prepared as above, was added 250 ml. of acetic anhydride. The mixture was heated, with stirring, on a steam-bath for 1.25 hours and allowed to stand at room temperature overnight. The solution was filtered and concentrated to small volumes below 60° under reduced pressure. The addition of absolute ether precipitated a gum. On long standing the gum crystallized poorly. Acetone was added and after standing in the refrigerator 13.3 g. of a white solid was obtained; m.p. 135–142°. This was dissolved in hot methyl ethyl ketone, filtered after a small amount of the first precipitate had separated and cooled. A yield of 6.53 g. of white solid, m.p. 143–146°, was obtained; $[\alpha]^{23}D$ −8° (2% in H_2O).

Anal. Calcd. for $C_{21}H_{28}BrNO_6$: C, 53.63; H, 6.00; Br, 17.00. Found: C, 53.36; H, 6.11; Br, 17.19.

Scopoline Phenylcyclopentylacetate.—A mixture of 7.0 g. (0.032 mole) of scopoline nitrate and a solution of 4 g. of sodium hydroxide in 5 ml. of water was extracted with 50 ml. of benzene. The benzene solution of the scopoline free base was dried over potassium carbonate and distilled to about 12 ml. Then 10 ml. of dry pyridine and 7.85 g. (0.035 mole) of phenylcyclopentylacetyl chloride[18] were added. After standing overnight at room temperature dilute sodium hydroxide solution was added. The benzene layer was washed with water and dried over sodium sulfate. The solvent was removed and the product was distilled under reduced pressure giving 4.4 g. (40%) of oily free base, b.p. 189° (0.03 mm.), $n^{23}D$ 1.5372.

Anal. Calcd. for $C_{21}H_{27}NO_3$: C, 73.86; H, 7.97; N, 4.10. Found: C, 74.35; H, 8.06; N, 3.77.

Methobromide (No. 27).—To a cold solution of 2.0 g. (0.006 mole) of this free base in 50 ml. of benzene was added a large excess of cold methyl bromide. The flask was stoppered, clamped and allowed to stand at room temperature overnight. The white crystalline product was collected and dried; yield 2.2 g. (85%), m.p. 210–212°.

Anal. Calcd. for $C_{22}H_{30}BrNO_3$: C, 60.55; H, 6.93; Br, 18.31; N, 3.21. Found: C, 60.99; H, 7.12; Br, 18.00; N, 3.05.

(18) H. G. Kolloff, J. H. Hunter and R. B. Moffett, THIS JOURNAL, **72**, 1650 (1950).

KALAMAZOO, MICHIGAN

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, PARKE, DAVIS AND COMPANY]

Synthetic Amebicides. I. Heterocyclic 2,2-Dichloro-N-(2-hydroxyethyl)-N-substituted Acetamides[1]

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Various heterocyclic 2,2-dichloro-N-(2-hydroxyethyl)-N-substituted acetamides containing the 2-, 3- and 4-pyridyl, 4-quinolyl, 7-chloro-4-quinolyl, 6-methoxy-2-methyl-4-quinolyl, 6-chloro-2-methoxy-9-acridinyl and 7-benz[c]acridinyl nuclei have been prepared by dichloroacetylation of the corresponding heterocyclic N-(2-hydroxyethyl)-amines. When tested against *Endamoeba histolytica in vitro* and against experimentally induced intestinal amebiasis in rats, several of these compounds were found to possess high activity.

Recently, several publications have appeared in the literature regarding the antiamebic activity of haloacetamides,[2–5] with particular reference to 2,2-dichloro-N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-acetamide (I) and related compounds. Further, biological studies conducted in these laboratories indicate that antiamebic activity among haloacetamide derivatives is not confined to compounds of general type I, but is widespread among diverse chemical types.[6] Although compound I possesses good activity against spontaneous *Endamoeba criceti* infections in hamsters[2,5] and against experimentally induced *Endamoeba histolytica* infections in rats,[7] it is ineffective against *E. histolytica*-induced amebic hepatitis in hamsters and against amebic dysentery in dogs.[7] In view of the observed activity of amodiaquin (Camoquin[8]) (IIa), chloroquine (IIb) and quinacrine (III) against experimental amebic hepatitis[9] and against hepatic amebiasis in man, it was of interest to prepare certain related dihaloacetamide derivatives (Vb, VIa and VII) containing the 7-chloro-4-quinolyl and 6-chloro-2-methoxy-9-acridinyl nuclei. This work was also extended to include other quinoline derivatives (Va and VIb), as well as certain pyridine (IVa through c) and benz[c]acridine (VIIIa and b) analogs.

2,2-Dichloro-N-(7-chloro-4-quinolylmethyl)-N-(2-hydroxyethyl)-acetamide (Vb) was prepared by acylation of 2-(7-chloro-4-quinolylmethylamino)-ethanol[10] with dichloroacetyl chloride in dimethylformamide; the related 2,2-dichloro-N-(2-hydroxyethyl)-N-(4-quinolylmethyl)-acetamide (Va) and 2,2-dichloro-N-(2-hydroxyethyl)-N-(3- and 4-pyridylmethyl)-acetamides (IVb and c) (Table II) were synthesized by treating the appropriate 2-(pyridyl or quinolylmethylamino)-ethanol (Table I) with methyl dichloroacetate in ethylene dichloride. Although compounds Va and IVb and c were isolated by the latter procedure as glistening colorless crystals, the product believed to be the dichloroacetamide (IVa) derived from 2-(2-pyridylmethylamino)-ethanol could be obtained only as an amber-colored gum. Numerous attempts to crystallize IVa from a variety of organic solvents failed to yield a solid product, as did several variations in reaction conditions. However, the crude gum showed a characteristic amide absorption in the infrared at 6.00 μ, indicating that the desired dichloroacetamide probably had been formed.

The intermediate 2-(pyridyl or quinolylmethyl-

(1) Presented before the Division of Medicinal Chemistry at the 129th National A.C.S. Meeting, April, 1956, in Dallas, Texas.

(2) A. R. Surrey, THIS JOURNAL, **76**, 2214 (1954).

(3) A. R. Surrey and M. K. Rukwid, *ibid.*, **77**, 3798 (1955).

(4) A. R. Surrey, G. Y. Lesher and S. O. Winthrop, *ibid.*, **77**, 5406 (1955).

(5) E. W. Dennis and D. A. Berberian, *Antibiotics and Chemotherapy*, **4**, 554 (1954).

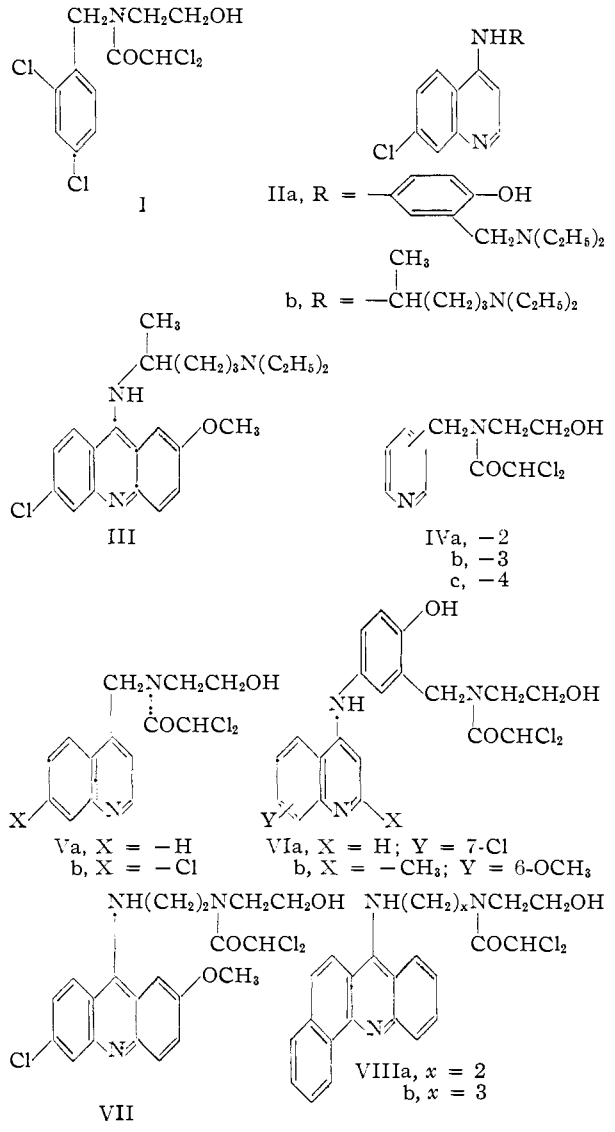
(6) P. E. Thompson and E. F. Elslager, unpublished results.

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

(8) Parke, Davis and Company trade name for 4-(7-chloro-4-quinolylamino)-α-diethylamino-o-cresol, dihydrochloride.

(9) For a description of test methods, see P. E. Thompson and J. W. Reinertson, *Am. J. Trop. Med.*, **31**, 707 (1951).

(10) K. N. Campbell, A. H. Sommers, J. F. Kerwin and B. K. Campbell, THIS JOURNAL, **68**, 1851 (1946).



amino)-ethanols (Table I) were synthesized by low pressure catalytic (palladium-on-charcoal) hydrogenation of either the crude or purified 2-(pyridyl or quinolylmethyleneamino)-ethanols, prepared by allowing the corresponding quinoline and pyridine aldehydes to react with ethanolamine. Attempts to prepare 2-(4-pyridylmethylamino)-ethanol from pyridine-4-aldehyde, formic acid and ethanolamine *via* the Leuckart reaction were unsuccessful.[11]

The hydrochloride salt of 2,2-dichloro-N-(2-hydroxyethyl) - N - (4 - pyridylmethyl) - acetamide (IVc) was successfully prepared by bubbling dry hydrogen chloride into a cold chloroform solution of the base under anhydrous conditions. However, when the base was heated on the steam-bath with isopropyl alcohol freshly saturated with hydrogen chloride, an N → O acyl migration to 2-(4-pyridylmethylamino)-ethanol, dichloroacetate ester, dihydrochloride IX occurred, analogous to that previously observed[4] with 2,2-dichloro-N-(2,4-dichlorobenzyl)-N-(2-hydroxyethyl)-acetamide. The in-

(11) The method of E. A. Weilmuenster and C. N. Jordan, THIS JOURNAL, **67**, 415 (1945), for the preparation of N,N-diethylfurfurylamine was used

TABLE I: 2-(PYRIDYL AND QUINOLYLMETHYLAMINO)-ETHANOLS, R–CH$_2$NHCH$_2$CH$_2$OH

R (heterocycle)	Bases: Yield, %	B.p., °C.	Mm.	$n^{25}D$	M.p., °C.	Recrystn. solv.	Color	Formula	Hydrochlorides: Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found
2-Pyridyl	84	129–140	0.8–1.5	1.5387	130–131	[a]	Colorless	$C_8H_{12}N_2O\cdot 2HCl$	42.68	42.29	6.27	6.37	12.44	12.28	31.50	31.13
3-Pyridyl	71	143–150	1.5	1.5432	153–155	[a]	Colorless	$C_8H_{12}N_2O\cdot 2HCl$	42.68	43.09	6.27	6.39	12.44	12.58		
4-Pyridyl	47	138–140	1.0	1.5421	196–198	[b]	Colorless	$C_8H_{12}N_2O\cdot 2HCl$	42.68	42.89	6.27	6.11	12.44	12.28	31.50	31.87, 31.68
4-Quinolyl	84				160 dec.	[c]	Tan	$C_{12}H_{14}N_2O\cdot 2HCl$	52.37	52.53	5.86	6.03	10.18	10.06		

[a] Absolute ethanol. [b] 95% ethanol. [c] Isopropyl alcohol–water.

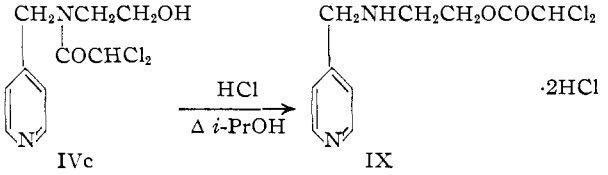
TABLE II

2,2-DICHLORO-N-(2-HYDROXYETHYL)-N-(PYRIDYL AND QUINOLYLMETHYL)-ACETAMIDES[d] R—CH$_2$NCH$_2$CH$_2$OH
COCHCl$_2$

No.	R (heterocycle)	M.p., °C.	Yield pure, %	Pro. cedure	Recrystn. solv.	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	Chlorine, % Calcd.	Found	Infrared Amide abs., μ[21]
IVb	3-Pyridyl	107–109	30	A	[a]	$C_{10}H_{12}Cl_2N_2O_2$	45.64	46.13	4.56	4.22	10.65	10.61	26.95	26.77, 26.82	5.97
IVc	4-Pyridyl	130–132	63	A	[b]	$C_{10}H_{12}Cl_2N_2O_2$	45.64	45.74	4.56	4.92	10.65	10.71	26.95	26.42, 26.88	5.94
Va	4-Quinolyl	162–165	21	A	[b]	$C_{14}H_{14}Cl_2N_2O_2$	53.69	53.84	4.51	4.66	8.95	8.90	22.64	22.39, 22.12	5.93
Vb	7-Chloro-4-quinolyl	183–184	74	B	[c]	$C_{14}H_{13}Cl_3N_2O_2$	48.37	48.30	3.77	3.81	8.06	8.40			5.96

[a] Absolute ethanol–petroleum ether (b.p. 30–60°). [b] Absolute ethanol. [c] Dimethylformamide–water. [d] All compounds were colorless.

frared absorption of a sample of the 7-chloro-4-quinolylmethyl derivative Vb which had been stored for one year at room temperature indicated



IVc IX

that approximately 50% of this material had undergone a similar N → O acyl migration.

2-[5-(7-Chloro-4-quinolylamino)-2-hydroxybenzylamino]-ethanol, required as an intermediate for the synthesis of the amodiaquin (Camoquin[8]) analog VIa, was synthesized by condensing 2-(2-hydroxyethylaminomethyl)-4-aminophenol (prepared *in situ* from monoethanolamine, paraformaldehyde and 4-acetylaminophenol) with 4,7-dichloroquinoline in aqueous solution at *p*H 3.[12] Dichloroacetylation of this amine with methyl dichloroacetate in ethylene dichloride gave 72% of the dichloroacetamide VIa as a hygroscopic orange solid. 2,2-Dichloro-N-(2-hydroxyethyl)-N-[2-hydroxy-5-(6-methoxy-2-methyl-4-quinolylamino)-benzyl]-acetamide (VIb) was prepared in an analogous manner.

The quinacrine analog VII was prepared from 2-[2-(6-chloro-2-methoxy-9-acridinylamino)-ethylamino]-ethanol by acylation with methyl dichloroacetate in ethanol; the amine was readily obtained by condensing 6,9-dichloro-2-methoxyacridine and 2-aminoethylethanolamine[13] in phenol. The benz[c]acridine analogs N-[2-(7-benz[c]acridinylamino)-ethyl]-2,2-dichloro-N-(2-hydroxyethyl)-acetamide (VIIIa) and N-[3-(7-benz[c]acridinylamino)-propyl [-2,2-dichloro-N-(2-hydroxyethyl)-acetamide (VIIIb) were similarly prepared from 7-chlorobenz[c]acridine[14,15] and the appropriate aminoalkylethanolamine[13] *via* the intermediate 7-benz[c]-acridinylaminoalkylaminoethanols.

The heterocyclic 2,2-dichloro-N-(2-hydroxyethyl)-acetamides described above were tested against *Endamoeba histolytica in vitro* (48-hour test[16]) by P. E. Thompson and co-workers of these laboratories; when indicated, expanded studies were carried out against *E. histolytica* infections in rats, hamsters and dogs. Details of these test results will be published in a separate communication,[17] but the following highlights might be mentioned here. Eight of these heterocyclic acetamides were amebicidal *in vitro* at concentrations of 7 to 1,333 μg./ml.; seven were active against intestinal amebiasis in rats,[18] the most active being 2,2-dichloro-N-(2-hydroxyethyl)-N-(3- and 4-pyridylmethyl)-acetamide (IVb and c). The latter compound possessed activity against amebic dysentery in dogs,[19] but was ineffective against amebic hepatitis in hamsters.[9]

Acknowledgment.—The authors thank Dr. Loren M. Long and Dr. George Rieveschl, Jr., for advice and encouragement, Dr. Paul E. Thompson, Mr. D. A. McCarthy and Miss Anita Bayles for the biological testing, and Dr. Ralph E. Bowman and Mrs. Sylvia D. Cavalla of the Parke, Davis Research Laboratories, Hounslow, England, for synthesizing one of the compounds described herein. We are also 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[20]

2-(4-Pyridylmethyleneamino)-ethanol.—To a solution of 44.5 g. (0.42 mole) of pyridine-4-aldehyde in 100 ml. of anhydrous benzene was added dropwise with stirring a suspension of 25.5 g. (0.42 mole) of ethanolamine in 50 ml. of dry benzene over a period of one-half hour. During the exothermic reaction which occurred the temperature rose to 38°. The mixture was stirred at room temperature for two hours, then boiled gently under reflux for three hours. The water which separated was collected in a Barrett distilling receiver. Dry nitrogen was passed into the reaction flask throughout the reaction. The benzene was removed *in vacuo* and, upon cooling, the residue solidified. The crude product was dissolved in boiling benzene, the solution filtered, and petroleum ether (b.p. 30–60°) added until crystallization occurred; yield 58.5 g. (94%). For analysis, a sample was crystallized from an ethyl acetate–petroleum ether (b.p. 30–60°) mixture to give a yellow-brown powder, m.p. 47–54°.

Anal. Calcd. for $C_8H_{10}N_2O$: C, 63.95; H, 6.71; N, 18.67. Found: C, 63.57; H, 7.22; N, 18.47.

2-(2- and 3-Pyridylmethyleneamino)-ethanol.—Utilizing the above procedure, 1.66 moles of 2-pyridine aldehyde and 0.83 mole of 3-pyridine aldehyde were converted to the corresponding 2-(2- and 3-pyridylmethyleneamino)-ethanols; both compounds were obtained as viscous amber oils which could not be crystallized from various organic solvents.

2-(4-Quinolylmethyleneamino)-ethanol.—This compound was obtained from 0.83 mole of 4-quinoline aldehyde and 0.83 mole of ethanolamine as a yellow solid, m.p. 73–77°, according to the procedure cited above for the preparation of 2-(4-pyridylmethyleneamino)-ethanol.

Anal. Calcd. for $C_{12}H_{12}N_2O$: C, 72.01; H, 6.04; N, 14.00. Found: C, 71.90; H, 6.05; N, 13.98.

General Method for Preparing 2-(Pyridyl and quinolylmethylamino)-ethanols (Table I).—A mixture of 0.376 to 1.55 moles of the crude or recrystallized 2-(pyridyl or quinolylmethyleneamino)-ethanol, 200 to 800 ml. of hot 95% ethanol and 1 to 2 g. of 5% palladium-on-charcoal catalyst was hydrogenated in a Parr shaker under 20 to 60 p.s.i.g. of hydrogen until the theoretical amount of hydrogen had been absorbed. In general, the hydrogenation initially proceeded rapidly, but slowed down when approximately one-half of the calculated amount of hydrogen had been absorbed. Therefore, 0.5 to 3 g. of fresh catalyst was added, the reduction mixtures were heated to 70°, and hydrogenation resumed until the hydrogen uptake was complete. The catalyst was collected by filtration, and the alcohol removed *in vacuo*. Except for the quinolyl compound, the residues were distilled *in vacuo* through a six-inch Vigreux column to give the pure bases. For analysis, the bases were treated with hydrogen chloride in isopropyl alcohol, and the crude hydrochlorides isolated by the addition of ether. Recrystallization from the appropriate solvents yielded the pure dihydrochlorides.

(12) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb and A. L. Rawlins, THIS JOURNAL, **70**, 1363 (1948).

(13) The authors are indebted to Dr. Franklin Johnston and Dr. G. W. Fowler of the Carbide and Carbon Chemicals Co. for the samples of 2-aminoethylethanolamine and 3-aminopropylethanolamine.

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

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

(16) P. E. Thompson, J. W. Reinertson, D. A. McCarthy, A. Bayles and A. R. Cook, *Antibiotics and Chemotherapy*, **5**, 433 (1955).

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

(18) 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).

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

(20) Melting points are uncorrected.

Methods for Preparing 2,2-Dichloro-N-(2-hydroxyethyl)-N-(pyridyl and quinolylmethyl)-acetamides (Table II). Method A.—A mixture of 0.17 to 0.71 mole of the appropriate 2-(pyridyl or quinolylmethylamino)-ethanol, 100 to 1350 ml. of ethylene dichloride and 25 to 125 ml. of methyl dichloroacetate was stirred at room temperature for 24 hours and cooled. In some cases, the desired product crystallized from the reaction mixture and was separated at this point. In others, the ethylene dichloride and excess methyl dichloroacetate were removed *in vacuo* at 60°, and the oily residues triturated with several portions of petroleum ether (b.p. 30–60°), whereupon they crystallized. Several crystallizations (Darco) from the indicated solvents yielded the pure dichloroacetamides, which were collected by filtration, washed thoroughly with petroleum ether (b.p. 30–60°), and dried *in vacuo* at 35°.

Method B.—To a solution of 0.35 g. (0.0015 mole) of 2-(7-chloro-4-quinolylmethylamino)-ethanol[10] in 4.5 ml. of dimethylformamide was added 1.1 g. (0.0075 mole) of dichloroacetyl chloride. An exothermic reaction occurred. After standing for 20 minutes, the mixture was diluted with 20 ml. of water, and the resulting solid collected by filtration. The crude product was dissolved in dimethylformamide, precipitated with ammonium hydroxide solution, and crystallized from aqueous dimethylformamide.

2,2-Dichloro-N-(2-hydroxyethyl)-N-(4-pyridylmethyl)-acetamide, Hydrochloride.—Dry hydrogen chloride was bubbled into a solution of 0.5 g. (0.0019 mole) of 2,2-dichloro-N-(2-hydroxyethyl)-N-(4-pyridylmethyl)-acetamide in 50 ml. of cold anhydrous chloroform. The colorless oil which immediately separated was caused to crystallize by trituration with cold anhydrous ether. The colorless precipitate became sticky as it was collected on the filter, but turned granular when dried *in vacuo* (0.5 mm.) over phosphorus pentoxide at room temperature for one hour. The hygroscopic salt melted at 143–144°.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2O_2 \cdot HCl \cdot H_2O$: C, 37.81; H, 4.76. Found: C, 37.70, 37.74; H, 4.50, 4.80.

The freshly prepared salt possessed a strong amide carbonyl absorption[21] at 5.98 μ; however, upon standing for 10 days at room temperature in a stoppered glass flask, approximately 50% of the amide hydrochloride rearranged to the O-acyl derivative IX as indicated by the presence of both an amide band at 5.98 μ and an ester band at 5.68 μ.

2-(4-Pyridylmethylamino)-ethanol, Dichloroacetate Ester, Dihydrochloride (IX).—A mixture of 25 g. (0.095 mole) of 2,2-dichloro-N-(2-hydroxyethyl)-N-(4-pyridylmethyl)-acetamide and 200 ml. of isopropyl alcohol freshly saturated with hydrogen chloride was heated on the steam-bath until the solid dissolved. The mixture was subsequently cooled in an ice-bath, and hydrogen chloride was bubbled through the mixture for 5 minutes. The solid which separated was collected by filtration, digested for 30 minutes with boiling absolute ethanol, and the mixture cooled in an ice-bath. The colorless crystals were collected by filtration and dried *in vacuo;* weight 24.2 g. (76%). The product was twice recrystallized from 300 ml. of 95% ethanol and dried *in vacuo* at 78° for one hour to give the ester dihydrochloride as colorless hygroscopic crystals, m.p. 162–166°.

Anal. Calcd. for $C_{10}H_{12}Cl_2N_2O_2 \cdot 2HCl$: N, 8.34; Cl, 42.20. Found: N, 8.61, 8.68; Cl, 42.23, 42.21.

The infrared spectrum showed a strong ester carbonyl absorption[21] at 5.76 μ but no amide absorption.

2-[5-(7-Chloro-4-quinolylamino)-2-hydroxybenzylamino]-ethanol.—A mixture of 40.3 g. (0.66 mole) of monoethanolamine, 18 g. (0.6 mole) of paraformaldehyde and 100 ml. of ethanol was boiled under reflux for 30 minutes and cooled, whereupon a solution of 90.6 g. (0.6 mole) of 4-acetylaminophenol in 250 ml. of ethanol was added. The resulting solution was allowed to stand at room temperature for 2 days, boiled under reflux for 4 hours, and the solvent removed *in vacuo*. The residue was boiled under reflux for 1 hour with 340 ml. of 20% hydrochloric acid, cooled, diluted with 400 ml. of water, and adjusted to *p*H 3. A slurry of 118 g. (0.6 mole) of 4,7-dichloroquinoline and 100 ml. of ethanol was added, and the mixture heated on the steam-bath for 3 hours with mechanical stirring. The hot reaction mixture was filtered and neutralized with ammonium hydroxide. The product was collected by filtration, washed thoroughly with water, and dried at 60° for 18 hours; crude yield 204 g. (97%), m.p. 90°.

(21) Nujol mull.

A 98-g. portion of the crude product was treated with an excess of an alcoholic hydrogen chloride solution. Upon the addition of acetone, a waxy material separated, which slowly crystallized (111 g., m.p. 90–100° with foaming). This product was dissolved in hot methanol, and diluted with two volumes of hot isopropyl alcohol; a dark oil separated, from which the solution was decanted. The dark oil was extracted twice more by the same process, the solutions were combined, treated with Darco, concentrated to a small volume, and the product reprecipitated with acetone. The solid was collected by filtration, dissolved in hot water (Darco), and the solution treated with ammonium hydroxide solution. The final product was collected by filtration, washed thoroughly with water, and dried *in vacuo;* yield 46 g., m.p. 100–110°, foaming at 117°.

Anal. Calcd. for $C_{18}H_{18}ClN_3O_2 \cdot {}^1/_2H_2O$: C, 61.28; H, 5.43; N, 11.91. Found: C, 61.62; H, 5.29; N, 11.95.

2,2-Dichloro-N-[5-(7-chloro-4-quinolylamino)-2-hydroxybenzyl]-N-(2-hydroxyethyl)-acetamide (VIa).—A mixture of 10.3 g. (0.03 mole) of 2-[5-(7-chloro-4-quinolylamino)-2-hydroxybenzylamino]-ethanol, 4.8 g. (0.033 mole) of methyl dichloroacetate and 50 ml. of ethylene dichloride was stirred for one hour at room temperature. No change was apparent. Subsequently, 25 ml. of ethylene dichloride was added, and the mixture heated for 5 hours at 60° with mechanical stirring. At this point, the reaction mixture had become so thick that it stopped the stirrer. The orange precipitate was collected by filtration, washed with ethylene dichloride, and dried *in vacuo;* yield 11.7 g. (72%), m.p. 91° dec. The compound was very hygroscopic, and attempts to recrystallize the material from methanol yielded only oily residues. The dichloroacetamide was insoluble in chloroform, benzene and ethyl acetate.

Anal. Calcd. for $C_{20}H_{18}Cl_3N_3O_3 \cdot H_2O$: C, 50.81; H, 4.26; N, 8.89. Found: C, 50.76; H, 4.78; N, 9.05.

The infrared spectrum showed a characteristic amide carbonyl absorption[21] at 6.09 μ, but no ester absorption.

2,2-Dichloro-N-(2-hydroxyethyl)-N-[2-hydroxy-5-(6-methoxy-2-methyl-4-quinolylamino)-benzyl]-acetamide (VIb).—A mixture of 25.7 g. (0.42 mole) of monoethanolamine, 11.5 g. (0.38 mole) of paraformaldehyde and 100 ml. of ethanol was heated on the steam-bath for 30 minutes; the reaction mixture was allowed to cool, and was added to a cold solution of 57.8 g. (0.38 mole) of 4-acetylaminophenol in 250 ml. of ethanol. After standing for 30 minutes, the mixture was boiled under reflux for 4 hours, and the solvent removed *in vacuo*. The residue was heated on a steam-bath for 2 hours with 160 ml. of 20% hydrochloric acid; the solution was cooled, diluted with 160 ml. of water, and adjusted to *p*H 3. Subsequently, 79.5 g. (0.38 mole) of 4-chloro-6-methoxyquinaldine and 50 ml. of ethanol was added, and the mixture boiled under reflux for 3 hours; a clear solution was obtained. Upon neutralization with concentrated ammonium hydroxide, a gummy mass separated, which could not be crystallized from various solvents. The gum was dissolved in a methanol–ethanol mixture, and evaporated to dryness *in vacuo* in a tared flask; weight 77 g. (57%). The crude dry ethanolamine derivative was used directly in the dichloroacetylation.

To a solution of the above ethanolamine in 200 ml. of absolute ethanol was added 62.5 g. (0.44 mole) of methyl dichloroacetate, and the mixture heated under reflux for 2 hours. The solvent and excess methyl dichloroacetate were removed *in vacuo*, and the residue was cooled and triturated with petroleum ether (b.p. 30–60°). The product was dissolved in hot ethanol (Darco), the solvent partially evaporated, and the solution decanted from a layer of tar and stirred slowly into several volumes of ethyl acetate. The waxy precipitate was again dissolved in ethanol and precipitated with ethyl acetate. After triturating several times with dry ether, the product was collected by filtration and dried *in vacuo;* yield 14.7 g. (14%) of light tan powder, m.p. indefinite.

Anal. Calcd. for $C_{22}H_{23}Cl_2N_3O_4 \cdot {}^1/_2H_2O$: C, 55.81; H, 5.11; N, 8.88. Found: C, 56.00; H, 5.41; N, 8.44.

The infrared spectrum showed a characteristic amide carbonyl absorption[21] at 6.07 μ, and was free of any ester absorption.

2-[2-(6-Chloro-2-methoxy-9-acridinylamino)-ethylamino]-ethanol.—To a stirred mixture of 100 g. (0.36 mole) of 6,9-dichloro-2-methoxyacridine and 350 g. of phenol, which had been heated on the steam-bath for 15 minutes, was added 40

g. (0.39 mole) of 2-aminoethylethanolamine.[13] Stirring and heating were continued for 2 hours, the mixture was cooled, and poured slowly into a solution of 90 ml. of concentrated hydrochloric acid in 2 l. of acetone. The product was collected by filtration and recrystallized from ethanol to give 126 g. (80%) of yellow crystals, m.p. 280–283° dec.

The free base was prepared by neutralizing a solution of 77 g. of the dihydrochloride monohydrate in 4 l. of warm water with excess ammonium hydroxide. A gum separated, which crystallized upon scratching. The bright yellow crystals were collected by filtration, washed with water and air-dried; yield 62 g. (98%), m.p. 183°. Recrystallization from a methanol–ethyl acetate mixture yielded yellow crystals, m.p. 182–184°.

Anal. Calcd. for $C_{18}H_{20}ClN_3O_2$: C, 62.51; H, 5.83; N, 12.15. Found: C, 62.61; H, 5.63; N, 12.12.

2,2-Dichloro-N-[2-(6-chloro-2-methoxy-9-acridinylamino)-ethyl]-N-(2-hydroxyethyl)-acetamide (VII).—A suspension of 61 g. (0.18 mole) of 2-[2-(6-chloro-2-methoxy-9-acridinylamino)-ethylamino]-ethanol in a solution of 52 g. (0.36 mole) of methyl dichloroacetate and 250 ml. of absolute ethanol was boiled under reflux for 24 hours. The mixture was cooled in an ice-bath, and the golden yellow rods were collected by filtration and air-dried; yield 49.2 g. (58%), m.p. 169° dec.

Anal. Calcd. for $C_{20}H_{20}Cl_3N_3O_3 \cdot 1^1/_2H_2O$: C, 49.65; H, 4.71; N, 8.68. Found: C, 49.47, 49.77; H, 4.71, 4.79; N, 8.27.

The infrared spectrum showed a characteristic amide carbonyl absorption[22] at 6.04 μ; no ester absorption was observed.

2-[2-(7-Benz[c]acridinylamino)-ethylamino]-ethanol.—A mixture of 50 g. (0.19 mole) of 7-chlorobenz[c]acridine, 19.8 g. (0.19 mole) of 2-aminoethylethanolamine[13] and 200 g. of phenol was stirred and heated on a steam-bath for two hours. The cooled reaction mixture was poured into a solution of 50 ml. of concentrated hydrochloric acid in 1 l. of acetone, the resulting mixture chilled, and the precipitated solid collected by filtration, washed with acetone, and dried. A solution of the crude hydrochloride in 500 ml. of water was made alkaline by the addition of a solution of 20 g. (0.5 mole) of sodium hydroxide in 25 ml. of water, and the solid base collected by filtration and dried. Extraction of the aqueous filtrates with ether and benzene afforded additional free base. Recrystallization of the combined crude base fractions from ethyl acetate (Darco) yielded 45.4 g. (72%) of yellow-green crystals, m.p. 99–100°.

Anal. Calcd. for $C_{21}H_{21}N_3O$: C, 76.10; H, 6.39; N, 12.68. Found: C, 76.16; H, 6.52; N, 12.70.

N-[2-(7-Benz[c]acridinylamino)-ethyl]-2,2-dichloro-N-(2-hydroxyethyl)-acetamide (VIIIa).—A solution of 40 g. (0.12 mole) of 2-[2-(7-benz[c]acridinylamino)-ethylamino]-ethanol and 25 ml. (0.24 mole) of methyl dichloroacetate in 100 ml. of absolute ethanol was boiled under reflux for 15 hours. The mixture was cooled, diluted with petroleum ether (b.p. 30–60°) to a volume of 1 l., and the taffy-like material which separated was solidified by grinding under anhydrous ether. The solid was collected by filtration and dried *in vacuo;* yield 46.2 g. (83%) of hygroscopic yellow solid, m.p. indefinite. Attempts to recrystallize the compound from several organic solvents failed.

Anal. Calcd. for $C_{23}H_{21}Cl_2N_3O_2 \cdot H_2O$: C, 60.00; H, 5.04; N, 9.13. Found: C, 59.68; H, 5.15; N, 9.33.

The infrared spectrum showed a characteristic amide carbonyl absorption[22] at 6.04 μ, and was free of ester absorption.

2-[3-(7-Benz[c]acridinylamino)-propylamino]-ethanol, Dihydrochloride.—A mixture of 50 g. (0.19 mole) of 7-chlorobenz[c]acridine, 23.6 g. (0.20 mole) of 3-aminopropylethanolamine[13] and 200 g. of phenol was stirred and heated on the steam-bath for two hours. The cooled reaction mixture was poured into a solution of 33 ml. of concentrated hydrochloric acid in 1 l. of acetone, the resulting mixture was chilled, and the solid which separated was collected by filtration, washed with acetone and dried; crude yield 82.1 g. (99%). A portion of the crude product precipitated from a methanol–ethyl acetate mixture yielded a hygroscopic yellow solid, m.p. 215–220° (softens 135° with apparent loss of water).

Anal. Calcd. for $C_{22}H_{23}N_3O \cdot 2HCl \cdot H_2O$: C, 60.55; H, 6.24; N, 9.63. Found: C, 60.91, 61.08; H, 6.08, 6.22; N, 10.02, 9.86.

N-[3-(7-Benz[c]acridinylamino)-propyl]-2,2-dichloro-N-(2-hydroxyethyl)-acetamide (VIIIb).—A filtered solution of 48.2 g. (0.110 mole) of the crude 2-[3-(7-benz[c]acridinylamino)-propylamino]-ethanol, dihydrochloride, monohydrate in 300 ml. of hot water was made alkaline by the addition of a solution of 12 g. (0.3 mole) of sodium hydroxide in 20 ml. of water. The mixture was extracted with benzene and butanol, the combined extracts were dried over anhydrous potassium carbonate, and the solvents removed *in vacuo* to give 36 g. (0.104 mole) of the crude amine. A solution of the crude amine in 200 ml. of absolute ethanol was boiled under reflux with 16 ml. (0.15 mole) of methyl dichloroacetate for 6 hours. When the cooled solution was diluted with petroleum ether (b.p. 30–60°) to a volume of 2 l., a viscous sirup separated, which was triturated thoroughly with petroleum ether (b.p. 30–60°) and ether. After one week, the sirup solidified and was pulverized and dried to give 35.9 g. (74.3%) of a yellow powder of indefinite melting point.

Anal. Calcd. for $C_{24}H_{23}Cl_2N_3O_2 \cdot 1/_2H_2O$: C, 61.94; H, 5.20; N, 9.03. Found: C, 61.67, 61.76; H, 5.40, 5.29; N, 9.04.

The infrared spectrum showed a characteristic amide carbonyl absorption[22] at 6.03 μ, and was free of ester absorption.

DETROIT, MICHIGAN

(22) Pressed KBr disc.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Unsaturated Amines. VII. Introduction of α,β-Unsaturation by Means of Mercuric Acetate: Methylquinolizidines

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The mercuric acetate dehydrogenation of 1-, 2-, 3- and 4-methylquinolizidine (I) results in the introduction of a double bond at the bridgehead carbon (C-10). The enamines thus obtained form salts (perchlorates were used for characterization) having 5(10)-unsaturation which are of the ternary iminium type. Hydroxylation accompanies the dehydrogenation of 1-methylquinolizidine to some extent, with the coformation of 1-hydroxy-1-methyl-Δ⁹-dehydroquinolizidine. Accurate characterization of the two racemates of 2-methylquinolizidine has been effected along with the dehydrogenation study.

Following the investigation of the mercuric acetate dehydrogenation of quinolizidine[3] and other bicyclic tertiary amines,[4] it was of interest to study the dehydrogenation of the isomeric methyl-substituted quinolizidines (I), in part to answer the fol-

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