylamino)-quinaldine were isolated from the interaction of methylamine and 4-(2-chloroethylamino)-quinaldine, while 2-anilino-4-benzylaminoquinoline together with 2-anilino-4-(2-benzylaminoethylamino)-quinoline were obtained from benzylamine and 2-anilino-4-(2-chloroethylamino)-quinoline. The proportion of the 4-methyl- and 4-benzylaminoquinolines increased with elevation of reaction temperatures.

Absorption in the ultraviolet and low wave length visible range was advantageously employed in the characterization of many of the 7-aminobenz[c]acridines reported herein. Absorption curves for representative 7-aminobenz[c]acridines have been described previously.[2]

A number of the intermediate N-(alkyl and aralkyl)-diaminoalkanes (Table I) which were prepared have not been reported previously. A majority of these new diamines were synthesized by alkylation of a diaminoalkane with an alkyl bromide or chloride. Where this reaction yielded a solid crude product, it was expedient to convert the crude material to the dihydrochloride for purification and characterization. N-Heptyl-1,3-diaminopropane was obtained by cyanoethylation of heptylamine followed by catalytic hydrogenation of the intermediate 3-heptylaminopropionitrile according to standard procedures.[4]

Two N-acetyl derivatives in the 7-alkylaminoalkylaminobenz[c]acridine series were prepared in order to study the influence of acetylation on antiamebic activity. Acylation of 7-(3-hexyl and heptylaminopropylamino)-benz[c]acridines with acetic anhydride gave the corresponding N-[3-(benz[c]acridin - 7 - ylamino) - propyl] - N - hexyl- and heptylacetamides (Xa and b).



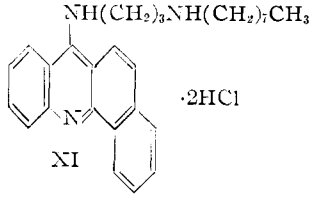
When an aqueous solution of two molar equivalents of potassium penicillin G was added in one portion to a methanol solution of 7-(3-octylaminopropylamino)-benz[c]acridine dihydrochloride, a monopenicillin salt was obtained. However, when more dilute solutions were used and the benzacridine solution was added dropwise to the penicillin solution, a dipenicillin salt separated. Identification of the salts was based upon elementary analysis.

The 7-(alkyl- and aralkylaminoalkylamino)-benz[c]acridines and N-[3-(benz[c]acridin-7-ylamino)-propyl]-N-hexyl and heptylacetamides described in the present communication were tested by Thompson and co-workers of these laboratories

(3) J. D. Fulton, L. P. Joyner, H. King, J. M. Osbond and J. Wright, *Proc. Roy. Soc., Ser. B*, **137**, 339 (1950).

(4) D. S. Tarbell, N. Shakespeare, C. J. Claus and J. F. Bunnett, THIS JOURNAL, **68**, 1218 (1946).

against *Endamoeba histolytica in vitro*,[5] and when indicated, against acute intestinal amebiasis in rats,[6] amebic colitis in dogs[7] and amebic hepatitis in hamsters.[8] Although details of these test results will be published in a separate communication,[9] it might be mentioned here that 7-(3-octylaminopropylamino)-benz[c]acridine, dihydrochloride (XI) (PAA-2056) was one of the most promising compounds tested. This compound was active against



XI

intestinal amebiasis in rats and dogs and against amebic hepatitis in hamsters.[10] The salts of 7-(3-octylaminopropylamino)-benz[c]acridine with 8-hydroxy-7-iodo-5-quinolinesulfonic acid and benzyl penicillin were likewise observed to have particularly interesting antiamebic properties. N-[3-(Benz[c]acridin-7-ylamino)-propyl]-N-hexyl and heptylacetamide possessed only slight antiamebic activity *in vitro* and in rats.

Acknowledgment.—We thank Dr. Loren M. Long and Dr. George Rieveschl, Jr., for encouragement in this investigation, Dr. Paul E. Thompson, Miss Anita Bayles, Mr. D. A. McCarthy and Mr. J. W. Reinertson for the biological testing, and Miss Gladys Z. Manougian and Mrs. Doris R. Thomas for synthesizing several of the compounds described herein. The authors also are indebted to Mr. Charles E. Childs and associates for the microanalyses, and to Dr. J. M. Vandenbelt and associates for determination and interpretation of the infrared and ultraviolet absorption spectra.

Experimental[11]

Methods for Preparing N-(Alkyl- and Aralkyl)-1,3-diaminopropanes (Table I). Method I.—The following procedure is illustrative of the method involving cyanoethylation of an alkylamine followed by catalytic hydrogenation of the intermediate alkylaminopropionitrile:

A procedure analogous to that employed by Tarbell, *et al.*,[4] for the preparation of the butyl homolog was used; 32.9 ml. (0.50 mole) of acrylonitrile was added dropwise with stirring over a period of 80 minutes to 111 ml. (0.75 mole) of heptylamine, maintaining the temperature below 30°. The solution was allowed to stir at room temperature for 5 hr., heated on a steam-bath for 1.5 hr. and distilled *in vacuo*. 3-Heptylaminopropionitrile was obtained as a colorless liquid, b.p. 95–98° (1 mm.), $n^{25}D$ 1.4440, yield 78.5 g. (93%).

Anal. Calcd. for $C_{10}H_{20}N_2$: N, 16.65. Found: N, 16.83.

Subsequently, a solution of 75 g. (0.445 mole) of 3-heptylaminopropionitrile in 200 ml. of ethanol saturated with ammonia was hydrogenated over Raney nickel (W-4) at 1500 p.s.i.g. and 147° initial pressure and temperature. The mixture was filtered, the volatile materials were removed and the residue distilled *in vacuo* through a six-inch Vigreux column.

Method II.—The following procedure illustrates the general method employed for the alkylation of 1,3-diaminopropane with an alkyl bromide:

1,3-Diaminopropane (100 ml., 1.20 moles) was stirred and heated to 100°. 3-Bromoheptane (53.5 g., 0.30 mole) was then added dropwise over a period of 30 minutes, the mixture was boiled gently under reflux for 3 hr. and stirred at room temperature for 18 hr. A solution of 15 g. (0.38 mole) of sodium hydroxide in 25 ml. of water was added, the mixture was extracted with several portions of ether and the combined ether extracts were dried over anhydrous potassium carbonate. The ether was removed, and the residue distilled *in vacuo* through a Vigreux column.

Method III.—The following procedure is typical for the alkylation of a diaminoalkane with an alkyl chloride:

Utilizing the above procedure, 50 g. (0.49 mole) of 1,5-diaminopentane and 20.5 ml. (0.12 mole) of octyl chloride gave 19 g. (74%) of crude semi-solid product. A solution of this crude diamine in 2-propanol was treated with a 2-propanol–hydrogen chloride solution to give the crude N-octyl-1,5-diaminopentane dihydrochloride. Crystallization from 2-propanol gave the pure salt as colorless crystals, m.p. 295° dec.

Anal. Calcd. for $C_{13}H_{30}N_2 \cdot 2HCl$: N, 9.75. Found: N, 9.61.

Methods for Preparing 7-(Alkyl- and Aralkylaminoalkylamino)-benz[c]acridines (Table II). Method I.—A mixture of 0.042 to 0.200 mole of the appropriate amine, 40 to 70 g. of phenol and 0.038 to 0.120 mole of the 7-chlorobenz[c]acridine[2] 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 II.—A mixture of 0.079 to 0.358 mole of the 7-chlorobenz[c]acridine, 0.075 to 0.300 mole of the appropriate amine and 60 to 160 g. of phenol was stirred and heated on the steam-bath for 3 to 4 hr. The reaction was protected from moisture by a calcium chloride tube. The reaction mixture was cooled, and poured slowly with stirring into 2 to 4 l. of acetone containing an excess of ethanolic hydrogen chloride. The crude product was collected by filtration, washed with acetone and dried *in vacuo* at 60° for 18 hr. The hydrochloride was dissolved in water and the water solution extracted thoroughly with chloroform. The combined chloroform extracts were washed twice with dilute hydrochloric acid and the acid extracts combined with the original acid layer. The chloroform solution was discarded. The acid solution was filtered and made strongly alkaline with concentrated ammonium hydroxide. The base which separated was extracted with several portions of chloroform, and the combined chloroform extracts were washed thoroughly with dilute sodium hydroxide solution and water, treated with decolorizing charcoal and evaporated to an oil. The oily residue was dissolved in ethanol, treated with excess ethanolic hydrogen chloride and the mixture diluted with several volumes of acetone and chilled. The product was collected by filtration, washed with acetone and dried *in vacuo* at 60° for 18 hr. The hygroscopic sample was equilibrated in the air prior to analysis.

Method III.—A mixture of 1.8 g. (0.005 mole) of 7-(3-bromopropylamino)-benz[c]acridine, 1.3 g. (0.010 mole) of octylamine and 5 ml. of 1-pentanol was heated on the steam-bath for 16 hr. with mechanical stirring. The solvent and excess octylamine were removed *in vacuo*, 5 ml. of water was added and the mixture again concentrated *in vacuo*. The residue was made strongly alkaline with 10% sodium hydroxide solution and the base extracted with ether. The combined ether extracts were washed thoroughly with water, dried for 24 hr. over anhydrous potassium carbonate and the drying agent collected by filtration. Dry hydrogen chloride was bubbled into the dry ether solution, the yellow precipitate was collected by filtration and dried *in vacuo* at 40° for

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

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

(9) P. E. Thompson, unpublished results.

(10) P. E. Thompson, D. A. McCarthy, J. W. Reinertson, A. Bayles and H. Najarian, *Antibiotics and Chemotherapy*, **7**, in press.

(11) Melting points are uncorrected.

18 hr. Crystallization from water gave 1.1 g. (44%) of the desired salt, m.p. 255–257°. The melting point of a mixture with a sample prepared by method I was 253–256°.

Method IV.—A solution of 6 g. (0.019 mole) of 4-chloro-N-1-naphthanthraniloyl chloride in 100 ml. of dry thiophene-free benzene was added dropwise over a period of 45 minutes to a hot stirred solution of 6.3 g. (0.040 mole) of N-hexyl-1,3-diaminopropane in 100 ml. of dry thiophene-free benzene and the mixture stirred and boiled under reflux for 1 hr. Subsequently, 14 ml. (23.3 g., 0.152 mole) of phosphorus oxychloride in 20 ml. of dry thiophene-free benzene was added dropwise to the mixture over a period of 15 minutes and the resulting mixture stirred and boiled under reflux for an additional 11 hr. The cooled reaction mixture was poured slowly into ice-water and heated to evaporate most of the benzene. The aqueous suspension was made strongly alkaline with concentrated ammonium hydroxide and extracted with chloroform. The combined chloroform extracts were washed with four portions of water, filtered and the chloroform solution evaporated *in vacuo* to an amber oil. This residue was dissolved in ethanol, treated with excess ethanolic hydrogen chloride, diluted with several volumes of acetone and chilled. The yellow precipitate was collected by filtration, washed successively with acetone and ether and dried *in vacuo* at 60° for 18 hr. The product was exposed to the air for 18 hr. prior to analysis.

7-[3-(2,3-Dimethyl-3-piperidyl)-propylamino]-benz[c]-acridine.—A mixture of 7.4 g. (0.028 mole) of 7-chlorobenz-[c]acridine[2] and 25 g. of phenol was heated on the steam-bath for 15 minutes with shaking. To this mixture was added 5 g. (0.029 mole) of 3-(3-aminopropyl)-2,3-dimethylpiperidine[12] and the mixture was stirred and heated on the steam-bath for 3 hr. The cooled reaction mixture was poured into a solution of 10 ml. of concentrated hydrochloric acid in 300 ml. of acetone; the supernatant liquid was decanted from the red oil which separated. The oil was dissolved in water and poured slowly with vigorous stirring into an excess of 5% sodium hydroxide solution. The precipitated olive-green base was collected by filtration, dried *in vacuo*, pulverized and submitted for analysis; yield 6.0 g. (50%), m.p. 60–65°.

Anal. Calcd. for $C_{27}H_{31}N_3$: C, 81.57; H, 7.86; N, 10.57. Found: C, 81.43; H, 7.07; N, 10.83.

7-(3-Octylaminopropylamino)-benz[c]acridine, Salt with Two Formula Weights of 8-Hydroxy-7-iodo-5-quinolinesulfonic Acid.—A filtered solution of 15.1 g. (0.030 mole) of 7-(3-octylaminopropylamino)-benz[c]acridine dihydrochloride monohydrate in 1 l. of hot water was added with stirring to a filtered solution of 2.4 g. (0.060 mole) of sodium hydroxide and 22.1 g. (0.063 mole) of 8-hydroxy-7-iodo-5-quinolinesulfonic acid in 1 l. of hot water. The red oil which deposited solidified on cooling, was ground up with water, collected by filtration, washed with water and dried at room temperature *in vacuo* giving 30.0 g. (90%) of the salt as a red solid of indefinite melting point.

Anal. Calcd. for $C_{28}H_{35}N_3 \cdot 2C_9H_6INO_4S$: C, 49.51; H, 4.24; N, 6.28. Found: C, 49.14; H, 4.17; N, 6.19.

7-(3-Octylaminopropylamino)-benz[c]acridine, Salt with One Formula Weight of Penicillin G.—A solution of 14.5 g. (0.0390 mole) of potassium penicillin G in 100 ml. of water was added in one portion to a solution of 10.0 g. (0.0195 mole) of 7-(3-octylaminopropylamino)-benz[c]acridine dihydrochloride sesquihydrate in 40 ml. of methanol. A gold-colored gum deposited. The mixture was chilled, the supernatant liquid decanted and the gum washed with water by decantation and triturated with ether. The yellow solid obtained was collected rapidly by filtration, washed with ether and petroleum ether (b.p. 30–60°) and dried at room temperature *in vacuo*, giving 13.5 g. (87%) of a hydrated salt with indefinite melting point.

Anal. Calcd. for $C_{28}H_{35}N_3 \cdot C_{16}H_{18}N_2O_4S \cdot 2.5H_2O$: C, 66.64; H, 7.37; N, 8.83; S, 4.04. Found: C, 66.81, 66.93; H, 7.61, 7.54; N, 8.85; S, 4.18, 4.29.

7-(3-Octylaminopropylamino)-benz[c]acridine, Salt with Two Formula Weights of Penicillin G.—A chilled, filtered solution of 50.5 g. (0.10 mole) of 7-(3-octylaminopropylamino)-benz[c]acridine dihydrochloride monohydrate in 750 ml. of methanol was added dropwise to a chilled, filtered solution of 82.0 g. (0.22 mole) of potassium penicillin G in 1.5 l. of water. The yellow gum which separated was washed by decantation with water and then with ether, and obtained solid by grinding successively under benzene, ether and petroleum ether (b.p. 30–60°). The product was collected and dried at room temperature *in vacuo* giving 93 g. (84%) of a hydrated salt, m.p. 75° dec.

Anal. Calcd. for $C_{28}H_{35}N_3 \cdot 2C_{16}H_{18}N_2O_4S \cdot 1.5H_2O$: C, 64.95; H, 6.72; N, 8.84; S, 5.78. Found: C, 65.42, 65.05; H, 6.97, 6.82; N, 8.87, 8.70; S, 5.53, 5.70.

N-[3-(Benz[c]acridin-7-ylamino)-propyl)-N-hexylacetamide, Salt with One Formula Weight of 3-Hydroxy-2-naphthoic Acid.—A dry ether solution of 7-(3-hexylaminopropylamino)-benz[c]acridine, prepared from 5.0 g. (0.0105 mole) of the dihydrochloride monohydrate, was treated with 5 ml. (0.0500 mole) of acetic anhydride and kept at room temperature for 2.5 hr. Upon the addition of a solution of 2.0 g. (0.0106 mole) of 3-hydroxy-2-naphthoic acid in 50 ml. of dry ether, an oil separated which solidified on standing for 20 hr. The ether solution was decanted, the solid was triturated with ether, collected by filtration, pulverized under petroleum ether (b.p. 30–60°) and dried, giving 4.8 g. (74%) of the desired product as a yellow powder, m.p. 91–92°.

Anal. Calcd. for $C_{29}H_{33}N_3O \cdot C_{11}H_8O_3$: C, 76.07; H, 6.71; N, 6.82. Found: C, 75.92; H, 6.54; N, 6.72.

N-[3-(Benz[c]acridin-7-ylamino)-propyl]-N-heptylacetamide, Salt with One Formula Weight of 3-Hydroxy-2-naphthoic Acid.—This compound was prepared by the procedure described above for the hexyl homolog, starting from 5.0 g. (0.0102 mole) of 7-(3-heptylaminopropylamino)-benz-[c]acridine dihydrochloride monohydrate; yield 5.2 g. (81%) of yellow solid, m.p. 99–100°.

Anal. Calcd. for $C_{29}H_{35}N_3O \cdot C_{11}H_8O_3$: C, 76.28; H, 6.88; N, 6.67. Found: C, 76.68; H, 6.96; N, 7.19, 6.89.

7-(2-Chloroethylamino)-benz[c]acridine, Hydrochloride.—A mixture of 27 g. (0.089 mole) of 2-(benz[c]acridin-7-ylamino)-ethanol,[2] 100 ml. of thionyl chloride and 100 ml. of dry chloroform was stirred and heated on a steam-bath for 1.5 hr., then kept at room temperature for 18 hr. The yellow solid was collected by filtration, washed thoroughly with chloroform and petroleum ether (b.p. 30–60°) and dried *in vacuo* at 75° for 18 hr.; yield 28.6 g. (91%), m.p. >300°.

Anal. Calcd. for $C_{19}H_{15}ClN_2 \cdot HCl \cdot 0.5H_2O$: C, 64.78; H, 4.87; N, 7.95. Found: C, 64.89; H, 4.71; N, 8.10.

10-Chloro-7-(2-chloroethylamino)-benz[c]acridine, Hydrochloride.—A mixture of 26 g. (0.081 mole) of 2-(10-chlorobenz[c]acridin-7-ylamino)-ethanol[2] and 100 ml. of thionyl chloride was stirred and heated under reflux for 1 hr. The mixture was cooled, and the product collected by filtration and washed with water. Crystallization from ethanol yielded 20 g. (66%) of yellow crystals, m.p. 260–262°.

Anal. Calcd. for $C_{19}H_{14}Cl_2N_2 \cdot HCl$: N, 7.42. Found: N, 7.28.

7-(3-Chloropropylamino)-benz[c]acridine, Hydrochloride.—A mixture of 60.5 g. (0.2 mole) of 3-(benz[c]acridin-7-ylamino)-propanol[2] and 300 ml. of thionyl chloride was stirred and heated on the steam-bath for 1 hr. The excess thionyl chloride was removed *in vacuo*, the residue was triturated with ether, and the product crystallized from absolute ethanol; yield 63.5 g. (87%) of yellow crystals, m.p. 228–230°.

Anal. Calcd. for $C_{20}H_{17}ClN_2 \cdot HCl \cdot 0.5H_2O$: C, 65.58; H, 5.23; N, 7.65; Cl, 19.36. Found: C, 65.44; H, 5.31; N, 7.70; Cl, 19.39.

7-(3-Bromopropylamino)-benz[c]acridine.—A mixture of 82 g. (0.28 mole) of 3-(benz[c]acridin-7-ylamino)-propanol,[2] 90 ml. of redistilled colorless constant boiling hydrobromic acid (sp. gr. 1.48) and 30 ml. of sulfuric acid (sp. gr. 1.84) was boiled under gentle reflux for 1.5 hr. The mixture was quenched in ice-water and made basic with ammonium hydroxide. The resulting insoluble mass was induced to crystallize by scratching and the yellow crystalline product was collected by filtration, washed with water and dried *in vacuo* at 45°. Crystallization from methanol (decolorizing charcoal) gave yellow crystals, m.p. 200–202°.

Anal. Calcd. for $C_{20}H_{17}BrN_2 \cdot 0.5H_2O$: C, 64.17; H, 4.85; N, 7.49; Br, 21.35. Found: C, 63.81, 63.84; H, 4.90, 4.89; N, 7.24; Br, 21.80, 21.71.

(12) We are indebted to Dr. C. F. H. Allen of the Eastman Kodak Co. for making this diamine available to us.

10-Chloro-7-hexylaminobenz[c]acridine. A. From 10-Chloro-7-(2-chloroethylamino)-benz[c]acridine, Hydrochloride.—A mixture of 6.0 g. (0.016 mole) of 10-chloro-7-(2-chloroethylamino)-benz[c]acridine hydrochloride and 100 ml. of hexylamine was boiled under reflux for 4 hr. Upon cooling, the reaction mixture was poured into a large volume of ice-water and the precipitate collected by filtration and washed with water. Crystallization from ethanol yielded 4.5 g. (77%) of yellow crystals. For analysis, a sample was crystallized from isopropyl alcohol, m.p. 90–92°.

Anal. Calcd. for $C_{23}H_{25}ClN_2$: C, 76.12; H, 6.39; N, 7.72; Cl, 9.77. Found: C, 76.94; H, 6.58; N, 7.90; Cl, 9.91.

B. From 7,10-Dichlorobenz[c]acridine.—A mixture of 0.5 g. (0.0017 mole) of 7,10-dichlorobenz[c]acridine[2] and 100 ml. of hexylamine was boiled under reflux for 4 hr. The excess hexylamine was removed *in vacuo*, the residue was treated with 10% hydrochloric acid, the aqueous solution was decanted and the residue dissolved in absolute ethanol. The ethanol solution was made alkaline with ammonium hydroxide, and the precipitated base was collected by filtration, dried and crystallized from ethanol; yield 0.4 g. (66%), m.p. 90–92°; the melting point of a mixture with the product from A above showed no depression.

C. From 10-Chloro-7-[5-(1-piperidinyl)-pentylamino]-benz[c]acridine, Dihydrochloride.—A mixture of 2.0 g. (0.037 mole) of 10-chloro-7-[5-(1-piperidinyl)-pentylamino]-benz[c]acridine dihydrochloride dihydrate[2] and 100 ml. of hexylamine was boiled under reflux for 16 hr., cooled, and 75 ml. of hexylamine was removed *in vacuo*. The residue was poured with vigorous stirring into 500 ml. of water, the aqueous mixture was acidified with 10% hydrochloric acid, and the waxy precipitate which separated was collected by filtration, washed with water and air-dried. The crude product was dissolved in 95% ethanol, made alkaline with ammonium hydroxide and the base collected by filtration, dried and crystallized from ethanol. The base weighed 1.1 g. (82%), m.p. 90–92°; the melting point of a mixture with the product from A above showed no depression.

4-Chloro-N-1-naphthylanthraniloyl Chloride.—Phosphorus pentachloride (30.8 g., 0.148 mole) was added portionwise to a suspension of 40 g. (0.135 mole) of 4-chloro-N-(1-naphthyl)-anthranilic acid in 350 ml. of dry petroleum ether (b.p. 80–110°). As each portion was added, the mixture was warmed gently until the reaction subsided. The mixture was boiled under reflux for 40 minutes and the petroleum ether solution decanted from the heavy sediment which separated. The residue was boiled with petroleum ether (b.p. 80–110°) and the petroleum ether solutions were discarded. The residue was dissolved in boiling benzene and diluted with petroleum ether (b.p. 80–110°), whereupon a flocculent purple solid separated. This impurity was collected by filtration and discarded. The filtrate was chilled and the crude acid chloride collected by filtration. A second crop was obtained by concentration of the filtrate; crude yield 36 g. (84%). Crystallization from a benzene–petroleum ether (b.p. 80–110°) mixture (decolorizing charcoal) gave 35 g. (82%) of yellow needles, m.p. 145° dec.

Anal. Calcd. for $C_{17}H_{11}Cl_2NO$: C, 64.57; H, 3.51; N, 4.43. Found: C, 65.00; H, 3.75; N, 4.57.

DETROIT, MICHIGAN

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF COLUMBIA UNIVERSITY]

The Reaction of Acyl Peroxides with Phenols[1]

BY CHEVES WALLING AND RUSSELL B. HODGDON, JR.[2]

RECEIVED JULY 15, 1957

The reaction between benzoyl (and similar) peroxides and phenols follows second-order kinetics, first order in peroxide and in phenol. The reaction is accelerated by electron-supplying groups on the phenol and retarded by bulky *ortho*-substituents. Measurements with O-deuterated phenols give $k_H/k_D = 1.32 \pm 0.03$ in several systems. The reaction shows neither acid nor base catalysis, but the rate varies significantly with solvent, being slow in strongly hydrogen bonding media. Radical traps, polymerizable monomers and iodine, have no effect on reaction rate. It is concluded that the reaction is not a radical chain process, but probably involves a simple bimolecular "four-center" process without radical formation, and a possible reaction path is proposed.

In 1944 it was reported[3] that, while styrene undergoes an only slightly retarded thermal polymerization in phenolic solvents, the benzoyl peroxide initiated polymerization was essentially inhibited. At the same time, it was noted that benzoyl peroxide decomposed very rapidly in *m*-cresol solution, and both results were suggested as arising from either a fast non-radical reaction between peroxide and phenol, or a radical-forming process yielding radicals which were too rapidly consumed by reaction with each other or the phenol to initiate polymerization. In 1947, as part of their now-classic investigation of the induced decomposition of benzoyl peroxide, Bartlett and Nozaki[4] obtained more quantitative data on the decomposition rate in various phenols, noted that the reaction rate was first order in peroxide, and interpreted their results as the consequence of an induced radical chain process. Subsequently, the nature of the products formed on refluxing equimolecular quantities of phenols and benzoyl peroxide in chloroform solution have been studied by Cosgrove and Waters[5] who found that phenols with free *o*-positions give chiefly catechol monobenzoates (I), 2,6-dimethylphenol is converted to 3,3,3′3′-tetramethyldiphenoquinone (II) in high yield and 2,4,6-trimethylphenol gives chiefly 2,4,6-trimethyl-4-benzoyloxycyclohexa-2,5-dienone (III). In every case most of the benzoyl peroxide residues not attached to aromatic nuclei are recovered as benzoic acid. In their discussion, Cosgrove and Waters have interpreted their products as the results of radical coupling and disproportionation, without considering the possible consequences of induced decomposition. Subsequently Wesseley and Schinzel[6] have investigated the decomposition of acetyl peroxide in acetic acid in the presence of each of the three isomeric cresols, obtaining catechol monoacetates (together with lac-

(1) Taken from the dissertation of Russell B. Hodgdon, Jr., submitted in partial fulfillment of the requirements of the Ph.D. degree, 1957. Support of this work by a research contract with the Office of Ordnance Research, U. S. Army, is gratefully acknowledged.

(2) Texas Co. Fellow, 1955–1956.

(3) C. Walling, THIS JOURNAL, **66**, 1602 (1944).

(4) P. D. Bartlett and K. Nozaki, *ibid.*, **69**, 2299 (1947).

(5) S. L. Cosgrove and W. A. Waters, *J. Chem. Soc.*, 3189 (1949); *ibid.*, 388 (1951).

(6) F. Wesseley and M. Schinzel, *Monatsh.*, **84**, 969 (1953).