Each of the broths to which precursor had been added was tested qualitatively for the presence of ketone by the addition of an acidic solution of 2,4-dinitrophenylhydrazine. An aliquot of the neutral volatile fraction was analyzed quantitatively for methyl ketone as described above. Only when caproic acid was added to the flask, was an appreciable amount of ketone obtained. The structure assigned to this ketone was methyl *n*-propyl ketone. The quantitative iodoform method was mild enough that alcohols such as isopropyl alcohol reacted very slowly. The compound must then be a methyl ketone. The recrystallized 2,4-dinitrophenylhydrazone melted at 140–141°, which corresponded with the value given[13] for the hydrazone of methyl *n*-propyl ketone.

(13) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 221.

MADISON, WISCONSIN

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

New Anthelmintics. The Synthesis of Some 9-Hydroxyalkyl- and Dihydroxylalkyl-aminoalkylaminoacridines

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A series of substituted 9-aminoacridines containing a primary or/and a secondary or tertiary hydroxyl group in the basic side chain has been prepared. The preparation of N-(2-hydroxypropyl)- and N-(3-hydroxybutyl)-1,3-propanediamine and N-(2,3-dihydroxypropyl)-ethylenediamine is also described. Some of the acridines have been found to possess marked anthelmintic activity.

The present communication reports the synthesis of 9-aminoacridine derivatives (Table I) containing a primary, or/and a secondary or tertiary hydroxyl group in the basic side chain. In addition, one compound having a morpholino group in the side chain is also included. Some of the compounds have been found to be unexpectedly effective as anthelmintic agents.

The acridines described in Table I were prepared from the corresponding 9-chloroacridine by the reaction with phenol to give the 9-phenoxyacridine (not isolated) followed by treatment with the appropriate primary–secondary diamine. The products were isolated as yellow crystalline dihydrochlorides containing varying amounts of water. It was found that in most instances complete removal of water from these salts is very difficult.

Two of the basic side chains, N-(2-hydroxyethyl)-ethylenediamine and 2-morpholinoethylamine employed in the present work are commercially available.[1] The preparation of N-(2-hydroxypropyl)- and N-(2-hydroxyisobutyl)-ethylenediamine have been reported by Kitchen and Pollard.[2] The 2-hydroxyethyl-,[3] 2-hydroxypropyl and 3-hydroxybutyl-1,3-propanediamines were prepared by condensing ethanolamine, 2-hydroxypropylamine and 3-hydroxybutylamine with acrylonitrile to give the substituted aminopropionitriles which were then reduced catalytically with Raney nickel. The reaction of glycidol with ethylenediamine gave N-2,3-dihydroxypropylethylenediamine which was used without purification. The same diamine was also obtained directly from glycerol α-monochlorohydrin by reaction with ethylenediamine and potassium hydroxide.

Of the compounds listed in Table I, 9-(2-hydroxyethylaminoethylamino)-2-methoxyacridine,[4] 6-chloro-9-(3-(2-hydroxyethylamino)-propylamino)-2-methoxyacridine and 9-(2-(2,3-dihydroxypropylamino)-ethylamino)-2-methoxyacridine appear to be the best anthelmintic agents[5] when tested in Swiss mice against the oxyurid worms, *Aspicularis tetraptera* and *Syphacea obvelata*.

Experimental

2-Hydroxypropylaminopropionitrile.—Acrylonitrile (66.5 g.) was added dropwise with stirring over a period of 90 minutes to 141.2 g. of monoisopropanolamine (temperature below 30°). After stirring for five additional hours the reaction mixture was heated on the steam-bath for 30 minutes and then allowed to stand overnight at room temperature. The product was fractionally distilled, 40 g. (25%); 111–113° at 0.6 mm. The product solidified on standing, m.p. 47–51°.

Anal. Calcd. for $C_6H_{12}N_2O$: N (basic), 10.93. Found: N (basic), 11.01.

3-Hydroxybutylaminopropionitrile.—Prepared as above in 74% yield, b.p. 132–135° at 0.8 mm., $n^{25}D$ 1.4615.

Anal. Calcd. for $C_7H_{14}N_2O$: N (basic), 9.85. Found: N (basic), 9.98.

N-2-Hydroxypropyl-1,3-propanediamine.—2-Hydroxypropylaminopropionitrile (38 g.) in 200 ml. of ammoniacal ethanol (approx. 12%) was reduced catalytically with Raney nickel at 120° and an initial hydrogen pressure of 1180 pounds. The product 19 g. (48%) distilled at 105–110° at 1.5 mm., $n^{25}D$ 1.4747.

Anal. Calcd. for $C_6H_{16}N_2O$: N, 21.30. Found: N, 21.50.

N-3-Hydroxybutyl-1,3-propanediamine.—Prepared as above in 58% yield, b.p. 95–100° at 0.25 mm., $n^{25}D$ 1.4738.

Anal. Calcd. for $C_7H_{18}N_2O$: N, 19.00. Found: N, 18.98.

N-(2,3-Dihydroxypropyl)-ethylenediamine.—Glycidol (17.5 g.) was added dropwise with stirring at 70–80° to 91 g. of ethylenediamine over a period of 90 minutes. Fractional distillation gave a crude product, b.p. 171° at 0.4 mm., which solidified on standing.

Glycerol α-monochlorohydrin (110 g.) was added dropwise with stirring over a period of 90 minutes to a mixture of 54 g. of potassium hydroxide in 400 g. of ethylenediamine at 70–80°. After the addition was complete the mixture was allowed to stand overnight at room temperature, filtered, and the filtrate was distilled under reduced pressure. After

(1) Samples of these amines were obtained through the courtesy of the Carbide and Carbon Chemicals Corporation.

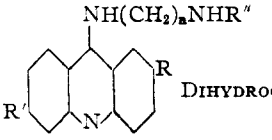
(2) L. J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8**, 342 (1943).

(3) A. R. Surrey and H. F. Hammer, THIS JOURNAL, **72**, 1814 (1950).

(4) The compound can be regarded as an ethylenediamine derivative. N'-(2-hydroxyethyl)-N¹-(2-methoxy-9-acridyl)-ethylenediamine.

(5) The authors are indebted to Dr. E. W. Dennis and Dr. D. A. Berberian of this Institute for the testing of these compounds, the details of which will be published elsewhere.

TABLE I



DIHYDROCHLORIDES

R	R'	n	R''	M.p., °C. cor.	Analyses, %[a] Chlorine⁻ Calcd.	Chlorine⁻ Found	Nitrogen Calcd.	Nitrogen Found	H_2O
H	H	2	CH_2CH_2OH	244.5–246.5	20.02	19.95	11.80	12.08	3.69
							C, 57.63	57.35	
							H, 5.98	5.96	
H	Cl	2	CH_2CH_2OH[b]	199–201	17.44[c]	17.36	C, 50.20	50.03	4.64[d]
							H, 5.45	5.23	
OCH_3	H	2	CH_2CH_2OH[e]	212–214.5	18.45	18.48	C, 56.25	56.25	1.20
							H, 6.03	6.18	
OCH_3	Cl	3	CH_2CH_2OH[f]	252.5–254	16.38	16.30	C, 52.72	52.54	2.85
							H, 5.59	5.50	
OCH_3	H	3	CH_2CH_2OH[g]	213.8–215.8	17.80	17.57	10.55	10.52	1.10
OCH_3	H	2	$CH_2CHOHCH_3$	202.6–205	17.81	17.52	10.55	10.41	0.85
OCH_3	Cl	2	$CH_2CHOHCH_3$	218–221	16.38	16.28	9.71	10.02	1.54
OCH_3	H	3	$CH_2CHOHCH_3$	266.6–267.4	17.20	17.21	10.19	10.21	1.67
OCH_3	Cl	3	$CH_2CHOHCH_3$	267–268	15.87	15.69	9.42	9.28	1.48
OCH_3	H	3	$CH_2CH_2CHOHCH_3$	265.4–266.2	16.63	16.56	9.86	9.83	0.70
OCH_3	Cl	3	$CH_2CH_2CHOHCH_3$	266.8–268 dec.	15.39	15.37	9.12	8.88	5.15
OCH_3	H	2	$CH_2C(OH)(CH_3)_2$	241.8–246 dec.	17.60	17.29	10.43	10.14	
OCH_3	Cl	2	$CH_2C(OH)(CH_3)_2$	228.2–230.2	15.56[h]	15.58	9.22	8.97	2.20[i]
OCH_3	H	2	$CH_2CHOHCH_2OH$	196.8–202.2	17.11	17.03	10.14	10.02	
OCH_3	Cl	2	$CH_2CHOHCH_2OH$	207.4–208.4	23.72[j]	23.72	9.36	9.30	
H	Cl	2	$CH_2CHOHCH_2OH$	179.7–181.7	25.41[j]	25.22	10.04	10.17	

[a] The analyses are reported on the dry basis unless otherwise indicated. [b] A. R. Surrey, U. S. Patent 2,531,011. [c] Analytical values for monohydrate. [d] Calcd. H_2O, 4.43. [e] U. S. Patent 2,531,012. [f] U. S. Patent 2,555,944. [g] U. S. Patent 2,531,013. [h] Analytical values for hemihydrate. [i] Calcd. H_2O, 1.98. [j] Total chlorine.

recovering the excess ethylenediamine, the product was collected, 65 g. (50%), b.p. 165–170° at 0.2 mm.

The picrate melted at 196–198° (dec.).

Anal. Calcd. for $C_{17}H_{20}N_8O_{16}$: N (basic), 4.73. Found: N (basic), 4.83.

6-Chloro-2-methoxy-9-(2-(1-morpholino)-ethylamino)-acridine Dihydrochloride.—The following is the general procedure employed for the preparation of the compounds listed in Table I.

A mixture of 14 g. (0.05 mole) of 6,9-dichloro-2-methoxyacridine and 50 g. of phenol was heated with mechanical stirring for 15 minutes on the steam-bath and 7.8 g. (0.06 mole) of morpholinoethylamine was added. Heating and stirring was continued for two hours and the reaction mixture was poured with stirring into 150 ml. of acetone containing 12.5 ml. of concentrated hydrochloric acid. After the mixture had cooled to room temperature the yellow dihydrochloride was filtered off, washed with acetone and then freed from most of the adhering phenol by stirring in hot acetone and refiltering. The product was recrystallized by dissolving it in hot water and adding a small amount of sodium chloride, yield 14 g., m.p. 257–258° cor.

Anal. Calcd. for $C_{20}H_{22}N_3O_2 \cdot 2HCl$: Cl^-, 23.86; N, 9.48. Found: Cl^- (dry basis), 23.64; N (dry basis), 9.52; H_2O, 3.47.

For the recrystallization of the other dihydrochlorides (Table I) the above procedure was employed or a mixture of ethyl alcohol and water was used. The salts were dried at 95° for 24 to 48 hours.

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