[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

The Synthesis of Some 7-Chloro-4-(3-alkylaminopropylamino)-quinolines[1]

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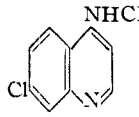
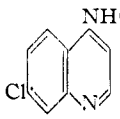
This paper reports the synthesis of a series of 7-chloro-4-(3-alkylaminopropylamino)-quinolines, of structure I, for testing as antimalarials.



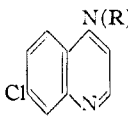
I



II

Investigation of this series was started when it was found that a metabolism product of 7-chloro-4-(3-diethylaminopropylamino)-quinoline (II) was probably the corresponding monoethyl compound I (R = C_2H_5). This compound was prepared, and was found to have a considerable degree of activity in avian malarial infections, so that the synthesis of a series of homolog was deemed advisable.

The compounds were all prepared by condensing the appropriate diamine, $H_2NCH_2CH_2CH_2NHR$, with 4,7-dichloroquinoline; there is of course a possibility that the alkylation might have occurred on the secondary nitrogen, to give compounds of type III. A decision between structures I and III could be made by a Hinsberg test or



III

by a Van Slyke amino nitrogen determination, since III should give a mole of nitrogen; such a determination was not carried out for lack of time, but the experience of other chemists who have found that 4,7-dichloroquinoline will not condense with a secondary amine under similar conditions supports structure I. Dr. Lyman C. Craig of Rockefeller Institute has examined a sample of the ethyl compound (R = C_2H_5) by the countercurrent extraction procedure and reports less than 3% inhomogeneity.[1a]

The diamines were prepared conveniently by the method of Holcomb and Hamilton,[2,3,4] which consists in addition of an amine to acrylonitrile, followed by catalytic reduction of the nitrile group.

$$RNH_2 + CH_2{=}CHCN \longrightarrow RNHCH_2CH_2CN \xrightarrow[Ni]{H_2} RNHCH_2CH_2CH_2NH_2$$

IV V

$$RNHCH_2CH_2CH_2NH_2 \longrightarrow RNCH_2CH_2CN \quad (IV)$$
$$\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad CONHC_6H_5 \quad (VI)$$

V

This reaction has usually been applied to secondary amines, but Whitmore[3] has made the compound from ethylamine, and there are a few scattered references in the patent literature to addition of primary amines to acrylonitrile, although the products are not well characterized.

The addition of the primary amines to acrylonitrile goes smoothly, without use of a catalyst, and our observations support Whitmore's statement that the addition is an equilibrium reaction. Even *t*-butylamine adds to acrylonitrile, although in somewhat lower yield than amines with a primary or secondary alkyl group; apparently the electron-repelling effect of the *t*-butyl group does not inactivate the hydrogens on the amino group enough to inhibit the addition reaction. This is the case, however, in the addition of alcohols to acrylonitrile to form β-alkoxypropionitriles; isopropyl alcohol gives poorer yields than primary alcohols[5] and *t*-butyl alcohol does not add at all.[6] The β-alkylaminopropionitriles IV were characterized by preparation of the phenylurea derivatives VI with phenyl isocyanate; these formed very readily in all cases except when R was *t*-butyl or cyclohexyl. In these cases, it was difficult to get a pure product with phenyl isocyanate, perhaps because of the readier dissociation of the nitrile IV into acrylonitrile and the primary amine and, since the usefulness of a derivative is slight unless it can be readily prepared, the reaction in these two cases was not pursued.

The reductions were carried out with Raney nickel at pressures of about 2500 lb. and at temperatures of 100–120°, using alcohol saturated with ammonia to repress the formation of secondary amine.[3,7] The reduction is usually complete in about fifteen minutes and the yields are good. The diamines were characterized as dipicrates.

The reaction of the diamines with 4,7-dichloroquinoline proceeded with vigorous evolution of heat at about 150°. The quinoline bases I were frequently difficult to purify to a constant melting point, because they rapidly formed hydrates of varying composition. The monosulfates ob-

(1) The work described in this paper was done under a contract recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Rochester.

(1a) Craig, private communication; *J. Biol. Chem.*, **155**, 519 (1944).

(2) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

(3) Whitmore, Mosher, Adams, Taylor, Chapin, Weisel and Yanko *ibid.*, **66**, 725 (1944).

(4) Wiedeman and Montgomery, *ibid.*, **67**, 1994 (1945).

(5) Utermohlen, *ibid.*, **67**, 1505 (1945).

(6) Bruson, *ibid.*, **64**, 2457 (1942); Bruson and Riener, *ibid.*, **64**, 2850 (1942).

(7) Schwoegler and Adkins, *ibid.*, **61**, 3499 (1939).

TABLE I

β-ALKYLAMINOPROPIONITRILES, $RNHCH_2CH_2CN$

R	Yield, %	B. p., °C.	Mm.	$n^{20}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3[a]	71	101–104[b]	49	1.4320[b]	$C_4H_8N_2$				
C_2H_5[a]	84	97–98[c]	30	1.4333[c]	$C_5H_{10}N_2$				
n-C_3H_7	92	119–121	30	1.4362	$C_6H_{12}N_2$	64.22	64.13	10.80	10.71
n-C_4H_9	98	104–106[d]	10	1.4392	$C_7H_{14}N_2$	66.62	66.48	11.20	11.28
s-C_4H_9	83	92–96[e]	10	1.4379[e]	$C_7H_{14}N_2$	66.62	66.43[e]	11.20	11.32
t-C_4H_9	56	81–83	10	1.4329	$C_7H_{14}N_2$	66.62	66.60	11.20	11.37
C_6H_{11}, cyclohexyl	92	122–124[f]	4	1.4764	$C_9H_{16}N_2$	70.98	71.03	10.61	10.52

[a] In the preparations of methyl- and ethylaminopropionitrile, 33% amine in water was used instead of the pure amine. After standing overnight, 150 g. of anhydrous potassium carbonate was added for every 180 g. of water present, and the mixture was shaken until all the solid had dissolved. The organic layer was then distilled to yield the desired product. [b] A. H. Cook and Reed, *J. Chem. Soc.*, 399 (1945), report b. p. 74° (16 mm.); $n^{15}D$ 1.4342. [c] Whitmore, *et al.* (ref. 3), report b. p. 92–95° (30 mm.); $n^{20}D$ 1.4318. [d] French Patent 742,358 (*C. A.*, **27**, 3483 (1933)) reports a b. p. of 114–116° (20 mm.); German Patent 598,185 (*C. A.*, **28**, 5474 (1934)) gives it as 114–116° (12 mm.). No other information is given. [e] A private communication from W. H. Jones, S. M. Nagy and Arthur C. Cope reports the foolwing: b. p. 95° (13.5 mm.); $n^{25}D$ 1.4340; d^{25}_{25} 0.8688; mol. wt., calcd., 126.2; found (glass electrode titration), 124.6. [f] French Patent 742,358 (*C. A.*, **27**, 3483 (1933)) reports b. p. 149–151° (11 mm.). The same value is given in German Patent 598,185 (*C. A.*, **28**, 5474 (1934)).

tained from them also formed hydrates in some instances which held water extremely tenaciously; the sulfates gave titration curves corresponding to one mole of sulfuric acid per mole of base I.

TABLE II

PHENYLUREA DERIVATIVES, $RNCH_2CH_2CN$ with $CONHC_6H_5$

R	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	93.5–94.5	$C_{11}H_{13}N_3O$	65.00	64.91	6.45	6.54
n-C_3H_7	81.5–82	$C_{13}H_{17}N_3O$	67.50	67.46	7.41	7.28
i-C_3H_7	126–126.5	$C_{13}H_{17}N_3O$	67.50	68.02	7.41	7.39
n-C_4H_9	132.5–134	$C_{14}H_{19}N_3O$	68.53	68.62	7.81	7.66
s-C_4H_9	127.5–128.5	$C_{14}H_{19}N_3O$	68.53	68.54	7.81	7.76

physical properties and analyses for the n-butyl compounds are given in the various tables.

n-Butylaminopropionitrile (IV, R = n-C_4H_9).—Acrylonitrile (24.2 g.) was added dropwise with stirring during ninety minutes to 50 g. of n-butylamine, the temperature being kept below 30° by a cold-water-bath. Stirring was continued for five hours after the addition was complete, the mixture was then refluxed on the steam-bath for ninety minutes and allowed to stand overnight. Vacuum distillation of the mixture yielded 55.4 g. (98%) of n-butylaminopropionitrile.

The **phenylurea derivatives** were best prepared by adding 1 cc. of phenyl isocyanate to 1 cc. of the nitrile dissolved in 10 cc. of petroleum ether; there was a vigorous reaction, and the product, if not crystalline immediately, became so on standing in the ice-box. The compounds were recrystallized from methanol–water or benzene–petroleum ether.

TABLE III

γ-ALKYLAMINOPROPYLAMINES, $RNHCH_2CH_2CH_2NH_2$

R	B. p., °C.	$n^{20}D$	Dipicrate M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	138–141[a]	1.4479	224.5–226.5[a]					
C_2H_5	150–151[b]	1.4455[b]	191–193[b]					
n-C_3H_7[c]	169–174	1.4460	166.5–167.5	$C_{18}H_{22}N_8O_{14}$	37.63	37.48	3.86	3.89
i-C_3H_7			185–186.5	$C_{18}H_{22}N_8O_{14}$	37.63	37.93	3.86	3.73
n-C_4H_9[d]	190–191	1.4490	150–151	$C_{19}H_{24}N_8O_{14}$	38.77	38.67	4.11	4.10
s-C_4H_9	178–186[e]	1.4480[e]	165–166	$C_{19}H_{24}N_8O_{14}$	38.77	38.63	4.11	4.18
t-C_4H_9[f]	170–173	1.4431	216–217	$C_{19}H_{24}N_8O_{14}$	38.77	38.87	4.11	3.80
C_6H_{11}[g], cyclohexyl	80 (0.5 mm.)	1.4820	182.5–183.5	$C_{21}H_{26}N_8O_{14}$	41.04	41.05	4.26	4.29

[a] v. Braun, *et al.*, *Ber.*, **70**, 979 (1937), report b. p. 138–139°; m. p. of picrate 227°. [b] Whitmore (ref. 3) reports b. p. 156° (735 mm.); $n^{20}D$ 1.4441; m. p. of picrate 193°. [c] *Anal.* of diamine: Calcd. for $C_6H_{16}N_2$: C, 62.01; H, 13.91. Found: C, 61.99; H, 13.81. [d] *Anal.* of diamine: Calcd. for $C_7H_{18}N_2$: C, 64.52; H, 13.95. Found: C, 64.61; H, 13.75. German Patent 598,185 (*C. A.*, **28**, 5474 (1934)) reports b. p. 60° (1 mm.). [e] See footnote *e*, Table I. From the same source the following data are reported for this compound, stated to be probably slightly impure on the basis of analyses: d^{25}_{25} 0.8345. Calcd. for $C_7H_{18}N_2$: C, 64.52; H, 13.95: mol. wt., 130.2. Found: C, 65.19; H, 13.93; mol. wt. (glass electrode titration), 130.8. [f] *Anal.* of diamine: Calcd. for $C_7H_{18}N_2$: C, 64.52; H, 13.95. Found: C, 64.62; H, 13.81. [g] *Anal.* of diamine: Calcd. for $C_9H_{20}N_2$: C, 69.16; H, 12.92. Found: C, 69.10; H, 12.90.

Experimental[8]

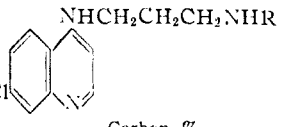
Experimental procedures were similar for all the compounds prepared, and are illustrated for the n-butyl series;

γ-n-Butylaminopropylamine (V, R = n-C_4H_9).—n-Butylaminopropionitrile (40 g.) was reduced in 150 cc. of alcohol saturated with ammonia, using Raney nickel at 120° and 2500 lb. of hydrogen; the reduction was complete in about fifteen minutes. The catalyst was removed by filtration, most conveniently with the use of Super-Filtrol, and the alcohol fractionated through a Vigreux column; 27.2 g. (66%) of the n-butylaminopropylamine was obtained. Yields for the reduction of the other nitriles ranged from about 55 to 70%. Analytical samples of the

(8) All melting points corrected; analyses by Dr. Carl Tiedcke, by Lois E. May and William Saschek of Columbia University, and the Micro-Tech Laboratories. We are indebted to Drs. R. C. Elderfield and W. J. Gensler of Columbia University for assistance in obtaining materials, and to Raymond Hasson for technical assistance.

TABLE IV

7-CHLORO-4-ALKYLAMINOPROPYLAMINOQUINOLINES



SN[a]	R	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
15,210	CH_3[b]	88.5–90.5	$C_{13}H_{16}N_3Cl\cdot H_2O$[c]	58.29	59.06	6.79	6.58
13,588	C_2H_5	80–83	$C_{14}H_{18}ClN_3\cdot H_2O$	59.67	60.67	7.15	7.47
4,034	n-C_3H_7	101–102.5	$C_{15}H_{20}ClN_3$	64.87	64.78	7.27	7.43
14,486	i-C_3H_7	98–100	$C_{15}H_{20}ClN_3\cdot H_2O$[d]	60.89	60.93	7.51	7.47
4,252	n-C_4H_9	100–103.5	$C_{16}H_{22}ClN_3$[e]	65.84	64.82	7.61	7.08
4,295	s-C_4H_9	96.5–98	$C_{16}H_{22}ClN_3$	65.84	64.50	7.61	7.13
15,294	t-C_4H_9	153–154	$C_{16}H_{22}ClN_3$	65.84	65.94	7.61	7.34
15,287	C_6H_{11}, cyclohexyl	109–112	$C_{18}H_{24}ClN_3$	68.01	67.91	7.63	7.54

[a] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these drugs will be tabulated in a forthcoming monograph. [b] Temperature of oil-bath during coupling was 135°. [c] Neut. equiv., calcd. for monohydrate, 140.9. Found: (from titration curve), 142.3. [d] The anhydrous drug and certain intermediates are described by D. E. Pearson, W. H. Jones and Arthur C. Cope, THIS JOURNAL, **68**, 1225 (1946). [e] Neut. equiv., calcd.: 145.9. Found (from titration curve), 157.

TABLE V

7-CHLORO-4-ALKYLAMINOPROPYLAMINOQUINOLINE MONOSULFATES

R	M. p., °C.[a]	Molecular[b] weight Calcd.	Molecular[b] weight Found	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
CH_3	230–232	347.9	346.8	$C_{13}H_{18}ClN_3O_4S$	44.87	44.40	5.23	5.46
C_2H_5	265–269	361.8	362.8	$C_{14}H_{20}ClN_3O_4S$	46.45	46.76	5.57	5.69
n-C_3H_7	271–274	375.8	371.2	$C_{15}H_{22}ClN_3O_4S$	47.94	47.75	5.91	6.05
i-C_3H_7	265–270	375.8	376	$C_{15}H_{22}ClN_3O_4S$	47.94	48.08	5.91	6.01
n-C_4H_9	278–286	389.8	393.4	$C_{16}H_{24}ClN_3O_4S$	49.28	48.93	6.22	6.35
s-C_4H_9	282–285	389.8	394.6	$C_{16}H_{24}ClN_3O_4S$	49.28	48.71	6.22	6.19
t-C_4H_9	250–252	389.8	402.0	$C_{16}H_{24}ClN_3O_4S$	49.28	49.23	6.22	6.47
C_6H_{11}, cyclohexyl	310–315	416.0	229.0	$C_{18}H_{26}ClN_3O_4S$	51.97	52.16[d]	6.31	6.57

[a] All of the salts melt with decomposition. [b] Molecular weights obtained by doubling the neutral equivalent, obtained from a titration curve using a *p*H meter. [c] This value was obtained after drying fourteen hours *in vacuo* at 140°; a sample dried two hours at 61° gave C, 43.25; H, 5.67. The salt contains somewhat less than one molecule of water of crystallization; calcd. water content of monohydrate: 4.9%; loss on drying to constant weight *in vacuo* at 140°: 3.2%. [d] Sample dried to constant weight at 140° *in vacuo*.

products of this and the preceding paragraph were obtained by fractionation in a small column under reduced pressure.

7-Chloro-4-(3-*n*-butylaminopropylamino)-quinoline (I, R = *n*-C_4H_9).—*n*-Butylaminopropylamine (24.7 g.) and 17.8 g. of 4,7-dichloroquinoline were placed in a 250 cc. three-neck flask fitted with a condenser and a mercury-seal stirrer, and heated in an oil-bath at 155°. After about fifteen minutes, a vigorous exothermic reaction occurred and it was necessary to cool the flask quickly with an ice-bath. After the reaction had subsided, heating at 155° was continued for five hours. An excess of 6 *N* sodium hydroxide was added and a copious yellow precipitate formed. The mixture was steam distilled until the odor of amine was no longer detectable in the distillate. The solid material was removed and washed with water. It was then dissolved in hot acetone, treated with anhydrous sodium sulfate and norite, and filtered. The crystals which formed on cooling melted at 91–101°. Four recrystallizations from acetone yielded 13.4 g. (51.3%) of 7-chloro-4-(3-*n*-butylaminopropylamino)-quinoline, m. p. 100–103.5°.

The other quinoline bases were likewise purified by repeated recrystallizations from acetone, in which 4,7-dichloroquinoline is very soluble; other solvents proved less useful.

7-Chloro-4-(3-*n*-butylaminopropylamino)-quinoline Monosulfate.—7-Chloro-4-(3-*n*-butylaminopropylamino)-quinoline (21.7 g.) was dissolved in 100 cc. of absolute alcohol and 23 cc. of 6 *N* sulfuric acid was added with cooling, which formed a copious white precipitate of the monosulfate. Water (65 cc.) was added so that all the solid was in solution at the boiling point of the mixture. On cooling, the monosulfate was again precipitated. This was recrystallized four times from a mixture of 75 cc. of alcohol and 50 cc. of water. The purified compound was dried at 115° in an oven overnight and yielded 20.5 g. (72.7%) of the dry monosulfate.

The following are the ratios of alcohol: water used to recrystallize the various compounds: CH_3, 35:30; C_2H_5, 75:30; *n*-C_3H_7, 65:30; *i*-C_3H_7, 50:30; *s*-C_4H_9, 45:30; *t*-C_4H_9, 20:30.

Summary

A series of eight 7-chloro-4-(3-alkylaminopropylamino)-quinolines and their sulfates has been prepared for testing as antimalarial agents; the alkyl derivatives made were the methyl, ethyl, *n*- and *i*-propyl, *n*-, *s*- and *t*-butyl, and cyclohexyl. The intermediates employed were the β-alkylaminopropionitriles, characterized as phenylurea derivatives, and the γ-alkylaminopropylamines, characterized by formation of the dipicrates. Most of the intermediates and the final compounds are new.

ROCHESTER, NEW YORK RECEIVED APRIL 5, 1946