of sulfuric acid was then added. Heating was continued while 132 g. (50% excess) of pyruvic acid in 250 ml. of anhydrous ethanol was added dropwise during two hours with mechanical stirring. The mixture was heated for twenty hours, half the alcohol was removed by distillation and the residue was chilled and induced to crystallize by rubbing with methanol. Yields of 30–35% were obtained.

Cinchonic esters were prepared without difficulty by refluxing with alcohol and sulfuric acid except for the 2,3-disubstituted acids which were esterified through the acid chlorides. New esters are summarized in Table III. They were usually crystallized from ligroin, methanol or ethanol (sometimes dilute). Ethyl acetate was used for ethyl 2,2′-bicinchoninate and ether for ethyl 2-(3-pyridyl)-cinchoninate.

α-(2-Piperidyl)-2-aryl-4-quinolinemethanol. VI.—The condensations of ethyl 2-arylcinchoninates with ethyl ε-benzamidocaproate[22] in the presence of sodamide and the hydrolyses of the products to amino ketones (III) were carried out by the procedure used for the 2-phenyl compound.[2] A larger proportion of sodamide did not improve the yields and led to a more pasty reaction mixture which was harder to stir and which never reached an oily state. After the condensation was complete it was advantageous, especially in the case of the 2-(*p*-xenyl) compound, to cool the reaction mixture to 0° and treat with 50% sulfuric acid also at 0° with ice cooling. The cooling sometimes made stirring very difficult. A modified procedure for working up the hydrolysis mixture was used in some cases as indicated in Table I. In those cases the chloroform extract of the basified hydrolysis mixture was washed with 5% sodium hydroxide and water, the solvent removed, the residual oil treated with an amount of 5% acetic acid calculated on the basis of the weight of the oil to yield a diacetate and the mixture heated to boiling. There was usually a small undissolved residue which was removed by adding decolorizing carbon and filtering. The filtrate was cooled and made basic with a volume of 5% sodium hydroxide equal to that of the 5% acetic acid used. This insured the complete separation of the aminoketone (III) and provided an excess of base to retain any of the cinchoninic acid still present. The basic mixture was extracted with chloroform or better three times with ether which had less tendency to take up remaining cinchoninic acid. The ether extracts were dried over anhydrous sodium sulfate, the ether removed and the residue treated with sufficient 48% hydrobromic acid to form a dihydrobromide. The mixture was heated until solution was complete, an equal volume of isopropyl alcohol was added, and after heating to boiling the solution was allowed to cool. Usually the product crystallized and was separated by filtration and washed with isopropyl alcohol and with a little ether. The yield of dihydrobromide was 20–50% based on the cinchoninic ester and not allowing for recovered cinchoninic acid. The amount of recovered acid varied greatly from case to case; it was negligible for 2-(2,5-dimethylphenyl)-cinchoninic acid and 50% for 2-(*p*-bromo or *p*-chlorophenyl)-cinchoninic acid. A Volhard titration was carried out on each aminoketone salt, but in some cases these compounds were mixtures of mono- and dihydrobromides.

The bromination, ring closure and reduction (IV → V → VI) were carried out according to the procedure of Koepfli and co-workers.[2] Data on the final compounds are given in Table I.

α-(2-Piperidyl)-2-(*p*-hydroxyphenyl)-4-quinolinemethanol (VI, R = *p*-hydroxyphenyl) was prepared by refluxing 15 g. of the methoxy derivative (VI, R = *p*-methoxyphenyl) with 500 ml. of 48% hydrobromic acid for seventy-two hours. Crystals began to separate during the heating and upon cooling 16.3 g. (92%) of the dihydrobromide, m. p. 299–300° was obtained. The dihydrobromide was dissolved in 20% sodium hydroxide, the solution filtered and acidified with hydrochloric acid to yield the dihydrochloride which crystallized in fine yellow crystals (Table I). The free amine was liberated from a solution of the dihydrochloride in 20% sodium hydroxide by treatment with carbon dioxide. It seems unusual that the hydrobromic acid treatment did not alter the hydroxyl in the side chain, but the analytical results (Table I) indicate that the product had the structure assigned. Furthermore, the product was remethylated in ethanol solution by treatment with an ether solution of diazomethane, and the methylated product had the same melting point as the starting material (VI, R = *p*-methoxyphenyl). A mixture showed no melting point depression.

(22) This ester was supplied by Dr. C. C. Price and co-workers of the University of Illinois.

Summary

Fourteen new α-(2-piperidyl)-2-aryl-4-quinolinemethanols have been prepared for testing as antimalarials. Data are given for these and for a number of new cinchoninic acids and esters, which were synthesized as intermediates.

LOS ANGELES, CALIF. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 1044]

The Synthesis of Potential Antimalarials. 2-Alkyl-α-(2-piperidyl)-4-quinolinemethanols[1]

BY J. F. MEAD, A. E. SENEAR AND J. B. KOEPFLI

For reasons elaborated upon in another communication,[2] it was of interest to prepare an Ainley and King type[3] of carbinol with a group (such as methyl) in the quinoline-2 position and this investigation was started with the limited objective of preparing IIId. While unsuccessful attempts were being made to synthesize IIId, the previously reported[2] (compare Brown, *et al.*,[4] and Buchman, *et al.*[5]) enhancement of the antimalarial activity of α-(2-piperidyl)-4-quinolinemethanol, occasioned by the introduction of an aryl group into the quinoline-2 position, became known and made advisable the broadening of the original scope of this investigation to include preparation of compounds with a secondary alkyl or alicyclic group in this position. The appropriate intermediate was also prepared with the hope of obtaining a

(1) This work 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.

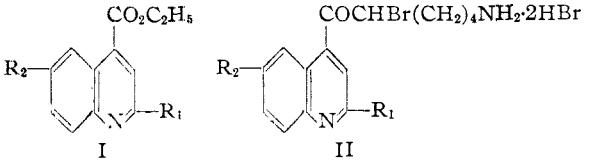
(2) Rapport, Senear, Mead and Koepfli, THIS JOURNAL, **68**, 2697 (1946).

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

(4) Brown, Jacobs, Winstein, *et al.*, THIS JOURNAL, **68**, 2705 (1946).

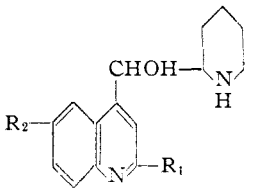
(5) Buchman, *et al.*, *ibid.*, **68**, 2692 (1946).

carbinol featuring a *t*-butyl group in the quinoline-2 position, thus providing an example without a reactive hydrogen (such as quinaldine offers).



I II

Series a: $R_1 = CH_3$, $R_2 = CH_3O$
Series b: $R_1 = (CH_3)_2CH$, $R_2 = H$
Series c: $R_1 = CH_2(CH_2)_4CH$, $R_2 = H$
Series d: $R_1 = CH_3$, $R_2 = H$



III

The carbinols IIIa, IIIb and IIIc were prepared from the appropriately substituted cinchoninic esters by the improved[6] Ainley and King synthesis.[3] The bromoketones corresponding to II were the only intermediates isolated in the course of the syntheses. In attempts to prepare IIId it was found that the acidic nature of the 2-methyl group of 2-methylcinchoninic ester complicated the condensation of this ester with ethyl ε-benzamidocaproic ester to such an extent that the synthesis was abandoned; this difficulty could have been overcome, as discovered later in the case of the 6-methoxy analog Ia, by allowing the sodium amide to react with the caproic ester before adding the cinchoninic ester.

The esters I were prepared by esterifying the appropriately substituted cinchoninic acids. The acids corresponding to Ia and Ib were previously known but, in the case of 2-cyclohexylcinchoninic acid, there are two descriptions given in the literature with different melting points. John and Pietsch[7] report the synthesis of this acid by the Pfitzinger method and give a melting point of 189°, whereas Skita and Wulff[8] prepared it by the Doebner method and give 137° as the melting point. The discrepancy seems to be explained by the observation reported here, that the acid prepared according to the former method[7] readily forms low-melting solvates.

In the preparation of 2-*t*-butylcinchoninic acid the Pfitzinger method failed and the acid was prepared from trimethylacetaldehyde by the Doebner synthesis in poor yield and then esterified; since trimethylacetaldehyde itself could be prepared only with difficulty, the synthesis of the corresponding final carbinol was not attempted.

(6) Sargent, THIS JOURNAL, **68**, 2688 (1946).
(7) John and Pietsch, *J. prakt. Chem.*, **143**, 236 (1935).
(8) Skita and Wulff, *Ber.*, **59**, 2683 (1926).

Experimental[9]

In order to avoid needless repetition only the deviations from the general method referred to[6] will be given here.

Series a

Ethyl 2-Methylquininate (Ia).—2-Methylquininic acid (54 g.), prepared according to Halberkann[10] from 5-methoxyisatin[11] was esterified with ethanolic sulfuric acid to give 52.5 g. of ester, which crystallized from ligroin (60–70°) in colorless prisms of m. p. 99–100°.

Anal. Calcd. for $C_{14}H_{15}O_3N$: C, 68.5; H, 6.2; N, 5.7. Found: C, 68.5; H, 6.3; N, 5.8.

ε-Bromo-ε-(6-methoxy-2-methylcinchoninyl)-*n*-amylamine Dihydrobromide (IIa).—Ethyl ε-benzamidocaproate[12] (107 g.) in 200 ml. of benzene was treated with sodium amide (from 12.5 g. of sodium). After one-half hour, 100 g. of Ia in 100 ml. of benzene was added and the condensation and hydrolysis carried out as usual.[6] There was thus obtained 33 g. of yellow IIa. A sample for analysis crystallized from 20% hydrobromic acid in clusters of yellow needles, m. p. 207° (dec.).

Anal. Calcd. for $C_{17}H_{21}O_2N_2Br \cdot 2HBr$: C, 38.8; H, 4.4; N, 5.3. Found: C, 38.6; H, 4.0; N, 5.1.

2-Methyl-6-methoxy-α-(2-piperidyl)-4-quinolinemethanol (IIIa), (SN 10,956).[13]—Twenty-eight grams of IIa upon ring-closure and reduction gave 13.5 g. of crude IIIa, which, after crystallization from isopropyl ether, had m. p. 171–172°.

Anal. Calcd. for $C_{17}H_{22}O_2N_2$: C, 71.3; H, 7.8; N, 9.8. Found: C, 71.2; H, 7.5; N, 10.1.

The dihydrochloride of IIIa was a yellow crystalline solid, m. p. 244–245° (dec.).

Series b

Ethyl 2-Isopropylcinchoninate (Ib).—2-Isopropylcinchoninic acid[14] (149 g.) was esterified in the usual way to yield 122 g. of ester, b. p. 135–140° (0.3 mm.).

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.1; H, 7.1; N, 5.8. Found: C, 74.1; H, 7.3; N, 5.9.

ε-Bromo-ε-(2-isopropylcinchoninyl)-*n*-amylamine Dihydrobromide (IIb).—Ethyl ε-benzamidocaproate (107 g.) and Ib (100 g.) were condensed using sodium amide from 13 g. of sodium to give 43 g. of crude IIb of m. p. 180–182° (dec.). A sample for analysis crystallized from ethanol as yellow prisms, m. p. 196–197° (dec.).

Anal. Calcd. for $C_{18}H_{23}ON_2Br \cdot 2HBr$: C, 41.2; H, 4.8; N, 5.3. Found: C, 41.2; H, 4.9; N, 5.3.

From the above reaction, 50 g. of 2-isopropylcinchoninic acid was recovered.

2-Isopropyl-α-(2-piperidyl)-4-quinolinemethanol (IIIb), (SN 10,748).—Ring-closure and reduction were carried out on 40 g. of IIb to give 19 g. of the dihydrochloride of IIIb as colorless needles, m. p. 209–210°. A sample was prepared for analysis by precipitating a 0.1 *N* hydrochloric acid solution of the dihydrochloride with acetone to yield a hydrated salt which sintered above 100° and then melted at 209–210°.

Anal. Calcd. for $C_{18}H_{24}ON_2 \cdot 2HCl \cdot H_2O$: C, 57.6; H, 7.5; N, 7.5. Found: C, 57.2; H, 8.1; N, 7.2.

(9) All melting points are corrected. The microanalyses are by Dr. Gertrude Oppenheimer and Mr. Alan Swinhart.
(10) Halberkann, *Ber.*, **54**, 3080 (1921).
(11) Prepared by method of D. R. V. Golding, unpublished.
(12) Dr. C. C. Price of the University of Illinois kindly supplied all of this ester used in this investigation.
(13) 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.
(14) This acid was prepared as described by Doebner [*Ann.*, **242**, 265 (1887)], when the Pfitzinger synthesis using isatin and methyl isopropyl ketone gave a compound, m. p. 183–184°, which was not identified.

The free base IIIb, prepared from the salt and crystallized from ethanol as colorless prisms, melted at 169–170°.

Anal. Calcd. for $C_{15}H_{24}ON_2$: C, 76.0; H, 8.5; N, 9.9. Found: C, 75.7; H, 8.5; N, 10.0.

Series c

2-Cyclohexylcinchoninic Acid and Ethyl Ester.—The acid was prepared in 66% yield as described by John and Pietsch[7] from isatin and methyl cyclohexyl ketone.[15] The crude acid (140 g.) was esterified in the usual way to give 120 g. of ethyl ester, b. p. 165–168° (0.3 mm.); a picrate of this ester melted at 155–157°, the value given by John and Pietsch. A sample of the ester was saponified and the resulting acid, after several recrystallizations from absolute ethanol, melted at 180–184° (John and Pietsch report 189°); after crystallization from 50% ethanol, the acid melted at 134–141° in a manner suggesting solvation (Skita and Wulff[3] give 137° as the m. p. of the acid prepared by the Doebner method).

ε-Bromo-ε-(2-cyclohexylcinchoninyl)-*n*-amylamine Dihydrobromide (IIc).—Ethyl 2-cyclohexylcinchoninate (89.5 g.) and ethyl ε-benzamidocaproate (86.5 g.) were condensed in the presence of sodium amide (from 11.5 g. of sodium) in the usual way. After hydrolysis and bromination the hydrobromic acid solution of IIc was evaporated *in vacuo* and the residual oil taken up in isopropanol, from which solution crystallized 56.2 g. of IIc, m. p. 145–150°. A sample for analysis crystallized from isopropanol in rosets of colorless crystals, m. p. 145–147° (dec.), which contained one mole of isopropanol of crystallization.

Anal. Calcd. for $C_{21}H_{27}ON_2Br \cdot 2HBr \cdot C_3H_8O$: C, 46.1; H, 6.0. Found: C, 45.8; H, 5.8.

2-Cyclohexylcinchoninic acid (40.7 g.) was recovered in the usual manner from the hydrolysate of the last experiment.

2-Cyclohexyl-α-(2-piperidyl)-4-quinolinemethanol (IIIc), (SN 10,749).—The dihydrochloride IIc (55 g.) was suspended in 600 ml. of ethanol and treated in the usual fashion to close the ring and effect reduction. After removing the ethanol the product was taken up in chloroform, the chloroform evaporated to dryness and the residue dissolved in 75 ml. of ethanol. The addition of 70 ml. of 6 *N* ethanolic hydrogen chloride precipitated the crude dihydrochloride of IIIc (30 g.) which crystallized from ethanol as microcrystals of m. p. 177–180°.

The free base (IIIc) was prepared from the dihydrochloride and recrystallized from acetonitrile in the form of long, silky needles, m. p. 157–159°.

Anal. Calcd. for $C_{21}H_{28}ON_2$: C, 77.7; H, 8.7; N, 8.6. Found: C, 77.5; H, 8.7; N, 8.5.

A sample of the dihydrochloride of IIIc for analysis was prepared from the free base in ethanol by precipitation with ethanolic hydrogen chloride; the salt was hydrated and melted at 178–181°.

Anal. Calcd. for $C_{21}H_{28}ON_2 \cdot 2HCl \cdot H_2O$: C, 60.7; H, 7.8. Found: C, 61.0; H, 7.9.

2-*t*-Butylcinchoninic Acid and Ethyl Ester.—Condensation between isatin and pinacolone, in the manner of the Pfitzinger reaction, resulted in recovery of the starting materials, even though the conditions were varied considerably.

Trimethylacetaldehyde (20 g.),[16] pyruvic acid (18 g.) and aniline (18 g.) were condensed under the usual conditions of the Doebner reaction. The resulting crude acid, after two crystallizations from ethanol and one from benzene, was obtained as light yellow prisms (5 g.), m. p. 147–149°.

Anal. Calcd. for $C_{14}H_{15}O_2N$: N, 6.1. Found: N, 6.1.

The crude acid (12 g.) was esterified in the usual way to give 10 g. of semi-crystalline material which was distilled at 115–118° (0.2 mm.) to yield 7.5 g. of light yellow crystalline ethyl ester, m. p. 47–48°.

Anal. Calcd. for $C_{16}H_{19}O_2N$: C, 74.7; H, 7.4; N, 5.4. Found: C, 74.9; H, 7.5; N, 5.4.

Summary

The synthesis of three 2-alkyl-α-(2-piperidyl)-4-quinolinemethanols as well as the requisite cinchoninic esters is described.

(15) Nenitzescu and Cioranescu, *Ber.*, **69**, 1821 (1936).

(16) Campbell, THIS JOURNAL, **59**, 1980 (1937).

PASADENA, CALIFORNIA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 1047]

Potential Antimalarials. (Chloro-2-phenylquinolyl-4)-α-piperidylcarbinols[1]

BY E. R. BUCHMAN, H. SARGENT, T. C. MYERS AND D. R. HOWTON

Koepfli and co-workers[2] have reported the synthesis of (2-phenylquinolyl-4)-α-piperidylcarbinol; a variety of substituted derivatives have also been prepared.[2,3] The present paper describes the preparation of additional analogs containing chlorine in the molecule.

Cinchoninic esters (I) used as starting materials were made from appropriate chlorinated isatins[4] *via* the Pfitzinger reaction.[5] From these the carbinols (V) were synthesized by the conventional Ainley and King[6] method employing modifications suggested by Sargent.[7] Only one of the diastereoisomeric racemic forms[7] of V was obtained in each series.

$$\underset{\text{I}}{RCOOC_2H_5} + \underset{\text{II}}{C_2H_5OOC(CH_2)_5NHCOC_6H_5} \longrightarrow \underset{\text{III}}{RCO(CH_2)_5NH_2 \cdot xHBr} \longrightarrow \underset{\text{IV}}{RCOCHBr(CH_2)_4NH_2 \cdot xHBr} \longrightarrow \underset{\text{V}}{RCHOH\text{-}\alpha\text{-piperidyl}}$$

Series a. R[8] = 6-chloro-2-phenylquinolyl-4
b. R = 8-chloro-2-phenylquinolyl-4
c. R = 6,8-dichloro-2-phenylquinolyl-4
d. R = 6,8-dichloro-2-(*p*-chlorophenyl)-quinolyl-4

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

(3) Brown, Jacobs, Winstein, *et al.*, *ibid.*, **68**, 2705 (1946).

(4) See Buchman, Sargent, Myers and Seneker, *ibid.*, **68**, 2692 (1946).

(5) Pfitzinger, *J. prakt. Chem.*, [2] **56**, 283 (1897).

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

(7) *Cf.* Sargent, THIS JOURNAL, **68**, 2688 (1946); also refs. 2, 3, 4.

(8) Other (chloro-2-phenylquinolyl-4)-α-piperidylcarbinols have been synthesized, refs. 2, 3 and Koepfli and co-workers, unpublished. Vb, Vc and Vd analogs of the type $RCHOHCH_2NR'_2$ have been prepared, Lutz, *et al.*, THIS JOURNAL, **68**, 1813 (1946).