Anal. Calcd. for $C_{15}H_{20}ClN_3O$: Cl, 12.1; N, 14.3; Found: Cl, 12.0; N, 14.4.

Reduced Mannich Product Derived from V.—The Mannich product was hydrogenated in the usual manner with palladized charcoal catalyst at two atmospheres for two hours using methanol as a solvent. The product after vacuum drying at 50° was a very hygroscopic yellow plastic solid which gave no definite melting point.

The dipicrate of the amino alcohol was prepared from the ethereal solutions of both the free base and picric acid, m. p. 92–94°.

Anal. Calcd. for $C_{27}H_{27}N_9O_{15}$: C, 45.2; H, 3.79; N, 17.6. Found: C, 45.6; H, 3.81; N, 17.3.

Summary

Directions for the synthesis of methyl 2,4-dimethyl-8-quinazolyl ketone and 4-hydroxy-8-quinazoline carboxylic acid from 2-nitroisophthalic acid are given.

CORVALLIS, OREGON RECEIVED MAY 4, 1948

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

Quinolines VI. Some 4-Aminoquinoline Derivatives

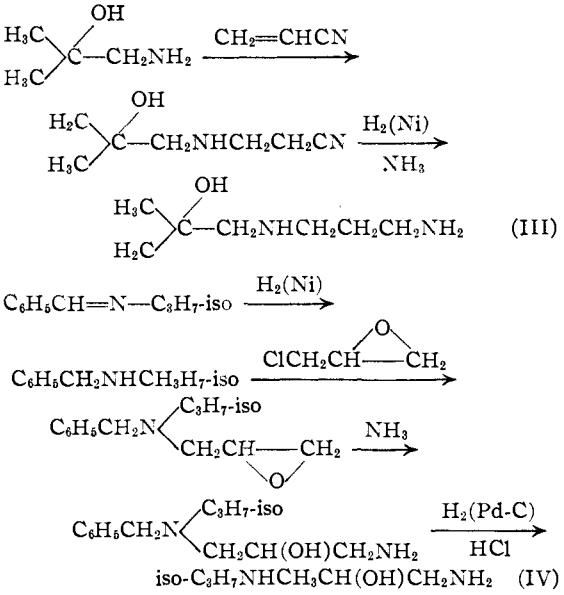
BY EDGAR A. STECK, LOUIS L. HALLOCK[1] AND C. M. SUTER

As has been well indicated in a monograph on the subject, a considerable portion of recent research on antimalarials has centered about 4-aminoquinoline derivatives,[2] chloroquine[3] (7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline[4–6] being the most important member of the series. The work described here was planned to determine certain aspects of the influence of structure upon activity in new 4-aminoquinoline types. Most of the compounds here reported bear an hydroxyl group in the basic side chain, as indicated in Table I.

The preparation of 4-(4-diethylamino-1-methylbutylamino)-quinoline has been mentioned in the patent literature,[7,8] but was synthesized from 4-chloroquinoline and 4-diethylamino-1-methylbutylamine (I) for purposes of comparison with related types and given the designation SN-6732.[2]

A number of amines were desired for reaction with 4,7-dichloroquinolines[5]; these included 3-isobutylaminopropylamine (II), 3-(2-hydroxy-2-methylpropylamino)-propylamine (III), 2-hydroxy-3-isopropylaminopropylamine (IV) and 2-(2-hydroxyethylamino)-ethylamine (V). Since only the last-mentioned of these was commercially available, the others were synthesized according to the equations.

$$CH_2{=}CHCN \xrightarrow{\text{iso-}C_4H_9NH_2} \text{iso-}C_4H_9NHCH_2CH_2CN \xrightarrow[NH_3]{H_2(Ni)} \text{iso-}C_4H_9NHCH_2CH_2CH_2NH_2 \quad (II)$$



(III)

(IV)

4,7-Dichloro-3-methylquinoline[9] was readily obtainable, but 4,7-dichloro-6-methylquinoline had to be prepared for reaction with 4-diethylamino-1-methylbutylamine (I). The application of recent modifications[10,11] of the Conrad–Limpach synthesis[12] to 4-amino-2-chlorotoluene gave satisfactory results. The products obtained in the synthesis were apparently free of isomeric compounds which might have been formed during the cyclization. Since this was true, it was assumed that the quinolines produced were all 6,7-disubstituted rather than the alternative 5,6-type. These assumptions are in harmony with earlier work using ethyl ethoxymethylenemalonate in the preparation of related quinoline types.[11,13]

Of all the 4-aminoquinoline derivatives prepared in this investigation, the one having the most prom-

(1) Present address: Commercial Solvents Corp., Terre Haute, Ind.

(2) Wiselogle, editor, "Antimalarial Drugs, 1941–1945," Edwards Bros., Ann Arbor, Mich. All drugs identified by Survey Numbers (SN) in the files of the Antimalarial Survey office have been tabulated, together with antimalarial activities, in this monograph.

(3) Loeb, *et al.*, *J. Am. Med. Assoc.*, **130**, 1069 (1946).

(4) Andersag, Breitner and Jung, U. S. Patent 2,233,970.

(5) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(6) Designated as SN-7618 by the Antimalarial Survey.[2]

(7) Zerweck and Kunze, German Patent 615,184; *Frdl.*, **22**, 485 (1939).

(8) Eli Lilly and Co., Brazilian Patent 35,166; *Diario Oficial (Brasil)* 934 (1945).

(9) Steck, Hallock and Holland, THIS JOURNAL, **68**, 380 (1946).

(10) Gould and Jacobs, *ibid.*, **61**, 2890 (1939).

(11) Price and Roberts, *ibid.*, **68**, 1204 (1946).

(12) Conrad and Limpach, *Ber.*, **20**, 944 (1887); Limpach, *ibid.*, **64**, 969 (1931).

(13) Riegel, *et al.*, THIS JOURNAL, **68**, 1264 (1946).

ising antimalarial activity was 7-chloro-4-(4-diethylamino - 1 - methylbutylamino) - 6 - methylquinoline. The high toxicity, however, caused it to be low in therapeutic index. It does not appear that the combined structural features of compounds herein studied result in satisfactory antimalarial activity.

Experimental[14]

A. 4-Chloroquinolines

4-Chloroquinoline.—4-Hydroxyquinoline was prepared by a slight modification[15] of the original Conrad–Limpach reaction [12,16] and interacted with phosphorus oxychloride.[17]

4,7-Dichloroquinoline and 4,7-Dichloro-3-methylquinoline.—These compounds were available from earlier work in these laboratories.[5,9]

4,7-Dichloro-6-methylquinoline.—4-Amino-2-chlorotoluene[18] was interacted with an equivalent amount of ethyl ethoxymethylenemalonate[19] by refluxing in an equal volume of methylene chloride for eight hours. Removal of the solvent left the anil in 96–99% yield; when crystallized from Skellysolve C the white needles so obtained melted at 74.5–75°.

Anal. Calcd. for $C_{15}H_{18}ClNO_4$: C, 57.78; H, 5.82; N, 4.49. Found: C, 57.67; H, 5.93; N, 4.68.

The cyclization of the anil to the quinoline ester was accomplished by adding it to four volumes of either mineral oil at 270–275° or refluxing Dowtherm A.[11,15] Crude yields of 88–92% of the ester resulted and were used directly for subsequent reactions. A sample was crystallized from nitrobenzene for analysis; white needles, m. p. >280°.

Anal. Calcd. for $C_{13}H_{12}ClNO_3$: C, 58.76; H, 4.55; N, 5.27. Found: C, 58.64; H, 4.79; N, 5.39.

Hydrolysis of the ester to the corresponding acid was accomplished with boiling 10% sodium hydroxide[9,11]; the yields were nearly quantitative and the product could be used directly. An analytical sample was prepared by crystallization from 2-methyl-2,4-pentanediol, from which the material separated in the form of creamy white microcrystals, m. p. >280°.

Anal. Calcd. for $C_{11}H_8ClNO_3$: C, 55.49; H, 3.39; N, 5.91. Found: C, 55.39; H, 3.47; N, 6.26.

The acid could be decarboxylated to 7-chloro-4-hydroxy-6-methylquinoline in refluxing Dowtherm A,[15] but considerable acid was recovered. Use of mineral oil (four volumes) at 280–285° was somewhat better. Yields of 77–81% were obtained with a recovery of 5–9% of the acid. The method of Riegel, *et al.*[17,20] was not tried. A sample crystallized from ethanol in the form of creamy needles, m. p. 280°.

Anal. Calcd. for $C_{10}H_7ClNO$: N, 7.27. Found: N, 7.51.

Preparation of 4,7-dichloro-6-methylquinoline from the 4-hydroxy compound was accomplished in yields of 92–95% by use of boiling phosphorus oxychloride. The purification from Skellysolve B gave snowy-white needles, m. p. 109–109.5°.

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.87; H, 3.34; N, 6.63. Found: C, 56.79; H, 3.19; N, 6.76.

(14) All melting points are corrected for thermometer emergence, whereas boiling points are not.

(15) Steck, Hallock and Holland, THIS JOURNAL, **68**, 1241 (1946); Price, Leonard and Reitsema, *ibid.*, **68**, 1258 (1946).

(16) Cavallito and Haskell, *ibid.*, **66**, 1166 (1944).

(17) Riegel, *et al.*, *ibid.*, **68**, 1264 (1946); Skraup, *Monatsh.*, **10**, 730 (1889).

(18) An intermediate in the synthesis of Atabrine (registered mark of Winthrop-Stearns, Inc. for its brand of Quinacrine), redistilled before use.

(19) Claisen and Haase, *Ann.*, **297**, 76 (1897).

(20) Baker, Lappin, Albisetti and Riegel, THIS JOURNAL, **68**, 1267 (1946).

B. Side Chains

3-Isobutylaminopropylamine (II).—The reaction of equivalent amounts of isobutylamine and acrylonitrile at 10° was carried out somewhat as described for *n*-butylamine.[21] An 85% yield of colorless 2-isobutylaminopropionitrile was obtained by fractionation; b. p. 78–79° (6 mm.), $n^{20}D$ 1.4347.

Anal. Calcd. for $C_7H_{14}N_2$: N, 22.20. Found: N, 22.20.

Reduction of the nitrile in ammoniacal alcohol was accomplished with Raney nickel catalyst at 110° under a hydrogen pressure of 2350 lb./sq. in. This is after the procedure employed by Huber[22] and Whitmore[23] on similar compounds. Upon fractionation, the 3-isobutylaminopropylamine (II) was secured in 56% yield; b. p. 57–58° (6 mm.), $n^{20}D$ 1.4440. The still residues, which contained secondary amine types, were neglected.

Anal. Calcd. for $C_7H_{18}N_2$: N, 21.52; neut. equiv., 65.1. Found: N, 21.30; neut. equiv., 64.9.

3-(2-Hydroxy-2-methylpropylamino)-propylamine (III).—Seventy-five grams (1.4 moles) of acrylonitrile was stirred well during the addition of 130 g. (1.46 moles) of 2-hydroxy-2-methylpropylamine[24,25] below 40°. The mixture was set aside overnight, after chilling several hours, and rectified. An 86.5% yield of colorless 3-(2-hydroxy-2-methylpropylamino)-propionitrile was collected at 94–96° (1 mm.); $n^{20}D$ 1.4562.

Anal. Calcd. for $C_7H_{14}NO$: N, 19.70. Found: N, 19.63.

The aforementioned nitrile was reduced slowly to 3-(2-hydroxy-2-methylpropylamino)-propylamine (III) in ammoniacal alcohol with Raney nickel at 120° and 2300 lb./sq. in. hydrogen pressure. A yield of 44–50% of product boiling at 70–72° (2 mm.) was secured: $n^{20}D$ 1.4700.

Anal. Calcd. for $C_7H_{18}N_2O$: N, 19.16; neut. equiv., 73.11. Found: N, 18.87; neut. equiv., 73.10.

2-Hydroxy-3-isopropylaminopropylamine (IV).—Benzylideneisopropylamine was prepared in the manner employed by Zaunschirm[26] for benzylidenepropylamine. The compound (b. p. 60–61° (1 mm.); $n^{25}D$ 1.5230) gave equally satisfactory results whether purified or reduced directly in alcoholic solution with Raney nickel catalyst at 90° (450 lb./sq. in. pressure of hydrogen). An over-all yield of benzylisopropylamine was 75–79%; b. p. 45–46° (1 mm.), $n^{25}D$ 1.5010.

Anal. Calcd. for $C_{10}H_{15}N$: neut. equiv., 149.2. Found: neut. equiv., 150.0.

When 0.6 mole of benzylisopropylamine was mixed with 0.67 mole of *epi*-chlorohydrin and heated at 85° with stirring, the exothermic reaction maintained that temperature for one hour. The reaction mixture was heated at 85–90° for an additional three hours, then set aside for a day. The crude product was shaken with 100 cc. of 20% sodium carbonate solution; the organic layer was then stirred one hour with 150 cc. of 35% sodium hydroxide solution and extracted with ether. Fractional distillation of the extracts (dried over potassium carbonate) gave 70–74% yields of benzylmethyloxiranylisopropylamine; b. p. 92–96° (0.2 mm.), $n^{25}D$ 1.5138.

Anal. Calcd. for $C_{13}H_{19}NO$: N, 6.82. Found: N, 6.68.

A mixture of 95.5 g. (0.47 mole) of epoxide, 125 g. of ammonia and 500 cc. of absolute alcohol was shaken at 100° for three hours, then the solvent removed. The residue (100 g.) was evaporatively distilled at 0.003 mm. with a bath at 135° and the crude product crystallized from

(21) Hoffmann and Jacobi, German Patent 598,185, *Frdl.*, **20**, 346 (1935).

(22) Huber, THIS JOURNAL, **66**, 876 (1944).

(23) Whitmore, *et al.*, *ibid.*, **66**, 725 (1944).

(24) Krassuski, *J. Russ. Phys.-Chem. Soc.*, **40**, 168 (1908).

(25) Boiling point 64–66° (10 mm.); $n^{20}D$ 1.4450.

(26) Zaunschirm, *Ann.*, **245**, 282 (1888).

TABLE I

4-AMINOQUINOLINE DERIVATIVES

Quinoline nucleus	Side chain in position 4[a]	Yield, %	Appearance	Solvent[b]	M. p., °C.	Analyses, % Calcd. C or Cl	Calcd. H	Calcd. N	Found C or Cl	Found H	Found N
Unsubstituted[c]	I	78	White needles	Sa	76–77	75.74	9.58	14.72	75.70	9.49	14.80
7-Chloro	II	86	White needles	Sc	102.5–103	12.15		14.40	11.98		14.25
7-Chloro	III	71	White needles	Ac	146–146.4	11.52		13.65	11.44		13.51
7-Chloro	IV	80	Creamy microcryst.	Ac	161–161.8	12.07		14.30	12.09		14.39
7-Chloro[d]	V	74	White needles	Ea	139–139.5	58.75	6.07	15.81	59.04	5.91	15.75
3-Methyl-7-chloro[e]	V	82	Pale yell. needles	E	222.5–223	20.68[f]		15.02	20.49[f]		15.29
6-Methyl-7-chloro	I	76	Creamy needles	Sb	129–129.6	68.40	8.40	12.62	68.29	8.22	12.47

[a] Same designations as in text. [b] Legend: Ac = acetone; E = ethanol; Ea = ethyl acetate; Sa, Sb, and Sc = Skellysolve A, B and C. [c] Cf. refs. 7 and 8. Tested as the methane bis-1,1′(2-hydroxy-3-naphthoate); yellow powder, m. p. >300°. *Anal.* Calcd. for $C_{18}H_{27}N_3 \cdot C_{23}H_{16}O_6$: base, 42.36; acid, 57.64. Found: base, 41.6; acid, 57.1; H_2O, 0.98. Given the designation SN-6732.[2] [d] Tested as the dihydrochloride monohydrate: white needles from ethanol, m. p. 239.5–240°. *Anal.* Calcd. for $C_{13}H_{16}ClN_3O \cdot 2HCl \cdot H_2O$: Cl^-, 20.45; H_2O, 5.05. Found: Cl^-, 20.58; H_2O, 4.93. Designated as SN-12,309.[2] [e] The base was oily; data given are the dihydrochloride, which was prepared from the crude base in alcohol–ether. [f] Ionic chlorine only.

Skellysolve B. The yield of 3-benzylisopropylamino-2-hydroxypropylamine was 60.8 g. (59%); m. p. 59–60°.

Anal. Calcd. for $C_{13}H_{22}N_2O$: neut. equiv., 111.2. Found: neut. equiv., 112.7.

One hundred grams (0.45 mole) of benzylamino compound was dissolved in warm alcohol and acidified with concd. hydrochloric acid. To the diamine hydrochloride there was added a slurry of 10% palladium–charcoal catalyst, prepared from 1.0 g. of palladium chloride, in alcohol. The mixture was diluted with alcohol to a volume of 500 cc. and reduced at 75° under a hydrogen pressure of 500 lb./sq. in. (*cf.* ref. 27). Upon completion of the reduction in two hours, the solvent was removed and the residue dissolved in water. The 2-hydroxy-3-isopropylaminopropylamine (IV) was liberated by basification, extracted with ether and dried over potassium carbonate. The base was obtained as a colorless, viscous liquid which boiled at 78–80° (2 mm.), $n^{25}D$ 1.4680. The yield was 49.1 g. (82.6%).

Anal. Calcd. for $C_9H_{16}N_2O$: N, 21.19; neut. equiv., 66.1. Found: N, 20.86; neut. equiv., 66.3.

C. 4-Aminoquinoline Derivatives

The reaction of the 4-chloroquinoline types with the requisite amino compound was carried out in phenol,[28] using sodium iodide as a catalyst. It was found to be most expedient to remove excess side chain by distillation with steam. The 4-aminoquinolines prepared are listed with pertinent data in Table I.

Acknowledgment.—The authors are indebted to Mr. M. E. Auerbach and his staff for the analyses recorded. To Mr. E. V. Ryan, Mrs. C. E. Dzembo and Mrs. M. S. Hawn we express appreciation for technical assistance.

Summary

Several aliphatic diamines were prepared for use in the synthesis of possible antimalarials of the 4-aminoquinoline type. The presence of a terminal secondary amino or an hydroxyl group was not a therapeutically satisfactory modification for the basic side chain in position 4 of the 7-chloroquinoline nucleus. Alkylation of the benzenoid or pyridine ring in that type was not desirable.

(27) Baltzly and Buck, THIS JOURNAL, **65**, 1984 (1943).

(28) Steck, Hallock and Holland, *ibid.*, **68**, 129 (1946).

RENSSELAER, N. Y. RECEIVED JUNE 25, 1948

[CONTRIBUTION FROM STERLING-WINTHROP RESEARCH INSTITUTE]

The Preparation of Some Amides of 4,6-Diaminoquinaldine[1]

BY MARGARET G. PRATT AND S. ARCHER

Over ten years ago several patents[2] appeared which indicated that derivatives of 4,6-diaminoquinaldine were useful as chemotherapeutic agents. In a short review which summarized his work up to that time, Jensch[3] pointed out that certain diamides were particularly useful in combating some tropical diseases which have hitherto resisted conquest. Since very few chemical or pharmacological data have appeared in the literature, it seemed of interest to prepare some malonamides and related compounds for chemotherapeutic study.

The 4,6-diaminoquinaldine, V, needed for this work was prepared according to the scheme shown.

Substance V had previously been reported by Jensch[2] and, after most of this work had been completed, in a Department of Commerce report.[4] Jacini,[5] Kermack[6] and Rubtsov[7] have carried out the ring closure of the anilinocrotonate, I.

(1) A part of this paper was presented before the Medicinal Division of the American Chemical Society at the Chicago meeting in September, 1946.

(2) Jensch, U. S. Patents 2,034,983, 2,050,971, 2,066,730, 2,092,352, 2,118,244.

(3) Jensch, *Angew. Chem.*, **50**, B91 (1937).

(4) Report No. PB-981, Office of the Publication Board, Department of Commerce, Washington, D. C.

(5) Jacini, *Gazz. Chim. Ital.*, **71**, 53 (1941).

(6) Kermack, *J. Chem. Soc.*, 563 (1939).

(7) Rubtsov and Bunina, *C. A.*, **40**, 7194 (1946).