hours). The resulting slurry was heated to boiling and insoluble inorganic solids were filtered off and washed well with benzene. On evaporation, the clear yellow filtrate left a light tan, crystalline residue which was washed well with water, yield 26.6 g. Three recrystallizations of a sample from acetonitrile–pyridine gave clusters of brilliant, colorless needles, m. p. 187.8–188.3° (prior sintering).

*Anal.* Calcd. for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43. Found: C, 79.40; H, 7.15; N, 8.45.

Crude Vb (26.2 g.) was dissolved in 400 ml. of boiling ethanol and treated with 13.9 ml. of 6 *N* hydrochloric acid; the mass of tiny white needles which formed was filtered off and washed with ethanol, yield 25.7 g. (24.7% over-all from Ib; 44.1% taking into account the recovered cinchoninic acid). Vb hydrochloride crystallized from ethanol–water in sparse clusters of colorless bars, m. p. 247° dec., analysis for $C_{22}H_{24}N_2O \cdot HCl$.

**ϵ-(2,8-Diphenylcinchoninyl)-*n*-amylamine Hydrobromide (IIIc).**—Ic (145.7 g. = 0.413 mole) was condensed with II (forty hours) and the product hydrolyzed (seventeen hours). After basifying the hydrolyzate in the presence of chloroform, the resulting emulsion was centrifuged and the solid at the interface was extracted further with benzene and chloroform and filtered off with the aid of Celite. The combined chloroform–benzene extracts were evaporated (solid which separated was filtered off) on the steam-bath, finally at 2 mm., leaving 143.4 g. of viscous brown oil. This was treated with 62 g. of 48% hydrobromic acid and 100 ml. of hot *i*-propanol, freed of the solvent, and the residual oil dissolved in 250 ml. of acetone and cooled. The resulting crystals weighed 38.5 g.; concentration and dilution of the mother liquors with acetone yielded two additional crops (43.5 g. and 16.7 g.); total yield of crude IIIc, m. p. 223–226°, about 43%. A sample was dissolved in a little boiling glacial acetic acid and, on cooling, a small quantity of tiny tan needle-clusters emerged which were recrystallized from the same solvent to give sparse clusters of glistening, colorless needles, m. p. 270.6–271.1°; the analysis (Found: C, 69.92; H, 5.68; N, 6.04) indicates the presence of IIIc monohydrobromide. Acetone-dilution of the mother liquors from this higher-melting compound gave a considerably larger quantity of golden-yellow, jagged clusters which were crystallized again from warm glacial acetic acid by diluting with acetone, m. p. 224–226° (prior sintering).

*Anal.* Calcd. for $C_{27}H_{26}N_2O \cdot 2HBr$: C, 58.29; H, 5.07; N, 5.04. Found: C, 58.08; H, 5.30; N, 4.62.

**ϵ-Bromo-ϵ-(2,8-diphenylcinchoninyl)-*n*-amylamine Hydrobromide (IVc).**—Crude IIIc (81.4 g.) was dissolved in 172 ml. of hot 48% hydrobromic acid and treated with a solution of 27.4 g. of bromine in 27 ml. of the same solvent, causing precipitation of a yellow oil which redissolved readily on warming. After removal of a small amount of tar, the solution was diluted with about 250 ml. of hot ethanol and cooled, giving clusters of fine, bright yellow needles which were filtered off and washed with acetone; concentration of the filtrates followed by dilution with ethanol gave altogether four crops (m. p.'s in the range 147–168°), total yield 84.7 g. (may contain dihydrobromide). Several recrystallizations from glacial acetic acid with the aid of Norite gave a product, m. p. 177.1–177.4° dec.

*Anal.* Calcd. for $C_{27}H_{25}BrN_2O \cdot HBr \cdot 1.5H_2O$: C, 55.78; H, 5.03; N, 4.82. Found: C, 55.67; H, 5.11; N, 4.96.

**(2,8-Diphenylquinolyl-4)-α-piperidylcarbinol (Vc) (SN12239).**[11]—Crude IVc (63.7 g.) was cyclized (ninety minutes) and reduced (1.5 g. of catalyst, thirty hours). Inorganic solids were filtered off and washed with hot ethanol; the filtrate was evaporated and the solid residue taken up in hot benzene. After again freeing from solvent, the base was dissolved in 6 *N* hydrochloric acid, liberated to benzene and finally crystallized from benzene–ethanol; yield 16.9 g. of light tan needles, m. p. 195–197°; the mother liquors yielded an additional 3.3 g. (total yield of Vc, 20.0% from Ic) and a solid by-product (17.8 g.). Recrystallization of Vc from ethanol–benzene gave clusters of fine white needles, m. p. 195.8–196.2°.

*Anal.* Calcd. for $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64; N, 7.10. Found: C, 81.95; H, 6.62; N, 7.10.

A solution of 20.1 g. of Vc in 100 ml. of hot 6 *N* hydrochloric acid was diluted with 650 ml. of acetone followed by 100 ml. of water; on cooling 12.7 g. of colorless bars slowly emerged, m. p. 242°. The salt was recrystallized from ethanol–6 *N* hydrochloric acid, m. p. 242–243° dec., analysis for $C_{27}H_{26}N_2O \cdot HCl$.

## Summary

(6-Methyl-2-phenylquinolyl-4)-α-piperidylcarbinol, (8-methyl-2-phenylquinolyl-4)-α-piperidylcarbinol and (2,8-diphenylquinolyl-4)-α-piperidylcarbinol have been prepared.

PASADENA 4, CALIF. RECEIVED APRIL 5, 1946

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# (Quinolyl-8)-α-piperidylcarbinol[1]

BY E. R. BUCHMAN AND H. SARGENT

In studies dealing with hydroquinine isomers, Rubtsov[2] has sought to determine the effect on the antimalarial potency in this series caused by a transfer of the quinuclidyl grouping from the 4-position to other positions on the quinoline ring. As a further contribution to this general problem, we have synthesized (quinolyl-8)-α-piperidylcarbinol (III) (SN10277)[3] by application of methods previously used[4] for preparation of the quinolyl-4 isomer.

In avian tests, SN10277[3] was devoid of activity; this finding strengthens the conclusion which may be drawn from Rubtsov's work[2] that quinolyl-8 carbinols are not of interest as antimalarials.

### Experimental[5]

**(Quinolyl-8)-α-piperidylcarbinol (III).**[6]—Ethyl quinoline-8-carboxylate[7] (54.0 g. = 0.269 mole) was condensed with ethyl ϵ-benzamidocaproate (twenty hours) and the product was hydrolyzed by refluxing for twenty-four hours with 200 ml. of 12 *N* hydrochloric acid and 100 ml.

(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) Rubtsov, *J. Gen. Chem.* (U. S. S. R.), **9**, 1493 (1939); **13**, 593 (1943) [*C. A.*, **34**, 2850 (1940); **39**, 705 (1945)]; see also Campbell, Helbing and Kerwin, THIS JOURNAL, **68**, 1840 (1946), and ref. 7b.

(3) 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.

(4) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938); see also Senear, Sargent, Mead and Koepfli, THIS JOURNAL, **68**, 2695 (1946).

(5) All melting points are corrected; microanalyses by Dr. G. Oppenheimer and her staff of this Institute.

(6) *Cf.* preparation (6-methoxyquinolyl-4)-α-piperidylcarbinol, Sargent, THIS JOURNAL, **68**, 2688 (1946).

(7) (a) Cook, Heilbron and Steger, *J. Chem. Soc.*, 413 (1943); (b) Campbell, Kerwin, LaForge and Campbell, THIS JOURNAL, **68**, 1844 (1946). This material was supplied by Dr. F. W. Bergstrom (Stanford University).

of water. The reaction mixture was basified and extracted with chloroform; the extracts were dried over potassium carbonate, filtered, and evaporated *in vacuo*. The resulting light brown oil (20.3 g.) was taken up in 24.4 g. of 48% hydrobromic acid and 50 ml. of *i*-propanol and heated to the boiling point. The solution was then diluted with 300 ml. of *i*-propanol (slow addition to prevent formation of oil); the crystalline precipitate of (quinolyl-8)-(ε-amino-*n*-amyl) ketone dihydrobromide (I) was filtered off, washed with *i*-propanol and ether, and dried *in vacuo*, yield 21.0 g.; the mother liquors gave another 3.0 g., total yield 22.9% (48.4% taking into account recovered quinoline-8-carboxylic acid). A small sample was treated with charcoal and recrystallized from ethanol containing a little aqueous hydrobromic acid, slightly colored rhombs, m. p. 230.0–230.5°.

*Anal.* Calcd. for $C_{15}H_{18}N_2O \cdot 2HBr$: C, 44.57; H, 4.99; N, 6.93. Found: C, 44.80; H, 4.87; N, 6.92.

A solution of 23.1 g. (0.0592 mole) of I in 25 ml. of 48% hydrobromic acid was heated to 80°, treated with 9.4 g. (0.0588 mole) of bromine in 6 ml. of the same solvent and heated to the boiling point. The solution was then evaporated *in vacuo* until sirupy and, on long standing, a buff-colored solid crystallized which was filtered off and washed with a 3:1 ethanol–*i*-propanol mixture; two crops (16.0 and 5.0 g.) were obtained. A small sample was recrystallized from 48% hydrobromic acid; the analysis (after correction for ash) indicated the presence of a hydrated (quinolyl-8)-(α-bromo-ε-amino-*n*-amyl) ketone dihydrobromide (II).

A portion (4.83 g.) of crude II in 150 ml. of ethanol was treated with 25 ml. of 14% aqueous sodium carbonate solution and shaken for an hour and a half. Adams catalyst (0.15 g.) was then added and the mixture reduced until the rate of hydrogen absorption was negligible; 360 ml. of hydrogen was taken up. The reduction mixture was filtered, the filtrate evaporated and the crude product extracted with chloroform. The extract was freed of solvent on a steam-bath (finally by boiling a 20-ml. portion of *i*-propanol from it), and the residue cooled, treated with 2.3 ml. of 48% hydrobromic acid, and diluted to about 15 ml. with *i*-propanol. The resulting slurry was filtered and the tan crystals rinsed with *i*-propanol, yield 1.8 g. These were dissolved in ethanol and the solution was treated with charcoal, evaporated to a volume of about 5 ml., allowed to crystallize, diluted with *i*-propanol, and filtered; yield 1.4 g. (26% from I) of nearly colorless needles, m. p. 273° dec.

*Anal.* Calcd. for $C_{15}H_{18}N_2O \cdot 2HBr$: C, 44.57; H, 4.99; N, 6.93. Found: C, 44.74; H, 5.13; N, 6.73.

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RECEIVED APRIL 5, 1946

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF STANFORD UNIVERSITY]

# The Synthesis of Some α-(2-Piperidyl)-quinolinemethanols[1]

BY R. A. SEIBERT, T. R. NORTON, A. A. BENSON AND F. W. BERGSTROM[2]

In continuation of work initiated[3] at the California Institute of Technology, we have prepared the remaining members in the series, α-(2-piperidyl)-*x*-quinolinemethanol (*x* = 2, 3, 5, 6, 7). The type of synthesis employed was that which had been used for the 4-quinolinemethanol[4] and 8-quinolinemethanol[3] isomers.

It is noteworthy that α-(2-piperidyl)-5-quinolinemethanol (SN 10049)[5] is the only compound in this series other than the 4-analog[4] which exhibits antimalarial activity (in avian tests). For this reason the synthetic work was extended to include 2-phenyl-α-(2-piperidyl)-5-quinolinemethanol[6] and 8-chloro-α-(2-piperidyl)-5-quinolinemethanol.[7] The former was prepared by direct phenylation of the parent compound using an excess of phenyllithium. The latter was prepared from 8-chloro-5-quinolinecarboxylic acid in the usual manner.

## Experimental[8]

**Ethyl Quinolinecarboxylates.**—7-Quinolinecarboxylic acid was prepared by a modification of the method of Skraup and Brunner.[9] To a solution of 105 g. (0.735 mole) of 7-methylquinoline in 1 liter of water and 500 ml. of concentrated sulfuric acid was added three 100-g. (1.0-mole) portions of chromium trioxide with four, fifteen and twenty-four hours of refluxing after additions. The flaky crystalline precipitate of the hydrosulfate which separated upon cooling was removed by filtration, dissolved in 10% sodium hydroxide solution and reprecipitated with acetic acid to give 53 g. (42%) of colorless 7-quinolinecarboxylic acid, m. p. 252–254°. The use of thionyl chloride in the usual manner gave yields of 83–91% of colorless ester, b. p. 145–150° (2 mm.), m. p. 52–53°.

*Anal.* Calcd. for $C_{12}H_{11}O_2N$: C, 71.60; H, 5.51. Found: C, 71.65; H, 5.50.

6-Quinolinecarboxylic acid was prepared in 54% yield according to the method of Schlosser and Skraup[10] with one modification; arsenic acid was used as the oxidizing agent rather than 4-nitrobenzoic acid. Esterification in the usual manner[11] using thionyl chloride gave a 78% yield of ethyl 6-quinolinecarboxylate, b. p. 155° (3 mm.), m. p. 55–57°.

Using arsenic acid as oxidizing agent the method of Cook, Heilbron and Steger[12] gave a 60% yield of 5-quinolinecarboxylic acid, m. p. 338–340°. The ethyl ester, b. p. 153–156° (4 mm.), was prepared using thionyl chloride.

(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 Stanford University.

(2) Dr. Bergstrom died March 29, 1946; this manuscript was prepared by his collaborators.

(3) Buchman and Sargent, *This Journal*, **68**, 2720 (1946).

(4) Ainley and King, *Proc. Roy. Soc.* (London), **125B**, 60 (1938); see also Senear, Sargent, Mead and Koepfli, THIS JOURNAL, **68**, 2695 (1946).

(5) 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.

(6) *Cf.* Rapport, Senear, Mead and Koepfli, THIS JOURNAL, **68**, 2697 (1946).

(7) *Cf.* Buchman, Sargent, Myers and Seneker, *ibid.*, **68**, 2692 (1946).

(8) All melting points are corrected.

(9) Skraup and Brunner, *Monatsh.*, **7**, 142 (1886).

(10) Schlosser and Skraup, *ibid.*, **2**, 518 (1881).

(11) Einhorn and Feibelmann, *Ber.*, **42**, 4854 (1909).

(12) Cook, Heilbron and Steger, *J. Chem. Soc.*, 413 (1943).