[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

SYNTHESES IN THE CINCHONA SERIES. IX. CERTAIN QUINICINE AND BENZOYLCINCHONA SALTS, CRYSTALLINE ETHYL DIHYDROCUPREINE (OPTOCHIN) BASE, AND OTHER DERIVATIVES[1]

BY MICHAEL HEIDELBERGER AND WALTER A. JACOBS

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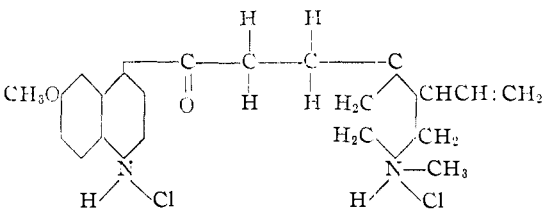
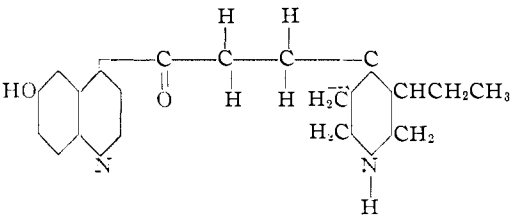
In the present communication experiments on a number of miscellaneous cinchona derivatives are assembled, many of which were used as initial material for other work, as will appear in the subsequent papers.

Very few quinicine (quinotoxine) bases or salts have been obtained crystalline up to the present, and recourse has usually been had to the oxalate or some similar salt if a crystalline compound was indeed obtained. In nearly every case investigated by us, however, either the monohydrochloride[2] or the dihydrochloride could be made to crystallize with little difficulty under suitable conditions, and in the exceptions noted the neutral sulfate or hydrobromide crystallized readily. Of these salts, besides dihydroquinicine sulfate, already studied by Hesse,[3] there are described in the present paper N-methyl-quinicine dihydrochloride (I), N-methyl-dihydroquinicine hydrochloride, N-ethyl-quinicine hydrochloride, N-ethyl-dihydroquinicine hydrochloride, N-benzyl-dihydroquinicine hydrochloride, ethyl-dihydrocupreicine (optotoxin) sulfate, and dihydrocupreicine hydrobromide, a salt of a new quinicine, (II)



I



II

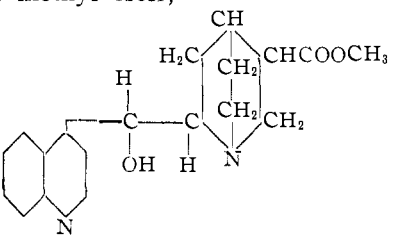
[1] Presented at the Annual Meeting of the American Chemical Society, New York, September, 1921.

[2] For the hydrochloride of quinicine itself, see THIS JOURNAL, **41**, 832 (1919).

[3] Hesse, *Ann.*, **241**, 273 (1887).

corresponding to dihydrocupreine and dihydrocupreidine.[4] Also in the quinicine series there are described the salts of two glycine derivatives in which the NH group of the piperidine nucleus has been condensed with chloro-acetyl derivatives of aromatic amines.

We have also described benzoyl-cinchonidine dihydrochloride, benzoyl-dihydrocinchonidine hydrochloride, benzoyl-quinine dihydrochloride, and benzoyl-dihydroquinine hydrochloride which, as far as we know, are new. Cinchotenine methyl ester,



cinchotenine ethyl ester hydrochloride, and cupretenine (quitenol) methyl ester dihydrochloride, we also believe have not been described.

Hitherto only crystalline salts of ethyl dihydrocupreine (optochin) have been prepared,[5] and Giemsa and Halberkann report their inability to crystallize the base. It was found, however, that after the initial crystals had been obtained by spontaneous evaporation of a toluene solution, the base could readily be obtained crystalline by seeding concentrated solutions in this solvent, separating as irregular leaflets containing toluene of crystallization, at least a part of which is retained on air drying.

Finally, the ethyl bromides of dihydroquinine and ethyl-dihydrocupreine are described, as well as the dihydrobromide of hydrobromocupreine (or hydrobromo-apoquinine), and existing data on hydrobromocinchonidine are completed.

Experimental[6]

A. Quinicine Salts

Dihydroquinicine Sulfate.[7]—Dihydroquinicine was prepared from dihydroquinine[8] sulfate according to v. Miller, Rohde and Fussenegger[9] and the crude, oily base neutralized to wet litmus in absolute alcohol with 30% aqueous sulfuric acid and treated with dry ether until the initial turbidity just redissolved. The salt separated on rubbing, and was recrystallized by dissolving in hot 95% alcohol, cooling, adding an equal volume of acetone, seeding and letting stand in the cold. It has the properties mentioned by Hesse, and in addition, comes to equilibrium in the air with 3 molecules of water of crys-

[4] THIS JOURNAL, **41**, 821, 827 (1919).

[5] *Ibid.*, **41**, 824 (1919). Giemsa and Halberkann, *Ber.*, **51**, 1332 (1918).

[6] Melting points and optical rotations were determined as in previous papers.

[7] Not fully described by Hesse, Ref. 3.

[8] THIS JOURNAL, **41**, 819 (1919). Ger. pat. 252,136.

[9] v. Miller, Rohde and Fussenegger, *Ber.*, **33**, 3228 (1900).

tallization (or its equivalent). When anhydrous, it gives $[\alpha]_D^{21.5}$ −8.3° in water, $c = 0.968$, and softens and turns yellow at 173°, melting at 174–176° to a brown liquid. The dried salt dissolves readily in absolute methyl or ethyl alcohol, separating from the latter on rubbing, presumably with alcohol of crystallization.

Analyses. Calc. for $(C_{20}H_{26}O_2N_2)_2.H_2SO_4.3H_2O$: H_2O, 6.72. Found: 6.67. Calc. for $(C_{20}H_{26}O_2N_2)_2.H_2SO_4$: N, 7.47; SO_4, 12.79. Found: N, 7.47, SO_4, 12.68.

N-Methylquinicine Dihydrochloride.—Quinidine methiodide was decomposed according to the method Freund and Rosenstein[10] used in the case of cinchonine methiodide, namely, heating in an autoclave with an excess of strong alkali. According to the literature the salts are oily, but a test portion eventually crystallized when treated with an excess of conc. hydrochloric acid, diluted with dry acetone, and allowed to evaporate spontaneously, with replacement of the acetone from time to time and rubbing. The base was accordingly dissolved in a little absolute alcohol, acidified to wet congo red paper with conc. hydrochloric acid, diluted with dry acetone until the initial turbidity just redissolved, and seeded. Crystallization of the salt as rhombic aggregates was completed by rubbing and adding more dry acetone from time to time. The dihydrochloride was recrystallized by a similar process. The air-dry salt dissolves readily in water with a bright yellow color, appearing greenish in thin layers and turning more greenish on dilution. It has a definite anesthetic effect on the tip of the tongue. Dried *in vacuo* at room temperature over sulfuric acid it gives $[\alpha]_D^{23}$ +16.6° in water, $c = 0.992$, and softens at 140–150° to a jelly, melting at 153–155° to give a yellow liquid containing bubbles. The substance gives the thalleoquinine test. The base obtained from the purified salt did not crystallize.

Analyses. Calc. for $C_{21}H_{26}O_2N_2.2HCl.H_2O$: H_2O, 4.20. Found: 4.63. Calc. for $C_{21}H_{26}O_2N_2.2HCl$: N, 6.82; Cl, 17.24. Found: N, 6.91; Cl, 16.89.

N-Methyl-dihydroquinicine Hydrochloride.—Sixty g. of dihydroquinine methiodide were heated for 4 hours at 160–165° in an autoclave with 300 cc. of water and 22 g. of sodium hydroxide.[10] The oil obtained from the ether extract was taken up in absolute alcohol. After neutralizing with absolute alcoholic hydrochloric acid the solution was concentrated *in vacuo*, dissolved in the minimum amount of dry acetone, and seeded with crystals obtained from a similarly treated test portion. Concentration of the mother liquor and addition of ether yielded a second crop, a total of 25 g. being obtained. Recrystallized from absolute alcohol by the addition of dry ether, the hydrochloride separates as cream colored microscopic prisms and needles with wedge-shaped ends. It dissolves in water to form a solution with a dull yellow color, which changes to the characteristic bright yellow-green of the quinicine di-acid salts on adding dil. hydrochloric acid. An aqueous solution has a slowly developing, definite anesthetic effect on the tip of the tongue. The air-dry salt softens to a jelly at about 120° and melts completely at about 145°. The anhydrous compound, when rapidly heated to 150°, then slowly, melts to a jelly at 150–153° and is completely fluid at 163°. It dissolves readily in absolute alcohol, dry acetone, or chloroform, and gives $[\alpha]_D^{26.5}$ −9.4° in water; $c = 1.015$.

Analyses. Calc. for $C_{21}H_{28}O_2N_2.HCl.0.5H_2O$: H_2O, 2.34. Found: 2.93. Calc. for $C_{21}H_{28}O_2N_2.HCl$: N, 7.44; Cl, 9.41. Found: N, 7.46; Cl, 9.27.

The base obtained from the purified salt failed to crystallize.

N-Ethyl-quinicine Hydrochloride.—The oily base obtained from quinidine ethyl bromide was converted into the salt as in the preceding cases. Recrystallized twice from 95% alcohol, it separates as faintly yellow, short rods which are anhydrous. It is quite soluble in dry methyl alcohol and slowly but freely soluble in water, the aqueous

[10] Freund and Rosenstein, *Ann.*, **277**, 279 (1893).

solution being weakly bitter and having definite anesthetic properties. It gives a dark blue-gray thalleoquinine test, changing to lilac. When rapidly heated to 200°, then slowly, it softens at 201°, and melts at 202–204° to a dark liquid which slowly decomposes. $[\alpha]_D^{23}$ is +68.1° in water, $c = 0.665$, a much higher value than that obtained in the case of other closely related salts.

Analyses. Calc. for $C_{22}H_{28}O_2N_2.HCl$: N, 7.21; Cl, 9.12. Found: N, 7.33; Cl, 9.02.

N-Ethyl-dihydroquinicine Hydrochloride.—This salt, obtained from dihydroquinine ethyl bromide (see below), was recrystallized from absolute alcohol and forms rosets of minute platelets which, when rapidly heated to 195°, then slowly, soften to a dark tar at 196–198° and melt completely at 202°. It dissolves readily in dry methyl alcohol or chloroform, less readily in absolute alcohol, and sparingly in boiling dry acetone. $[\alpha]_D^{27}$ is −14.4° in water; $c = 1.007$. It also has anesthetic properties.

Analyses. Calc. for $C_{22}H_{30}O_2N_2.HCl$: N, 7.17; Cl, 9.07. Found: N, 7.88; Cl, 8.98.

N-Benzyl-dihydroquinicine Hydrochloride.[11]—The crude base was taken up in dry acetone, neutralized with absolute alcoholic hydrochloric acid, and seeded with crystals obtained by evaporating a neutral alcoholic solution, adding dry acetone, and letting stand. The yield was 10.1 g. Recrystallized from absolute alcohol with the aid of dry ether the salt forms rosets of long, narrow platelets. It dissolves readily in methyl alcohol or chloroform, less easily in cold absolute alcohol, and turns gummy under a little water, dissolving on dilution without color, and turning pale yellow on adding hydrochloric acid. When rapidly heated to 160°, then slowly, it melts with slight preliminary softening at 161–164°, with slow decomposition. $[\alpha]_D^{24.5}$ in 50% alcohol is −65.9°; $c = 1.093$. It also has anesthetic properties.

Analyses. Calc. for $C_{27}H_{32}O_2N_2.HCl$: N, 6.19; Cl, 7.83. Found: N, 6.23; Cl, 7.71.

Ethyl-dihydrocupreicine (Optotoxine) Sulfate.—Although the quinicine prepared from ethyl-dihydrocupreine (optochin) is mentioned by Morgenroth[12] we have been unable to find any description of the base or its salts. The sulfate was found to crystallize readily, and was prepared as follows: 50 g. of ethyl-dihydrocupreine (Zimmer) were dissolved in 600 cc. of water and 100 cc. of 50% acetic acid and boiled in an oil-bath for 30–35 hours.[13] The free base obtained from the brown-orange solution was taken up in absolute alcohol and made very slightly acid with conc. sulfuric acid. The sulfate separated slowly when left in the cold and after rubbing. The filtrate yielded more when treated with dry acetone and ether. The yield was 28 g. Recrystallized from absolute alcohol it forms voluminous, hair-like needles which dissolve in water to form a solution with a pale greenish-yellow color changing to an intense lemon-yellow with a little mineral acid. The anhydrous salt melts at 164–166° to give a yellow liquid, has $[\alpha]_D^{28}$ −7.8° in water, $c = 1.090$, dissolves readily in methyl alcohol, rather sparingly in cold absolute alcohol, and gelatinizes under dry chloroform, dissolving with difficulty. It acts as an anesthetic on the tip of the tongue.

Analyses. Calc. for 2.5 H_2O: 5.47. Calc. for 1 C_2H_5OH: 5.59. Found: 5.81. Calc. for $(C_{21}H_{28}O_2N_2)_2.H_2SO_4$: N, 7.20; $SO_4^=$, 12.33. Found: N, 7.41; $SO_4^=$, 12.34.

Dihydrocupreicine Hydrobromide.—Twenty-five g. of crude, oily dihydroquinicine[14] were demethylated with aqueous hydrobromic acid (sp. gr. 1.49).[15] The solution

[11] THIS JOURNAL, **41**, 2102 (1919).

[12] Morgenroth, cf. *C. A.*, **13**, 2207 (1919).

[13] Cf. v. Miller and Rohde, *Ber.*, **28**, 1064 (1895).

[14] P. 1086.

[15] Cf. THIS JOURNAL, **41**, 821 (1919).

was concentrated to dryness *in vacuo*, taken up in a little hot water, cooled, and 10% aqueous sodium hydroxide was cautiously added until considerable precipitate formed but the solution still remained faintly acid to litmus. The collected salt was recrystallized from water, separating as olive-yellow aggregates of pointed platelets. The yield was 12.5 g. The hydrobromide melts slowly, with slight preliminary softening, at 213–215° to a brown liquid which gradually blackens. It dissolves in water to form a solution with a yellow color, which becomes more intense on further addition of acid. A dilute aqueous solution gives a deep olive-brown color with ferric chloride and, when made alkaline, couples readily with diazotized sulfanilic acid. It dissolves with difficulty in cold absolute alcohol, more easily on boiling, and is quite soluble in cold dry methyl alcohol. A concentrated aqueous solution gives an orange colored precipitate of the base with ammonia, but the base could not be made to crystallize. $[\alpha]_D^{21.5}$ in water is $-5.4°$; $c = 0.827$.

Analyses. Calc. for $C_{19}H_{24}O_2N_2.HBr$: N, 7.13; Br, 20.32. Found: N, 7.31; Br, 20.11.

B. Glycine Derivatives of Quinicine

Quinicylglycin-anilide Dihydrochloride, $R:N.CH_2CONHC_6H_5.2HCl$.—Four g. of quinicine oxalate, 1.7 g. of chloro-acetanilide, 2 g. of sodium iodide, 4 g. of crystalline sodium acetate, 25 cc. of alcohol, 10 cc. of *N* sodium hydroxide solution, and 15 cc. of water were boiled on the water-bath for 3 hours, with a little more alcohol to hold in solution the brown oil which soon began to separate. An additional 10 cc. of *N* sodium hydroxide was finally added and the mixture diluted with hot water, precipitating a greenish gum which resisted all efforts at crystallization. After washing with water it was treated with about 25 cc. of 1:1 hydrochloric acid. The dihydrochloride which crystallized was taken up in hot water, the solution boiled with bone black to remove impurities, and the filtrate chilled and treated with hydrogen chloride until just turbid. The salt separated as sheaves and rosets of delicate, pale yellow needles. Crystallization was completed by passing in more hydrogen chloride, the total yield being 2.3 g. The substance is rather sparingly soluble in cold water, more easily on warming, with a yellow color, and when dry gradually sinters to a jelly above 130°, melting and evolving gas at about 190°.

Analyses. Calc. for $C_{28}H_{31}O_3N_3.2HCl$: N, 7.93; Cl, 13.37. Found: N, 8.16; Cl, 13.95.

Quinicylglycine-*p*-hydroxyanilide Acid Sulfate.—This substance was prepared as in the case of the preceding compound, using *p*-chloro-acetylamino-phenol.[16] As neither the base nor the dihydrochloride crystallized, the crude product was rubbed with 25% sulfuric acid, when it soon became crystalline. Recrystallized from 50% alcohol containing a drop of dil. sulfuric acid, it formed rosets of orange colored leaflets and needles which were dried *in vacuo*. It melts at 212–215° with preliminary darkening and softening, and is very difficultly soluble in cold water but dissolves on boiling. It is also sparingly soluble in absolute alcohol or dry methyl alcohol, and dissolves in dil. sodium hydroxide solution with the formation of a pale yellow color.

Analyses. Calc. for $C_{28}H_{31}O_4N_3.H_2SO_4$: N, 7.36; $SO_4^=$, 16.82. Found: N, 7.28; $SO_4^=$, 17.12.

C. Hydrochlorides of Certain Benzoylated Cinchona Alkaloids

Benzoyl-cinchonidine Dihydrochloride.—Thirty g. of powdered cinchonidine were added in small portions to 60 g. of benzoyl chloride on the water-bath, with stirring.[17]

[16] THIS JOURNAL, **39**, 1442 (1917).

[17] Cf. Wunsch, *Compt. rend.*, **119**, 407 (1894).

The salt suddenly separated before all of the alkaloid had gone into solution and heating was continued for 45 minutes. An equal volume of dry acetone was added and the mixture boiled under a reflux condenser until the lumps had hardened, after which they were ground up in a mortar and again boiled for several hours. The yield was 33.8 g. Recrystallized from absolute alcohol by the addition of dry ether, the salt formed rosets of club-shaped, prismatic needles. The anhydrous salt darkens and sinters above 200°, melting and decomposing at 208–211°; it dissolves readily in water or methyl alcohol, less easily in dry chloroform, and sparingly soluble in cold absolute alcohol but readily on warming.

Analyses. Calc. for $C_{26}H_{26}O_2N_2.2HCl.H_2O$: H_2O, 3.68. Found: 3.05. Calc. for $C_{26}H_{26}O_2N_2.2HCl$: N, 5.95; Cl, 15.04. Found: N, 5.99; Cl, 14.77.

Benzoyl-dihydrocinchonidine Hydrochloride.—When 19.7 g. of benzoylcinchonidine dihydrochloride were dissolved in 150 cc. of water, treated with 5 cc. of 2% palladious chloride solution, and shaken with hydrogen, the calculated amount of gas was absorbed. The filtered solution was diluted and the base precipitated with ammonia, 15.4 g. of amorphous product being obtained. A solution of the base in absolute alcohol was neutralized with absolute alcoholic hydrochloric acid and treated with dry ether. The salt thus obtained was recrystallized by a similar process and formed rhombic crystals which were air-dried. It is rather sparingly soluble in water, dissolves slowly but freely in absolute alcohol or dry acetone, and is easily soluble in dry chloroform. The anhydrous salt gives $[\alpha]_D^{27.5}$ + 124.9° in absolute alcohol, $c = 1.093$, and softens to a jelly at 160–165°, gradually melting at 185–190° to form a yellow liquid filled with bubbles.

Analyses. Calc. for $C_{26}H_{28}O_2N_2.HCl.H_2O$: H_2O, 3.96. Found: 3.74. Calc. for $C_{26}H_{28}O_2N_2.HCl$: N, 6.42; Cl, 8.12. Found: N, 6.65; Cl, 8.19.

Benzoylquinine Dihydrochloride.—Anhydrous quinine when treated 45 minutes with benzoyl chloride yielded a crystalline salt.[17] This was recrystallized as in the preceding case, forming short, transparent prisms which were warmed to 60° for a few moments, evacuated and air-dried. It dissolves readily in water, methyl alcohol or chloroform, and somewhat less easily in absolute alcohol. The anhydrous salt gives $[\alpha]_D^{22}$ + 88.7° in water, $c = 0.892$, and when rapidly heated to 225°, then slowly, turns yellow and softens, finally melting and decomposing at 229–232°.

Analyses. Calc. for $C_{27}H_{28}O_3N_2.2HCl.H_2O$: H_2O, 3.59. Found: 4.21. Calc. for $C_{27}H_{28}O_3N_2.2HCl$: N, 5.59; Cl, 14.15. Found: N, 5.95; Cl, 13.96.

Benzoyl-dihydroquinine Hydrochloride.—Benzoylquinine dihydrochloride was reduced in the same way as the cinchonidine analog, and the crude, amorphous base was converted into the hydrochloride as in the case of the dihydrocinchonidine analog. The solution was concentrated to dryness *in vacuo* and the residue was dissolved in dry acetone, treated with dry ether, and then with ligroin until slightly turbid. The salt gradually crystallized and was purified by a repetition of the process, separating as flat, cream colored prisms which dissolve sparingly in cold water. The anhydrous salt melts and decomposes at 235–240° with preliminary softening and gives $[\alpha]_D^{24}$ +140.6° in absolute alcohol; $c = 1.298$.

Analyses. Calc. for $C_{27}H_{30}O_3N_2.HCl.0.5H_2O$: H_2O, 1.89. Found: 1.92. Calc. for $C_{27}H_{30}O_3N_2.HCl$: N, 6.00; Cl, 7.60. Found: N, 6.10; Cl, 7.55.

Tenine Ester Derivatives

Cinchotenine Methyl Ester.—Anhydrous cinchotenine was esterified in dry methyl alcoholic solution by saturation with dry hydrogen chloride. After removing the alcohol the ester was obtained from an aqueous solution of the residue by cautiously adding

sodium carbonate solution. Recrystallized from alcohol it forms glistening prismatic plates which dissolve rather sparingly in the cold in the usual neutral solvents. When rapidly heated to 240°, then slowly, the ester darkens and sinters above this point, melting and decomposing at 243–244.5°. $[\alpha]_D^{22}$ in methyl alcohol is +118.7°; $c=0.206$.

Analysis. Calc. for $C_{19}H_{22}O_3N_2$: N, 8.59. Found: N, 8.70.

Cinchotenine Ethyl Ester Hydrochloride.—This salt was prepared by neutralizing a solution of the ester base in absolute alcohol, and treating with dry ether. The salt separated as aggregates of minute plates which decompose at about 250°.

Analyses. Calc. for $C_{20}H_{24}O_3N_2.HCl.0.5H_2O$: H_2O, 2.34. Found: 2.31. Calc. for $C_{20}H_{24}O_3N_2.HCl$: Cl, 9.41. Found: 9.70.

Cupretenine (Quitenol)[18] Methyl Ester Dihydrochloride.—The ester was prepared and isolated as in the case of the cinchotenine analog. The dried, amorphous ester was converted into the dihydrochloride by means of an excess of absolute alcoholic hydrochloric acid and the solution treated with dry ether. Recrystallized in the same way it formed rosets of silky needles which gradually softened and turned yellow when heated, melting to a paste and evolving gas at about 200°. It is readily soluble in methyl alcohol and in water, the aqueous solution coupling with diazotized sulfanilic acid when made alkaline.

Analyses. Calc. for $C_{19}H_{22}O_4N_2.2HCl$: N, 6.51; Cl, 17.07. Found: N, 6.70; Cl, 16.30.

Crystalline Ethyl-dihydrocupreine (Optochin) and Other Simple Cinchona Derivatives

Ethyl-dihydrocupreine (Optochin).—Led by the ease with which we found dihydroquinine to crystallize from toluene we attempted to obtain ethyl-dihydrocupreine crystals from this solvent. The base dissolved easily, and on allowing the solution to evaporate spontaneously, crystals soon formed on the walls of the vessel. Five g. of the amorphous base (Zimmer) were accordingly dissolved in about 10 cc. of hot toluene, cooled, and seeded, the base gradually crystallizing as aggregates of irregular platelets which were again recrystallized from toluene, additional amounts being obtained from the mother liquors on adding ligroin and seeding. The crystals retained toluene of crystallization even on air drying, but as the combustions obtained on such products indicated that water was present as well, we are unable to say how much toluene was retained. The air-dry substance gives $[\alpha]_D^{26.5}$ −112.7° in absolute alcohol, $c=1.002$, melts at 80–4° with preliminary softening, and is less soluble in benzene, toluene, or ligroin than in the other usual organic solvents. After removing the toluene and water *in vacuo* first at room temperature, then at 100°, the residue melted at 123–128° with preliminary softening and gave $[\alpha]_D^{25}$ −136.2° in absolute alcohol, $c=1.005$, figures comparable with those given by the best commercial specimens of the amorphous base.

Analyses. Subs., air-dry, 0.3254: loss, 0.0510, or 15.67%; 15.66 on another preparation. Calc. for $C_{21}H_{28}O_2N_2$: C, 74.07; H, 8.29. Found: C, 74.31; H, 8.17.

Ethyl-dihydrocupreine Ethyl Bromide.—Two g. of the base and a slight excess of ethyl bromide were boiled in dry acetone for 4 hours, and the solvent then boiled off. The residue gradually crystallized on standing, as a radiating fibrous mass. This was recrystallized by dissolving in boiling dry acetone and adding dry ether. After further recrystallization it forms rosets of minute, rhombic plates which dissolve quite readily in water, especially on warming. The anhydrous bromide gives $[\alpha]_D^{25}$ −111.8° in water, $c=1.100$, softens to a viscous mass above 120° and at 185° yields a completely fluid,

[18] Quitenine was demethylated by boiling with hydrobromic acid (sp. gr. 1.49) instead of with hydriodic acid, as given by Bucher, *Monatsh.*, **14**, 603 (1893).

yellow mass containing bubbles. It dissolves readily in methyl or ethyl alcohol, acetone, or chloroform.

Analyses. Calc. for $C_{23}H_{33}O_2N_2Br.H_2O$: H_2O, 3.86. Found: 3.89. Calc. for $C_{23}H_{33}O_2N_2Br$: Br, 17.78. Found: 17.72.

Dihydroquinine Ethyl Bromide.—The components were boiled for 4 hours in a mixture of equal volumes of dry chloroform and dry acetone. Washed with acetone and recrystallized first from water and then from alcohol by adding ether, the salt formed rosets of glistening platelets. When anhydrous it gives $[\alpha]_D^{22.5}$ $-111.1°$ in water $c = 1.004$, and when rapidly heated to 185°, then slowly, melts slowly at 188–190° with slight decomposition. It is less soluble in acetone than the optochin derivative.

Analyses. Calc. for $C_{22}H_{31}O_2N_2Br.0.5H_2O$: H_2O, 2.03. Found: 2.06. Calc. for $C_{22}H_{31}O_2N_2Br$: Br, 18.36. Found: 18.31.

Hydrobromocinchonidine.—This substance was prepared as in the case of the hydrobromo compound described in the next paragraph, and to Leger's[19] description we can add only the following data. When rapidly heated to 175°, then slowly, the base discolors somewhat and melts to form a reddish liquid, with decomposition, at 176–177°. $[\alpha]_D^{21.5}$ is $-226.8°$ in dry methyl alcohol; $c = 0.1608$.

Analysis. Calc. for $C_{19}H_{23}ON_2Br$: N, 7.47. Found: N, 7.52.

Hydrobromocupreine (or hydrobromo-apoquinine)dihydrobromide.—Ten and a half g. of quinine were heated for 6 hours at 110° in an oil-bath with 60 cc. of hydrobromic acid (sp. gr. 1.49). On cooling and standing for several days the above salt crystallized. Recrystallized from water containing a little hydrobromic acid, the dihydrobromide separated as delicate, tawny, voluminous needles. The yield was 4.5 g. Like solutions of the di-acid dihydrocupreine salts, the very faintly yellow solution in water turns a deeper yellow on neutralization (the reverse of the phenomena observed in the case of the quinicines), and then gives a pale brown color with ferric chloride. The base is precipitated by sodium carbonate, redissolving on adding sodium hydroxide to yield a solution which couples with diazotized sulfanilic acid. The anhydrous salt gives $[\alpha]_D^{21}$ $-161.8°$ in water, $c = 1.022$, and softens slightly when heated, sintering at 190–195° and slowly intumescing at 197–203°. It is somewhat soluble in cold absolute alcohol, the solution crystallizing on rubbing.

Analyses. Calc. for $C_{19}H_{23}O_2N_2Br.2HBr.3.5H_2O$: H_2O, 10.23. Found: 10.24. Calc. for $C_{19}H_{23}O_2N_2Br.2HBr$: Br^-, 28.91. Found: 29.20.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

SYNTHESES IN THE CINCHONA SERIES. X. DIHYDROCINCHONICINOL AND THE DIHYDROQUINICINOLS[1]

BY MICHAEL HEIDELBERGER AND WALTER A. JACOBS

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In the course of the bacteriological study of certain cinchona derivatives undertaken in conjunction with Dr. Martha Wollstein and Dr. Lloyd D. Felton it developed that in general the dihydrogenated alkaloids of the quinicine type (I) were less pneumococcidal than the original alkaloids (II) from which they were derived. While it seemed possible

[19] Leger, *Bull. soc. chim.*, [4] **25**, 572 (1919).

[1] Presented at the Annual Meeting of the American Chemical Society, New York, September, 1921.