[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of 7-Chloro-4-(4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino)-quinoline and Related Compounds

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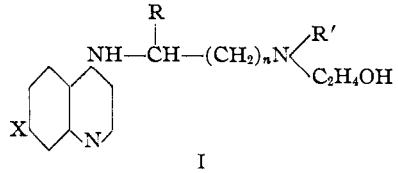
In the course of our search[2] for superior antimalarial drugs in the 4-aminoquinoline series, we have prepared several compounds containing an N-alkylethanolamino group in the basic side chain. The compounds studied in the present work (listed in Table I) can be represented by the formula I, in which X is H or Cl, R is H or CH_3,



I

n is 2 or 3, and R′ is C_2H_5 or n-C_4H_9. A search in the literature[3] indicated that of all the different side chains investigated in the 4-aminoquinoline series, compounds of this type have not been reported.

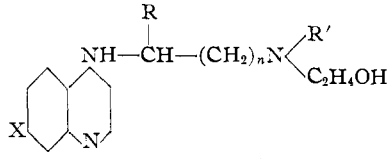
The most promising antimalarial in the present series is 7-chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino]-quinoline in which one of the terminal ethyl groups on the side chain of chloroquine is replaced by an hydroxyethyl group. Against *Plasmodium lophurae* the new compound is three to seven times as active as quinacrine. In a preliminary clinical trial the medicinal response was very favorable.

The compounds listed in Table I were prepared according to previously described procedures by condensing the appropriate diamine with 4,7-dichloroquinoline. The reactants were heated alone or in the presence of phenol. With the exception of 4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino]-quinoline all the bases were obtained as solids which were purified by recrystallization from a suitable solvent. Two of the bases were converted to the water soluble diphosphate salts.

Two of the diamines employed in the present work, N-ethyl-(and N-n-butyl)-N-β-hydroxyethyl-1,3-propanediamine, have been described previously.[4] Essentially the same procedure[5] was used for the preparation of N-β-hydroxyethyl-1,3-propanediamine.

The remaining two diamines, N^1-ethyl-(and N^1-n-butyl)-N^1-β-hydroxyethyl-1,4-pentanediamine, were prepared by condensing N-ethyl-(and N-n-butyl)-ethanolamine with 4-chloro-2-pentanone followed by reductive amination.

TABLE I



X	R	n	R′	M. p., °C.[a]	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Cl	H	2	H	130–131.5[b]	$C_{14}H_{18}ClN_3O$	60.10	60.42	6.48	6.06	15.03	14.78
Cl	H	2	C_2H_5	106–107.5[c]	$C_{16}H_{22}ClN_3O$	62.43	62.41	7.21	7.08	13.66	13.68
Cl	H	2	n-C_4H_9	91–92[d]	$C_{18}H_{26}ClN_3O$	64.37	64.11	7.82	7.85	12.51	12.20
H	CH_3	3	C_2H_5	[e]	$C_{18}H_{27}N_3O$						
Cl	CH_3	3	C_2H_5	89–91[f,g]	$C_{18}H_{26}ClN_3O$	64.37	64.64	7.82	7.78	12.51	12.78
Cl	CH_3	3	n-C_4H_9	116.5–118[h]	$C_{20}H_{30}ClN_3O$	66.01	66.04	8.31	8.31	11.55	11.67

[a] All melting points are corrected. [b] Recrystallized from dioxane and Skellysolve B, then acetone. [c] From Skellysolve C. [d] From Skellysolve B and benzene. [e] The base was obtained as an oil. The diphosphate salt melted at 177.3–180°. *Anal.* Calcd. for B·2H_3PO_4; N, 8.45; H_3PO_4, 39.81. Found: (dry basis) N, 8.41; H_3PO_4, 39.4. [f] From ethylene dichloride and the Skellysolve B. [g] The diphosphate salt melts at 168–170° dec. *Anal.* Calcd. for B·2H_3PO_4; N, 7.90; H_3PO_4, 36.85. Found: (dry basis) N, 7.64; H_3PO_4, 36.80. [h] From ethylene dichloride and Skellysolve C.

Experimental

β-(2-Hydroxyethylamino)-propionitrile.—Acrylonitrile (180 g.) was added dropwise with stirring over a period of ninety minutes to 305 g. of ethanolamine (temperature below 30°). After stirring for five additional hours the reaction mixture was heated on the steam-bath for thirty minutes and then allowed to stand overnight at room temperature. The excess of ethanolamine was removed by distillation *in vacuo* to yield 290 g. (75%) of crude product. A sample was distilled twice for analysis; b. p. 123° at 0.9 mm., $n^{25}D$ 1.4683.

Anal. Calcd. for $C_5H_{10}N_2O$: N,[6] 12.27. Found: N, 12.52.

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(2) For previous paper in this series see Surrey and Cutler, THIS JOURNAL, **68**, 2570 (1946).

(3) F. Y. Wiselogle, editor, "Survey of Antimalarial Drugs 1941–1945," J. W. Edwards, Ann Arbor, Michigan, 1946.

(4) Burckhalter, Jones, Holcomb and Sweet, THIS JOURNAL, **65**, 2013 (1943).

(5) Tarbell, Shakespeare, Claus and Bunnett, *ibid.*, **68**, 1217 (1946).

(6) Determination of basic nitrogen.

β-(N-Ethyl-N-β-hydroxyethylamino)-propionitrile.[7]—This nitrile was prepared in a manner similar to that above, with the exception that a slight excess of acrylonitrile was employed. The product distilled at 105° (0.2 mm.), $n^{25}D$ 1.4568.

Anal. Calcd. for $C_7H_{14}N_2O$: N, 19.71. Found: N, 19.56.

β-(N-n-Butyl-N-β-hydroxyethylamino)-propionitrile.[7]—This nitrile was prepared as above. The crude product after removal of excess acrylonitrile and any unreacted N-*n*-butylethanolamine was used directly in the next step.

Anal. Calcd. for $C_9H_{18}N_2O$: N, 16.46. Found: N, 16.35.

N-β-Hydroxyethyl-1,3-propanediamine.—The crude β-(2-hydroxyethylamino)-propionitrile was dissolved in 1.1 liters of ammoniacal ethanol (approx. 12%) and reduced in the presence of Raney nickel at 120° and an initial pressure of 1300 pounds. The product distilled at 92–94° at 0.3 mm., $n^{25}D$ 1.4844. The over-all yield from acrylonitrile was 270 g. (70%).

Anal. Calcd. for $C_5H_{14}N_2O$; N, 23.76. Found: N, 23.58.

N^1-Ethyl-N^1-β-hydroxyethyl-1,3-propanediamine.[8]—This diamine was prepared as above from the appropriate nitrile, b. p. 112° (0.6 mm.), $n^{25}D$ 1.4742.

Anal. Calcd. for $C_7H_{18}N_2O$: N, 19.16. Found: N, 19.00.

N^1-n-Butyl-N^1-β-hydroxyethyl-1,3-propanediamine.[8]—This compound distilled at 90–91° (0.3 mm.), $n^{20}D$ 1.4697.

Anal. Calcd. for $C_9H_{22}N_2O$: N, 16.08. Found: N, 16.09.

1-(N-n-Butyl-N-β-hydroxyethylamino)-4-pentanone.—A mixture of 30 g. of 1-chloro-4-pentanone and 58.5 g. of N-butylmonoethanolamine in 100 ml. of xylene was refluxed with stirring for three hours. The reaction mixture darkened and became turbid. On cooling, an oily crystalline solid separated which was filtered with suction. The filtrate was diluted with 100 ml. of ether and refiltered. After removing the solvents *in vacuo* on the steam-bath the residue was vacuum distilled. After a small amount of forerun was collected the main fraction distilled at 94–100° at 0.15 mm. Redistillation through an eight-inch Vigreux column gave 20 g. (40%) of a product which boiled at 94–96° (0.2 mm.), $n^{25}D$ 1.4569.

Anal. Calcd. for $C_{11}H_{23}NO_2$: N, 6.96. Found: N, 7.00.

1-(N-Ethyl-N-β-hydroxyethylamino)-4-pentanone.—This compound distilled at 85–87° at 0.4 mm., $n^{25}D$ 1.4583.

Anal. Calcd. for $C_9H_{19}NO_2$: N, 8.10. Found: N, 8.16.

N^1-n-Butyl-N^1-β-hydroxyethyl-1,4-pentanediamine.—The 1-(N-*n*-butyl-N-hydroxyethylamino)-4-pentanone (72 g.) was dissolved in 800 ml. of 17% ammoniacal methanol and reduced catalytically in the presence of Raney nickel at an initial pressure of one thousand pounds. The catalyst was filtered off and the filtrate evaporated on the steam-bath under slightly reduced pressure. The residue distilled at 101–106° at 0.3 mm.; yield 68 g. (96%). Redistillation through a Vigreux column gave a product boiling at 104–106° (0.35 mm.), $n^{25}D$ 1.4672.

Anal. Calcd. for $C_{11}H_{26}N_2O$: N, 13.85. Found: N, 13.53.

N^1-Ethyl-N^1-β-hydroxyethyl-1,4-pentanediamine.—The compound distilled at 93° at 0.6 mm., $n^{25}D$ 1.4703.

Anal. Calcd. for $C_9H_{22}N_2O$: N, 16.08. Found: N, 15.72.

7-Chloro-4-[4-(N-n-butyl-N-β-hydroxyethylamino)-1-methylbutylamino]-quinoline.—The following is the general procedure employed for the preparation of the compounds listed in Table I.

A mixture of 13.5 g. of 4,7-dichloroquinoline and 27 g. of N^1-*n*-butyl-N^1-β-hydroxyethyl-1,4-pentanediamine was heated with stirring for four hours at 150–170°.[9] After cooling, the reaction mixture was dissolved in 200 ml. of 25% acetic acid, filtered with charcoal, and treated with about 75 ml. of concentrated ammonium hydroxide. The thick oil which separated was extracted with chloroform and the combined extracts washed several times with water and dried over Drierite. After distilling off the chloroform the residue was heated at 160° at 0.2 mm. to remove any unreacted side chain.

The crude product (23.7 g.) was dissolved in hot ethylene dichloride, filtered with charcoal and the filtrate seeded.[10] The product was purified by recrystallization; yield 17.5 g., 71%.

7-Chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino)-1-methylbutylamino)-quinoline Diphosphate.—A mixture of 90 g. of 4,7-dichloroquinoline, 90 g. of phenol and 132 g. of N^1-ethyl-N^1-β-hydroxyethyl-1,4-pentanediamine was heated with stirring for eighteen hours at 125–130°. Methanol (1.9 liters) was added and the mixture was filtered with Norite. The filtrate was treated with the calculated amount of phosphoric acid in methanol solution and allowed to stand for two days. The solid diphosphate salt was filtered off, washed with methanol and dried; 101 g. (42%), m. p. 155–156°. Thirty grams of the base melting at 77–82° could be recovered from the filtrate.

The diphosphate salt was recrystallized by dissolving in 200 ml. of hot water and adding 600 ml. of ethanol. The product was dried at 100° for three hours; yield 85 g. (35%).

Acknowledgment.—The authors are indebted to Mr. M. E. Auerbach and Mr. K. D. Fleischer and staffs for the analytical data reported, and to Dr. E. W. Dennis and Dr. F. C. Goble for the chemotherapy reports.

Summary

The preparation of several basic side chains containing an N-alkylethanolamino group and their condensation with 4,7-dichloroquinoline is described.

One of the compounds, 7-chloro-4-[4-(N-ethyl-N-β-hydroxyethylamino-1-methylbutylamino]-quinoline appears to be a very promising antimalarial.

RENSSELAER, NEW YORK RECEIVED OCTOBER 28, 1949

(7) Ref. 4; only the analysis for the picrate is reported.

(8) Ref. 4; the amine was condensed directly with a substituted 9-chloroacridine. No analysis is reported.

(9) The reaction was considered to be complete when a sample of the reaction mixture dissolved in dilute nitric acid remained clear upon the addition of saturated sodium acetate solution.

(10) In most cases the seeds could be obtained by digesting a small sample of the crude product in either Skellysolve B or ether.