caution. The solution was made alkaline by the addition of about 60 ml. of 12 *N* sodium hydroxide, the precipitate collected, washed with water, and dried. The yield of crude product, was 7.6 g. or 59.9% of the theoretical amount.

After several recrystallizations from alcohol the 4,7-dichloro-8-methylquinoline melted at 87–89°.

Anal. Calcd. for $C_{10}H_7Cl_2N$: C, 56.62; H, 3.33; N, 6.60; Cl, 33.36. Found: C, 56.53; H, 3.37; N, 6.44; Cl, 33.29.

7-Chloro-8-methyl-4-(1-ethyl-4-piperidylamino)-quinoline.—Fifteen grams (0.0707 mole) of 4,7-dichloro-8-methylquinoline, 9.1 g. (0.0708 mole) of 1-ethyl-4-aminopiperidine, and 6.65 g. (0.708 mole) of phenol were heated for one-half hour at 100–160° and for twelve hours at 160–165°. During this period of heating the reaction mixture was agitated by a stream of nitrogen.

After the reaction mixture had cooled, it was poured into a solution of 60 ml. of 4 *N* hydrochloric acid. The red-brown solution was treated with Darco and filtered. It was then made alkaline with sodium hydroxide solution (15 g. in 50 ml. of water).

A yellow oil was obtained, which after it had been stirred for about fifteen minutes, solidified to a white granular solid. The crude product was recrystallized from benzene and a white, microcrystalline solid (m. p. 200–202°) was obtained. The yield was 15.9 g. or 73.8% of the theoretical amount.

To purify a sample for analysis and pharmacological testing it was necessary to recrystallize the material several times from benzene and then to allow it to stand in ether for an extended period of time to ensure complete removal of benzene from the product.

Anal. Calcd. for $C_{17}H_{22}ClN_3$: C, 67.20; H, 7.30; N, 13.83. Found: C, 67.05; H, 7.30; N, 13.58.

Summary

When ethyl β-carbethoxy-β-(*m*-chloroanilino)-acrylate was subjected to thermal cyclization in limited amounts of diluent, virtually all 3-carbethoxy-5-chloro-4-hydroxyquinoline was formed. On the other hand, when larger amounts of diluent were employed, as much as sixty per cent. of the corresponding 7-isomer was obtained.

7-Chloro-(1-ethyl-4-piperidylamino)-8-methylquinoline has been synthesized and found to be inactive against *Plasmodium lophurae* in ducks.

URBANA, ILLINOIS RECEIVED OCTOBER 21, 1946

CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 1041]

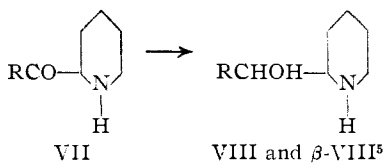
Potential Antimalarials. (6-Methoxyquinolyl-4)-α-piperidylcarbinols[1,2]

BY HERBERT SARGENT[3]

H. King and co-worker[4] have described the synthesis of (6-methoxyquinolyl-4)-α-piperidylcarbinol (VIII)[5] by the series of reactions shown in the chart. A reinvestigation of this synthesis, carried out under the supervision of Dr. E. R. Buchman, has resulted in substantial improvement (see Experimental).

$$RCOOC_2H_5^{6} + C_2H_5OOC(CH_2)_5NHCOC_6H_5 \longrightarrow$$
I II
$$RCOCH(CH_2)_4NHCOC_6H_5 \longrightarrow$$
$$COOC_2H_5$$
III

$$RCO(CH_2)_5NHCOC_6H_5 \longrightarrow RCO(CH_2)_5NH_2 \longrightarrow$$
IV V
$$RCOCHBr(CH_2)_4NH_2\cdot 2HBr \longrightarrow$$
VI



VII VIII and β-VIII[5]

The previously reported[4] studies dealing with N-alkylated derivatives of VIII have been extended in the course of this research.

Experimental[7]

ε-Bromo-ε-quininyl-*n*-amylamine Dihydrobromide (VI).—Sodamide was prepared by adding 38 g. (1.65 moles) of clean sodium in small pieces to 2 liters of liquid ammonia in a 3-liter, three-necked flask. A pinch of ferric chloride was added as a catalyst and after the blue color had disappeared (usually several hours) the excess of ammonia was allowed to evaporate. The residual gray cake of sodamide was broken up with a flattened stirring rod and used directly in the following condensation.

A solution of 310 g. (1.34 moles) of ethyl quininate (I)[8] and 353 g. (1.34 moles) of ethyl ε-benzamidocaproate (II)[8] in 700 ml. of dry thiophene-free benzene was added to the sodamide and the flask was equipped with a sealed Hershberg-type stirrer driven by a powerful motor; a reflux condenser carrying a drying tube containing potassium hydroxide pellets was fitted to one side-neck and the

(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 California Institute of Technology.

(2) This paper and the following papers in this issue dealing with applications of the Ainley and King method[4] to the synthesis of potential antimalarials were presented in part before the Division of Medicinal Chemistry of the American Chemical Society at the Atlantic City meeting, April, 1946.

(3) Present address: United States Rubber Company, Passaic, New Jersey.

(4) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

(5) Catalytic reduction of VII yields a mixture of the racemic forms of the carbinol; the predominant form is here designated VIII, the other isomer β-VIII. β-VIII is probably identical with the VIII-isomer obtained by Work, *J. Chem. Soc.*, 194 (1946); it is not identical with the "iso base" described by Ainley and King.[4] The latter substance, a specimen of which was kindly provided by Dr. King, was not encountered in this work.

(6) R = CH_3O— 

(7) All melting points are corrected; microanalyses were carried out by Dr. G. Oppenheimer and staff of this Institute and by Huffman Microanalytical Laboratories, Denver 2, Colorado.

(8) Supplied by Dr. R. C. Elderfield (Columbia University).

TABLE I

Run	Hydrobromic acid extractable, g.	Bromination conditions: Amount of bromine, g.	Time	Temp. °C.	First crop VI, g.	Second crop VI, g.	Impure VI 4 runs, g.	Crude IX 4 runs, g.
1[a]	185	109	1 hr. 10 min.	50	165.6	41.0		
2	213	130	1 hr. 15 min.	60	204.5		136.2	76.8
3[b]	223	130	45 min.	60	137.0	56.8		
4	200	95		*ca.* 50	249.0			

[a] Time of condensation nineteen hours. [b] Time of hydrolysis ten hours.

other was tightly stoppered (wired-in neoprene stoppers preferable). The slowly stirred reaction mixture was heated to refluxing temperature during *ca.* one hour and refluxed (bath temperature *ca.* 90°) for an additional twenty-six hours.[9] There was an initial copious evolution of ammonia; the pasty mixture became, first progressively stiffer (the stirrer remained frozen for about two hours), then decidedly oily and finally rather viscous again.

The condensation product was hydrolyzed directly. After cooling the reaction mixture to *ca.* 50°, 1 liter of 12 *N* hydrochloric acid and 700 ml. of water were added with vigorous shaking; the stirrer was inserted, and agitation continued until the viscous mass completely dissolved (*ca.* ten minutes). Finally, after removal of the benzene from the three-phase system by distillation, the mixture (single phase after *ca.* one hour of refluxing) was refluxed for seventeen hours.

The cooled contents of the reaction flask were basified by addition of aqueous 33% sodium hydroxide solution, maintaining the temperature below 25° by external cooling (*ca.* two hours). The resulting brown solution[10] was extracted in portions with 1 liter of chloroform and the combined chloroform extracts extracted[11] first with a 480-g. portion and then with a 120-g. portion of 40% hydrobromic acid; the increase in weight of the hydrobromic acid solution was *ca.* 200 g. (some chloroform was carried over into the hydrobromic acid extract).

Bromination[12,13] was carried out by the method given in the literature[4] (see Table I). In the best experiments the product started to crystallize from the hot reaction mixture during bromination. Usually at the end of the bromination the reaction mixture was heated rapidly (if necessary, with the addition of sufficient 48% hydrobromic acid to completely dissolve VI) to the boiling point (to destroy any perbromide) and then cooled immediately and allowed to stand at 0°. The first crop of crystals (reasonably pure VI) was filtered with suction, rinsed with ethanol and dried,[14] m. p. 192° dec. (lit.[4] m. p. 195° dec.); recrystallization from acetic acid–hydrobromic acid–water gave yellowish bars, analysis for $C_{16}H_{19}BrN_2O_2 \cdot 2HBr$.[4] The mother liquors were evaporated *in vacuo* (temperature of liquid *ca.* 50–55°) yielding in some cases a second crop of approximately the same purity. Impure VI (75–80% pure as judged by the results of ring-closure and reduction experiments) was obtained as a fine crystalline slurry by evaporating *in vacuo* to a sirup and diluting with ethanol, m. p. 178° dec. Additional material, possibly crude ε,ε-dibromo-ε-quininyl-*n*-amylamine dihydrobromide (IX), came out of these final mother liquors in large brown crystals (m. p. 136–139° dec.) and was separated mechanically from impure VI, than which it was considerably more soluble in ethanol. From four runs a total of 853.9 g. (1.66 moles) of first and second crop VI plus 136.2 g. of impure VI (*ca.* 0.2 mole) was obtained; this is equivalent to a 34.5% over-all yield (57% taking into account recovered I[10]).

ε-Quininyl-*n*-amylamine (V). (a) **From N-Benzoyl-ε-quininyl-*n*-amylamine (IV).**—One-half gram of IV picrate (pearly flakes from ethanol, m. p. 109–111°[4]) was refluxed with 10 ml. of 6 *N* hydrochloric acid for twenty-seven hours, after which time the mixture was diluted with water, extracted with benzene to remove picric acid and the aqueous layer basified and extracted with chloroform. After the removal of chloroform, the residue was converted to the salt with aqueous hydrobromic acid, water removed *in vacuo* and the residue seeded (see below). The resulting solid, after recrystallization, gave no depression of melting point when mixed with the product obtained from VI.

(b) **From VI.**—One gram of VI was dissolved in 10 ml. of redistilled methanol and 4 ml. of water and reduced after the addition of 0.05 g. of Adams platinum oxide catalyst. After five minutes of shaking with hydrogen at atmospheric pressure and room temperature, the theoretical amount (for conversion to V) had been absorbed; solvent was removed by evaporation on the steam-bath *in vacuo* and the residual sirup treated with several ml. of absolute alcohol. A crystalline paste formed which was recrystallized from *i*-propyl ether–ethanol (using Norite), then from ethanol and finally from *i*-propanol–water, buff-colored needles, m. p. 210.0–210.5° dec.

Anal. Calcd. for $C_{16}H_{20}N_2O_2 \cdot 2HBr$: C, 44.26; H, 5.11; N, 6.45. Found: C, 44.49; H, 5.09; N, 6.22.

(6-Methoxyquinolyl-4)-(ε-amino-*n*-amyl)-carbinol.—VI was reduced as described above except that the hydrogenation was continued until two moles of hydrogen had been absorbed (required one-half hour for 1.3 g. of VI). After centrifuging and freeing the product from solvent, it was dissolved in a small amount of warm ethanol; the solution was diluted with 30% of its volume of acetone, centrifuged and allowed to stand. The resulting mixture of crystals and oil was washed with *i*-propanol and the crystals, m. p. 125°, were dissolved in *i*-propanol and the solution treated with Norite. The addition of a few drops of water gave needles which, after re-solution, came out as rectangular tan plates, m. p. 213.0–213.5°.

(9) The seven-hour period of heating used by Ainley and King[4] was found insufficient for best yield.

(10) The combined basic solutions from four runs (after chloroform extraction) were concentrated, filtered from sodium chloride and brought to *p*H *ca.* 4. The crude RCOOH was filtered off, washed with water and with ethanol and esterified *via* the acid chloride; yield of recovered I, 52.5 g.

(11) Equally satisfactory results were obtained if the chloroform extracts were evaporated[4] *in vacuo*, and the weighed residue taken up[4] in hydrobromic acid and brominated.

(12) Bromination by addition of a solution of bromine in 48% hydrobromic acid (until perbromide started to form) was later shown to possess advantages here.

(13) Excess bromine leads to formation of oily precipitates, presumably perbromides. These may, in general, be avoided by decreasing rate of bromine addition and/or increasing bromination-rate by raising temperature, using a more concentrated hydrobromic acid, or both. Since the methoxy group is readily attacked by hydrobromic acid of strength above 40%, it is preferable to keep the acid concentration low (below 30%) and to raise the temperature (even above 60° if necessary). Perbromide may be separated due to relative insolubility in water; however, if perbromide is heated in aqueous hydrobromic acid, the solution evolves free bromine and, on cooling, deposits crystals of VI.

(14) Caution! Avoid inhaling particles of VI dust as they set up a persistent irritation.

Anal. Calcd. for $C_{16}H_{22}N_2O_2 \cdot 2HBr$: C, 44.05; H, 5.55; N, 6.42. Found: C, 44.04; H, 5.42; N, 6.60.

(6-Methoxyquinolyl-4)-α-piperidylcarbinols (VIII) (SN2157)[15] and β-(VIII) (SN8279).[15]—The yield of VIII by the Ainley and King method[4] was 48% from VI (plus 2% of β-VIII[5]); the remainder of the product was shown by chromatographic analysis[16] to consist mainly of high-molecular weight tars. In the improved method given below, side reactions have been very largely eliminated.

VI (102.6 g. = 0.2 mole) together with 1 liter of redistilled methanol was placed in a 3-liter, round-bottomed flask and 460 ml. of saturated aqueous sodium carbonate solution (density 1.15) was added, meanwhile sweeping the flask with a stream of nitrogen.[17] The flask was then stoppered and shaken for *ca.* fifty minutes on the shaking machine after which 2 g. of Adams platinum oxide catalyst was added and the mixture reduced in the usual manner (time from start of shaking to start of reduction, one hour). During the reduction (one and one-half hours), *ca.* 6.1 liters of hydrogen (calcd. *ca.* 5.8 l.) was absorbed at room temperature and atmospheric pressure and at the end the rate of hydrogen uptake had become negligible. After reduction, solids were filtered off, washed with methanol, and the light orange filtrate evaporated on the steam-bath to give an aqueous solution mixed with oil. The aqueous portion was decanted from the oil, extracted three times with chloroform, the extract freed of chloroform, and the residue dissolved in ethanol and evaporated to a sirup which was combined with the oil.

In one experiment this product, on recrystallization from about 70 ml. of water plus enough methanol to put the oil in solution, yielded solvated VIII crystals which were filtered, rinsed with butanone (better with methanol–water) and dried, yield 28.0 g. Evaporation of the filtrate and a similar recrystallization of the residue gave a second crop, 14.2 g. The mother liquors were then freed of solvent, the bases extracted with chloroform and the chloroform removed on a steam-bath. The residue was taken up in ethanol and the solution boiled to remove traces of chloroform, cooled and treated with anhydrous hydrogen chloride, which precipitated a crystalline slurry, yield 6.0 g. of VIII dihydrochloride; the total yield of VIII (as base and salt) was 86.2%. The final mother liquors plus 10 ml. of 48% hydrobromic acid (superior to 12 *N* hydrochloric acid for obtaining crystalline salts in this series) gave 2.0 g. (2.3%) of β-VIII dihydrobromide. In a second experiment the combined oil and chloroform-extractables were recrystallized from 20 ml. of water plus sufficient methanol to give a clear solution, yield 41.3 g. of VIII. From the mother liquors, 6.2 g. of VIII dihydrochloride was obtained (total yield of VIII, 84.8%) plus 2.2 g. of β-VIII dihydrobromide (2.5%). The over-all yield of VIII was thus 29.4% based on I (50.9% taking into account recovered I[10]).

From its dihydrochloride, VIII was regenerated by the method generally employed in this series, *viz.*, the salt was taken up in methanol–water and treated with excess of aqueous sodium hydroxide; VIII was deposited in rectangular bars which were recrystallized from ethanol–*i*-propyl ether, m. p. 163.0–164.5° (lit.[4] m. p. 162–163°); from methanol–water, rectangular crystals containing solvent (easily lost on drying) were obtained, m. p. *ca.* 90°, resolidifying and melting again *ca.* 162°. VIII dihydrochloride was obtained in quantity by dissolving VIII in ethanol and adding 12 *N* hydrochloric acid, m. p. 240° dec.[4]; VIII monohydrochloride melted at 226° dec.[4]

β-VIII, after regeneration, was recrystallized from ethanol–*i*-propyl ether (or methanol–acetone) and finally from ethanol, hexagonal prisms, m. p. 184.2–184.7°.[18]

Anal. Calcd. for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.28. Found: C, 70.78; H, 7.26; N, 10.24.

β-VIII dihydrobromide crystallized from methanol–water in needles, m. p. 227°; the monohydrochloride melted at 194° dec.; the dihydrochloride crystallized from water containing a small amount of hydrochloric acid in long silky needles, m. p. 225° dec., analysis for $C_{16}H_{20}N_2O_2 \cdot 2HCl \cdot H_2O$.

The ratio of VIII to β-VIII formed on catalytic reduction of VII was found to be dependent especially on *p*H conditions[19] (and/or time of hydrogenation). Under the above conditions (reduction in aqueous methanol in the presence of sodium carbonate) this ratio was 35 to 1; when VII dihydrohalide was reduced in methanol (see below), the ratio was approximately 3 to 1. In the following experiment, the ratio was *ca.* 2 to 1. Impure third crop VI (91.6 g.) was cyclized by shaking together with 900 ml. of methanol and 410 ml. of saturated aqueous sodium carbonate. After addition of 90 ml. of 12 *N* hydrochloric acid together with 0.75 g. of catalyst, the carbon dioxide liberated was removed by application of suction. On hydrogenation, 5.27 liters of hydrogen was taken up over a period of twenty hours. The reduction product was made basic, freed of methanol, taken up in chloroform and the chloroform replaced by about 200 ml. of ethanol. On passing in anhydrous hydrogen chloride, VIII dihydrochloride precipitated, yield, 23.3 g. The mother liquors soon deposited a second crop, consisting of β-VIII dihydrochloride, 13.7 g. (22%). The final mother liquors on treatment with hydrobromic acid gave 3.5 g. of VIII dihydrobromide (total yield of VIII, 42%).

α-Quininylpiperidine (VII). (a) From VI.—VI (10.26 g.), 80 ml. of water, 120 ml. of ether and 70 ml. of saturated sodium carbonate solution were brought together and shaken for forty minutes. At the end of this time the ether phase was separated and, after drying over potassium carbonate, was shaken with 8.0 ml. of 48% hydrobromic acid. The aqueous portion was treated with about 30 ml. of ethanol, warmed sufficiently to dissolve the crystals which had formed and placed in an icebox. The resulting crystals were filtered off, rinsed with acetone, and the orange-yellow powder (3.51 g.) recrystallized from 30% hydrobromic acid; yield 1.87 g. of cream-colored, thin, rectangular bars, m. p. 183–185° dec.

Anal. Calcd. for $C_{16}H_{18}N_2O_2 \cdot 2HBr \cdot H_2O$: C, 42.68; H, 4.93; N, 6.22. Found: C, 42.44; H, 4.62; N, 6.15.

(b) From Crude IX.—A mixture of 74.5 g. of crude XI (byproduct from bromination of crude V), 350 ml. of water, 870 ml. of ether and 510 ml. of saturated aqueous sodium carbonate solution was shaken for forty minutes, after which the ether phase was separated, dried over potassium carbonate, and evaporated *in vacuo* at room temperature. Before all of the solvent had been removed, 25 ml. of 12 *N* hydrochloric acid was added and evaporation continued. About 0.5 g. of crystalline residue was removed and converted to the dihydrobromide by recrystallization from 30% hydrobromic acid, fine yellow needles,

(15) 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 the Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(16) VIII in petroleum ether–benzene (9:1) was not adsorbed satisfactorily on calcium carbonate, calcium sulfate, silica or various aluminas; magnesium sulfate gave moderately good results, while tribasic calcium phosphate (Reagent, Merck) proved an excellent adsorbent. The column was developed with petroleum ether–benzene (1:1), the zone containing VIII fluoresced strongly in ultraviolet light; VIII could be recovered using aqueous sulfuric acid at *p*H 3–4 (alcohol extraction was not satisfactory). The behavior of β-VIII on the column paralleled that of VIII.

(17) All operations involving the air-sensitive (*cf.* Golding and McNeely, THIS JOURNAL, **68**, 1847 (1946)) intermediate (VII) were carried out rapidly and as much as possible in the absence of air.

(18) "Iso base" hydrochloride[5] melted at 210° dec.; the regenerated base at 190.3–190.5° (depressed the m. p. of β-VIII and of N-methyl-VIII). The titration curve of the "iso base" was indistinguishable from that of VIII; under ultraviolet light an aqueous solution of the "iso base" gave a weak fluorescence changed to a brilliant blue by addition of a drop of sulfuric acid (VIII and β-VIII exhibited the same behavior).

(19) Compare, for example, in the article by W. H. Strain in Gilman's "Organic Chemistry," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1943, page 1373; also *Helv. Chim. Acta*, **24**, 266E, footnote 1 (1941).

m. p. 288°, giving analytical figures for a hydrated X[20] dihydrobromide.

Anal. Calcd. for $C_{16}H_{16}N_2O_2 \cdot 2HBr \cdot H_2O$: C, 42.88; H, 4.50; N, 6.25. Found: C, 42.84; H, 4.35; N, 6.08.

The remainder of the crystalline residue was dissolved in 200 ml. of redistilled methanol and hydrogenated (0.65 g. of Adams platinum oxide catalyst). The initial rate of hydrogenation was negligible; 25 ml. of 6 *N* sodium hydroxde was added, after which a total of 4.26 liters of hydrogen was absorbed in four and one-half hours. The resulting mixture was centrifuged, freed of solvent and the residue basified and extracted with chloroform. After the chloroform had been replaced with 100 ml. of ethanol, 25 ml. of 12 *N* hydrochloric acid was added to the solution. Crystals deposited slowly which were filtered off (mother liquors, on further reduction, gave VIII and β-VIII) after eighteen hours, yield 7.1 g. of buff-colored powder, m. p. 197.5–199.5° dec. Recrystallization of a portion of this material from methanol–water gave tetragonal tan plates, m. p. 233° dec. (VII regenerated from a sample of this salt exhibited the expected instability).

Anal. Calcd. for $C_{16}H_{18}N_2O_2 \cdot 2HCl \cdot H_2O$: C, 53.19; H, 6.14; N, 7.76. Found: C, 52.70; H, 6.50; N, 7.82.

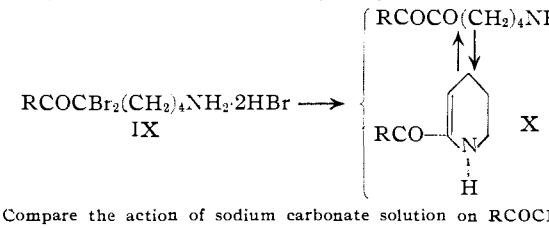
VII dihydrobromide (1.6 g. = 0.00355 mole) was dissolved in 20 ml. of methanol and reduced after addition of 0.075 g. of catalyst. Removal of solvent gave a non-oily crystalline mass from which was isolated 0.00267 mole of VIII (as base and dihydrochloride) and 0.00088 mole of β-VIII (as dihydrochloride) (together 100% yield). The reduction of VII dihydrochloride proceeded similarly.

ε,ε-Dibromo-ε-quininyl-*n*-amylamine Dihydrobromide (IX).—VI (15.4 g.), 40 ml. of 48% hydrobromic acid, and 10 ml. of water were brought together and 4.8 g. of bromine[21] in 10 ml. of 48% hydrobromic acid was added slowly while the temperature was maintained at about 40°; an oil formed which became crystalline. After the addition of bromine, the mixture was heated below the boiling point until the color indicated that no free bromine was present. The product was cooled to room temperature and then placed in an icebox; crystals were slowly deposited. After twenty-four hours, these were filtered off and the mother liquors evaporated *in vacuo*, leaving a solid, resin-like residue. The combined crystals plus residue were extracted with hot ethanol and, on cooling the extracts, bright yellow rectangular bars were obtained, m. p. 117° dec., weight 10.5 g. Recrystallization once from 96% ethanol (raised m. p. to 126.5° dec.) and again from *i*-propanol–water, yielded colorless hexagonal plates, m. p. 170–172°, which evolved bromine when heated with 48% hydrobromic acid.[22]

Anal. Calcd. for $C_{16}H_{18}Br_2N_2O_2 \cdot 2HBr$: C, 32.46; H, 3.41; N, 4.73. Found: C, 32.70; H, 3.25; N, 4.49.

Crude IX on ring-closure[20] and reduction gave VIII as expected (see preparation of VII).

(20) The course of the reaction may be represented as



Compare the action of sodium carbonate solution on $RCOCBr_2(CH_2)_3NH_2 \cdot 2HBr$, Buchman and Sargent, unpublished.

(21) Twice this amount of bromine gave a crystalline mixture which after recrystallization from 48% hydrobromic acid and finally from *i*-propanol–water yielded needles, m. p. 178.5° dec. (Found: C, 27.1; H, 3.1). Attempts to ring-close and reduce this material gave intractable products.

(22) This behavior appears to be typical of compounds in this series containing the grouping —$COCBr_2$—, *cf.* also D. R. Howton, unpublished.

N-Substituted Derivatives of VIII and β-VIII

(6-Methoxyquinolyl-4)-α-N-methylpiperidylcarbinols.

(a) N-Methyl-VIII[4] (SN2554).[15]—VIII was subjected in preliminary tests to methylation with methyl iodide,[4] with dimethyl sulfate, and with potassium methyl sulfate; the last method gave only unchanged starting material, while the dimethyl-sulfate method gave results superior to those obtained with methyl iodide. VIII (30 g.), dissolved in 100 ml. of hot methanol, was added to 1 liter of ether, a solution of 22.1 g. of anhydrous potassium carbonate dissolved in 120 ml. of water was added, and, after adding 20.0 g. of dimethyl sulfate, the mixture was shaken mechanically for four hours. The ether phase was separated (VIII was recovered from the aqueous phase), the solvent removed on a steam-bath, and the residue cooled to room temperature and allowed to crystallize. The crystals were filtered off and rinsed with small portions of ethanol, then acetone, then ether; yield 15.5 g. of slightly colored, elongated hexagonal plates, m. p. 190.5–193.0°; after recrystallization from ethanol, hexagonal prisms, m. p. 191.5–193.0° (lit.,[4] m. p. 183–184°). The picrate crystallized in rhombs from ethanol–acetonitrile, m. p. *ca.* 168° dec., analysis for $C_{17}H_{22}N_2O_2 \cdot 2C_6H_3N_3O_7$.

The dihydrochloride was prepared from 16.9 g. of carbinol by heating to boiling with 70 ml. of ethanol and adding slowly 16.0 ml. of 12 *N* hydrochloric acid. After cooling, the crystals were filtered off and rinsed with ethanol; yield 21.0 g. of white powder, m. p. 218.5–219.5°, long thin bars of the same m. p. from methanol–water plus a drop of 6 *N* hydrochloric acid, analysis for $C_{17}H_{22}N_2O_2 \cdot 2HCl \cdot H_2O$.

(6-Hydroxyquinolyl-4)-α-N-methylpiperidylcarbinol dihydrobromide was prepared by refluxing 0.15 g. of the above carbinol with 2.5 ml. of 48% hydrobromic acid for three hours, colorless tablets from ethanol–water, m. p. 196–198° dec., soluble in excess of sodium hydroxide solution.

Anal. Calcd. for $C_{16}H_{20}N_2O_2 \cdot 2HBr \cdot H_2O$: C, 42.49; H, 5.35; N, 6.20. Found: C, 42.57; H, 5.50; N, 5.91.

(b) N-Methyl-β-VIII (SN9548).[15]—Nine grams of β-VIII was nearly dissolved in 37 ml. of hot methanol and added to 300 ml. of ether; 7.6 g. of anhydrous potassium carbonate in 15 ml. of water and 6.9 g. of dimethyl sulfate were then added and the mixture shaken for five hours. The ether phase was decanted from the brown viscous aqueous phase and evaporated on the steam-bath, leaving about 9 g. of oil which was treated with 10.4 g. of 48% hydrobromic acid. The resulting crystalline paste was diluted with 20 ml. of *i*-propanol, cooled to 0°, filtered and the crystals were rinsed with acetone; yield, 7.4 g. of buff-colored solid, m. p. 121–156°. The solid was taken up in a minimum amount of boiling ethanol, the solution centrifuged and a small amount of water (to keep inorganic matter and β-VIII dihydrobromide in solution) added; after cooling rectangular bars were obtained which were washed with ethanol and with *i*-propanol, m. p. 121°, yield 5.4 g. This salt crystallized from ethanol in rectangular prisms, m. p. 121.3–121.8°, analysis for $C_{17}H_{22}N_2O_2 \cdot 2HBr \cdot 3H_2O$. The regenerated base crystallized in needles or rhombs, m. p. 138.3–139.5°.

Anal. Calcd. for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.75; N, 9.78. Found: C, 71.31; H, 7.90; N, 9.74.

(6-Methoxyquinolyl-4)-α-N-benzylpiperidylcarbinol (SN7725).[15]—A warm solution of 13.6 g. of VIII in 300 ml. of acetone and 10 ml. of methanol was mixed with 20 g. of anhydrous 100-mesh potassium carbonate and 8.6 g. of benzyl bromide in 25 ml. of acetone and the mixture heated under reflux for thirteen and one-half hours; after cooling, the reaction mixture was filtered, the filtrate evaporated on the steam-bath, and the residual sirup treated with 20 g. of 48% hydrobromic acid. The hydrobromide crystallized and was filtered off and rinsed with acetone; yield 21.0 g. of almost colorless solid. A portion was recrystallized by dissolving in ethanol and adding acetone, diamond-shaped crystals, m. p. 201.5–205.0° dec. The analytical sample was obtained by recrystal-

lization from methyl alcohol with the addition of a drop of 48% hydrobromic acid plus a few drops of water, bunches of colorless, rectangular plates, m. p. 197–213°.

Anal. Calcd. for $C_{23}H_{26}N_2O_2 \cdot 2HBr$: C, 52.68; H, 5.38; N, 5.34. Found: C, 52.53; H, 5.40; N, 5.15.

The regenerated free base was an ether-soluble oil which did not crystallize even on long standing. With ethereal picric acid an oily picrate was obtained which crystallized from dioxane–water in square plates of indefinite melting point.

(6 - Methoxyquinolyl - 4) - α - N - (β - hydroxyethyl) - piperidylcarbinol (SN8284).[15]—In a tightly-stoppered bottle was placed 15.0 g. of VIII together with 70 ml. of methanol and 12.5 ml. of ethylene oxide (addition made at 0°). The mixture was allowed to stand at room temperature for three and one-half hours, at the end of which time the contents of the bottle were evaporated on a steam-bath to remove solvent. A slight excess, 22 g., of 48% hydrobromic acid was added to the residue, giving a crystalline mass which was diluted with hot ethanol, treated with Norite and centrifuged. The solution deposited sword-like needles which were filtered off and washed with *i*-propanol; yield, 11.0 g. A further purification was obtained by dissolving in hot methanol, again treating with Norite and evaporating solvent on the steam-bath; this yielded cube-like crystals, m. p. 152° (rapid heating; m. p. 184–221° on slow heating).

Anal. Calcd. for $C_{18}H_{24}N_2O_3 \cdot 2HBr \cdot 1.5H_2O$: C, 44.37; H, 5.59; N, 5.75. Found: C, 44.43; H, 5.56; N, 6.05.

A portion of this salt dissolved in a small amount of water was redeposited as needles m. p. 143–149°, resolidifying, and melting again at *ca.* 184–215°.

The free base was regenerated as a colorless viscous oil, very soluble in ether; from a solution of the base in ethanol the dihydrochloride was prepared, rectangular plates, m. p. 194–215°, analysis for $C_{18}H_{24}N_2O_3 \cdot 2HCl \cdot 1.5H_2O$.

Summary

A study has been made of the Ainley and King synthesis of (6-methoxyquinolyl-4)-α-piperidylcarbinol (VIII). Modifications of this synthesis have been developed which permit the convenient preparation of VIII in considerably improved over-all yield. The isomeric racemate, β-VIII, and several N-substituted derivatives have been described.

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Potential Antimalarials. (Chloroquinolyl-4)-α-piperidylcarbinols[1]

BY E. R. BUCHMAN, H. SARGENT, T. C. MYERS AND J. A. SENEKER

A study[2] made in this Laboratory of the Ainley and King[3] synthesis of V (R = 6-methoxyquinolyl-4) resulted in an improved preparative-scale method for this substance. In an extension of this work, we have now prepared Va,[4] Vb and Vc *via* the intermediates shown.

$$\underset{\text{I}}{RCOOC_2H_5} + \underset{\text{II}}{C_2H_5OOC(CH_2)_5NHCOC_6H_5} \longrightarrow$$

$$\underset{\text{III}}{RCO(CH_2)_5NH_2 \cdot 2HBr} \longrightarrow$$

$$\underset{\text{IV}}{RCOCHBr(CH_2)_4NH_2 \cdot 2HBr} \longrightarrow \underset{\text{V}}{RCHOH\text{-}\alpha\text{-piperidyl}}$$

Series a R[5] = 6-chloroquinolyl-4
b R = 8-chloroquinolyl-4
c R = 6,8-dichloroquinolyl-4

The esters (I) were prepared from appropriate chloroisatins by a method which had been employed by Work[6] to obtain 6-chlorocinchoninic acid. In addition to the intermediates required in this research, a number of other halogenated cinchoninic acid derivatives are described in the Experimental Part.

The authors are grateful to Dr. D. R. Howton for aid in preparing the manuscript.

Experimental[7]

Halogenated Cinchoninic Acid Derivatives

Ethyl 6-Chlorocinchoninate (Ia).[8]— 5-Chloroisatin (VIa)[9] (m. p. 252.5–254.5°) from chlorination[10] of 300 g. (2.04 moles) of isatin was condensed[6] with pyruvic acid.[11] The reaction mixture, after standing for fourteen hours, was heated to boiling for one-half hour and then made strongly acid by addition of 12 *N* hydrochloric acid (half potassium salt precipitates first). The crude 6-chloroquinoline-2,4-dicarboxylic acid (VIIa)[6] was filtered off and washed with water; yield 320 g. (62% from isatin). A sample was recrystallized from 50% ethanol; m. p. (rapid heating) 265° dec. and resolidification; on slow heating, this m. p. was not observed.

Anal. Calcd. for $C_{11}H_6ClNO_4$: C, 52.50; H, 2.40; N, 5.57. Found: C, 52.30; H, 2.98; N, 5.51.

Crude VIIa (308 g. = 1.22 moles) was decarboxylated (five hours at *ca.* 200°; see under Ib) and the resulting crude 6-chlorocinchoninic acid (VIIIa)[6] esterified.[8] After excess ethanol was removed *in vacuo*, the residual sirup was cooled and treated with ice and water (precipitation

(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 California Institute of Technology.

(2) Sargent, THIS JOURNAL, **68**, 2688 (1946).

(3) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938).

(4) In series a-c, only one of the two diastereoisomeric racemic forms of V was isolated; the other form (*cf.* ref. 2) was presumably formed but in relatively smaller amount.

(5) Senear, Sargent, Mead and Koepfli, THIS JOURNAL, **68**, 2695 (1946), describe the preparation of V (R = 7-chloroquinolyl-4); Campbell and Kerwin[8] have reported carbinolamines $RCHOHCH_2NR'_2$ in which R = 6-chloroquinolyl-4.

(6) Work, *J. Chem. Soc.*, 426 (1942).

(7) All melting points are corrected; microanalyses by Dr. G. Oppenheimer and staff of this Institute and by Huffman Microanalytical Laboratories, Denver 2, Colorado.

(8) Campbell and Kerwin, THIS JOURNAL, **68**, 1837 (1946).

(9) Lit. in Sumpter, *Chem. Rev.*, **34**, 404 (1944).

(10) Liebermann and Krauss, *Ber.*, **40**, 2500 (1907).

(11) A technical product (*ca.* 50% aqueous solution) supplied by the Calco Chemical Division of the American Cyanamid Company was used directly.