TABLE I

PREPARATION AND PROPERTIES OF 4-AMINOBENZO(h)QUINOLINES

Product Benzo(h)quinoline	Condensation conditions Time	Temp., °C.	Yield, %	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
4-Benzylamino-	5	165	81	154.5–155.5	84.47	84.29	5.67	5.46
4-(4-Diethylaminobutylamino)-	10	165	55	73–75[a]	78.46	78.41	8.47	8.37
4-(3-Diethylaminopropylamino)-	8	165	81.5	60.5–62.5[b]	78.13	78.02	8.20	8.19
4-N-Morpholino-	7	130	48	98–100	77.24	77.02	6.10	5.86
4-(3-N-Morpholinopropylamino)-	9	170	31	122–123	74.73	74.53	7.21	7.58
4-N-Piperidino-	10	105	61	85–86	82.40	82.62	6.92	6.66

[a] Crystallized from aqueous alcohol, probably as a hydrate. Drying *in vacuo* resulted in a 6.3% loss in weight. [b] Crystallized from aqueous alcohol, probably as a hydrate. Drying *in vacuo* resulted in a 5.1% loss in weight and the formation of an oil, which was analyzed.

was refluxed for forty-five hours. The insoluble material present at this time was crystallized from alcohol; it was only partially soluble in this solvent. Unchanged chloro compound, 1.25 g., m. p. 88.5–89.5°, was recovered from the alcohol. The insoluble residue, 0.27 g., was 4-hydroxybenzo(h)quinoline; m. p. 238–241°. The aqueous reaction medium, when made basic, yielded no condensation product.

An attempted condensation in alcoholic alkali yielded only 4-ethoxybenzo(h)quinoline.

The chloro compound, 2.13 g., was mixed with 3 ml. of the diamine, and 0.56 g. of potassium hydroxide in 60 ml. of absolute alcohol. The mixture was refluxed for ninety-six hours. By this time, 0.55 g. of potassium chloride had separated. More potassium hydroxide (0.2 g.) and amine (2 ml.) were added and the solution was refluxed for forty-eight hours; 0.1 g. of additional potassium chloride was isolated. The reaction mixture was poured into water, and the solid which separated was crystallized from alcohol, in which it was completely soluble. The 4-ethoxybenzo(h)quinoline crystallized as colorless needles, m. p. 119–120°; yield, 1.2 g., (54%).

Anal. Calcd. for $C_{15}H_{13}ON$: C, 80.69; H, 5.87. Found: C, 80.54; H, 5.93.

1-(4-Diethylamino-1-methylbutylamino)-benzo(f)quinoline.—In a similar manner, 1-chlorobenzo(f)quinoline was condensed with 4-amino-1-diethylaminopentane by heating their mixture at 175–185° for seven hours. The yield of pure base distilling at 187–188.5° (0.14 mm.) was 47.5%.

Anal. Calcd. for $C_{22}H_{29}N_3$: C, 78.76; H, 8.71; N, 12.53. Found: C, 78.42; H, 8.88; N, 12.23.

This product also was converted to a phosphate salt.

The preparation and properties of other 4-aminobenzo(h)quinolines obtained are summarized in the accompanying table.

Summary

4-Chlorobenzo(h)quinoline and 1-chlorobenzo(f)quinoline have been prepared by an extension of the Price-Roberts synthesis of quinolines, employing ethyl ethoxymethylenemalonate. The first compound was also prepared by the ethyl ethoxalylacetate method.

These active chloro compounds have been condensed with several amines to yield nine products of possible pharmaceutical value.

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NOTE

Preparation of 7-Chloro-4-(2-piperidylmethylamino)-quinoline[1]

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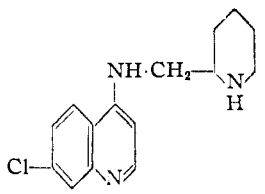
Antimalarials having a 4-amino-7-chloroquinoline nucleus and a basic side chain attached to the 4-amino group have been extensively investigated of late. In this report the preparation of 7-chloro-4-(2-piperidylmethylamino)-quinoline (I) is reported and a description is included of an unsuccessful attempt to obtain 7-chloro-4-[1-methyl-2-(2-piperidyl)-ethylamino]-quinoline through the condensation of 7-chloroquinoline-4-sulfonic acid with 1-(N-acetyl-2-piperidyl)-2-aminopropane.



I

2-Aminomethylpiperidine was prepared in good yield by reduction of 2-cyanopyridine with chromous acetate by the method of Graf[2] followed by catalytic hydrogenation of the pyridine nucleus. The method of Reihlen, *et al.*,[3] for the complete catalytic hydrogenation of 2-cyanopyridine in acetic anhydride gave yields of less than twenty per cent.

The condensation of 2-aminomethylpiperidine with 4,7-dichloroquinoline was carried out by a modification of a procedure reported by Drake *et al.*,[4] to give I in excellent yield. That the condensation took place as indicated and not on

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

(2) Graf, *J. prakt. Chem.*, **140**, 39 (1934); **146**, 88 (1936).

(3) Reihlen, Hessling, Hühn, Weinbrenner, *Ann.*, **493**, 20 (1932).

(4) Drake, *et al.*, THIS JOURNAL, **68**, 1208 (1946).

secondary piperidine nitrogen is highly probable on the basis of the experience of Tarbell and co-workers[5] to the effect that in similar reactions a primary amine condenses with dichloroquinoline in preference to a secondary amine.

Experimental[6]

2-Aminomethylpiperidine.—The theoretical amount of hydrogen was absorbed in ten hours when 4.2 g. of 2-aminomethylpyridine[2] in 15 ml. of acetic acid was hydrogenated at 2-3 atm. and 25° using Adams catalyst. The filtered and cooled solution was basified with 5 *N* sodium hydroxide and extracted with chloroform. The dried solution was distilled to give 2.7 g. (61%) of colorless liquid, b. p. 80–81° (18 mm.).

Anal. Calcd. for $C_6H_{14}N_2$: eq. wt., 57. Found: eq. wt., 61.

7-Chloro-4-(2-piperidylmethylamino)-quinoline (I) (SN 9212).[7]—A suspension of 4.7 g. (0.024 mole) of 4,7-dichloroquinoline[8] in 2.7g. (0.024 mole) of 2-aminomethylpiperidine was gradually heated to 145° in an oil-bath. The temperature of the reacting mixture was maintained below 150° by periodic cooling. Without this precaution the temperature rose beyond control and a smaller yield resulted. A cooled solution of the viscous product in 5% acetic acid was basified with 4 *N* potassium hydroxide and the liberated product taken up in chloroform. The solution was dried and evaporated to give a crystalline residue which was recrystallized from benzene. A yield of 6.3 g. (96%), m. p. 155–156°, was obtained.

Anal. Calcd. for $C_{15}H_{18}N_3Cl$: C, 65.32; H, 6.58. Found: C, 65.69; H, 6.81.

The free base was converted to a colorless dihydrochloride monohydrate, m. p. 292–294° dec.

Anal. Calcd. for $C_{15}H_{18}N_3Cl\cdot 2HCl\cdot H_2O$: eq. wt., 183. Found: eq. wt., 180 ($AgNO_3$ titration).

After drying at 110° *in vacuo* the anhydrous salt was obtained.

Anal. Calcd. for $C_{15}H_{18}N_3Cl\cdot 2HCl$: eq. wt., 174. Found: eq. wt., 171.

2-Bromo-1-(2-piperidyl)-propane Hydrobromide.—The method of Löffler and Kirschner[9] was modified by treating 1-(2-piperidyl)-2-propanol with 57% hydrobromic acid at 125° for ten hours to give a 65% yield of colorless needles, m. p. 163–166°. When recrystallized from absolute ethanol and ether a sample melted at 171–171.5° whereas Löffler and Kirschner report 148-150°.

Anal. Calcd. for $C_8H_{16}NBr\cdot HBr$: C, 33.46; H, 5.97. Found: C, 33.77; H, 6.41.

7-Chloroquinoline-4-sulfonic Acid.—To a solution of 4.1 g. (0.032 mole) of sodium sulfite in 35 ml. of water was added 3.2 g. (0.016 mole) of 4,7-dichloroquinoline and 3.0 ml. (0.019 mole of HCl) of 6 *N* hydrochloric acid. The mixture was refluxed for an hour at which time the solution had become clear. The warm solution was acidified with 10 ml. of concentrated hydrochloric acid to give a flocculent precipitate of needles. The precipitate was collected, washed with 6 *N* hydrochloric acid and dried *in vacuo* at 110° to yield 3.4 g. (86%) of product. A small sample, recrystallized by dissolving in concentrated hydrochloric acid and adding an equal volume of water gave needles of m. p. 345–347° (dec.).

Anal. Calcd. for $C_9H_6NSClO_3$: eq. wt., 243.5. Found: eq. wt., 245.5.

1-(N-Acetyl-2-piperidyl)-2-aminopropane.—Isopelletierine, prepared by the method of Meisenheimer and Mahler,[10] was acetylated with acetic anhydride and the product distilled to give N-acetylisopelletierine, b. p. 133–135° (3 mm.) in 78% yield (based on the 1-(2-piperidyl)-2-propanol used). The oxime had m. p. 132–136° and the phenylhydrazone was obtained in 74% yield as colorless crystals, m. p. 124–125°. The hydrogenation of 10 g. of phenylhydrazone in 50 ml. of acetic acid proceeded rapidly at 25° and three atmospheres pressure in the presence of Adams catalyst. After reduction the solution was filtered and excess 6 *N* sodium hydroxide added in the cold. The resulting oil was taken up in ether, dried and distilled to give 6.2 g. (92%) of the desired amine, b. p. 126° (2 mm.).

Anal. Calcd. for $C_{10}H_{20}N_2O$: eq. wt., 184. Found: eq. wt., 190.

The picrate, recrystallized from ethanol, melted at 205–206°.

Anal. Calcd. for $C_{16}H_{23}N_5O_8$: C, 46.48; H, 5.62. Found: C, 46.50; H, 5.69.

The condensation of 7-chloroquinoline-4-sulfonic acid with 1-(N-acetyl-2-piperidyl)-2-aminopropane with water as solvent and copper bronze as catalyst followed by acid hydrolysis did not give the desired 7-chloro-4-[1-methyl-2-(2-piperidyl)-ethylamino]-quinoline.

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(5) Tarbell, *et al.*, THIS JOURNAL, **68**, 1217 (1946).

(6) All melting points are corrected.

(7) The Survey number, designated SN, identifies a drug in the Records of the Survey of Antimalarial Drugs. The antimalarial activities of those compounds to which Survey numbers have been assigned will be tabulated in a forthcoming monograph.

(8) The 4,7-dichloroquinoline used in these experiments was kindly supplied by Dr. R. C. Elderfield of Columbia University.

(9) Löffler and Kirschner, *Ber.*, **38**, 3337 (1905).

(10) Meisenheimer and Mahler, *Ann.*, **462**, 301 (1928).