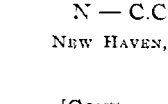
pyrimidine, but we did not succeed in isolating this combination,



NEW HAVEN, CONN.

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

SYNTHESES IN THE CINCHONA SERIES. I. THE SIMPLER CINCHONA ALKALOIDS AND THEIR DIHYDRO DERIVATIVES.

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Interest in the cinchona alkaloids as material for chemotherapeutic study has recently been revived by the remarkable specificity for the pneumococcus shown by ethylhydrocupreine.[1] The present paper is part of an investigation undertaken to test the possibilities for synthetic work in this field and deals with a number of the cinchona alkaloids, their reduction products, and certain synthetic homologs of the latter.

The cinchonine, cinchonidine, quinine, and quinidine used were purchased in the open market, and the constants obtained in the case of their monohydrochlorides are given below for comparison with the corresponding data for the other alkaloids considered.

The reduction of the four alkaloids to hydrocinchonine, hydrocinchonidine, hydroquinine, and hydroquinidine was very easily accomplished according to German patent 252,136, method 2, using palladious chloride in dilute sulfuric acid solution. Details of the method are given below for the case of hydroquinine. The properties of the hydrogenated alkaloids agreed with those recorded in the literature for the naturally occurring substances, and a direct comparison was made in the case of hydrocinchonine with a quantity of this alkaloid isolated as a by-product in the oxidation of commercial cinchonine (which contains hydrocinchonine) to the carboxylic acid cinchotenine.[2]

Considerable quantities of hydrocupreine were demanded in our synthetic work, and although this alkaloid is used in large amounts in the preparation of its ethers[3] we were unable to find recorded any satisfactory method for obtaining this substance in fairly large quantities. Hesse[4] heated hydroquinine in sealed tubes with hydrochloric acid (sp. gr. 1.125)

[1] Morgenroth and Levy, *Berl. klin. Wochschr.*, 48, 1560, 1979 (1911).

[2] Skraup, *Ann.*, 197, 376 (1879).

[3] *D. R. P.* 254,712.

[4] *Ann.*, 241, 279 (1887).

at 140–50° for 6–8 hours, while Pum[1] heated the dihydriodide with hydriodic acid (sp. gr. 1.7) on the water bath for 3 hours, but neither of these methods seemed suitable for the purpose in mind. Recourse was finally had to the well known method of de-etherifying by means of boiling aqueous hydrobromic acid, a process which could easily be applied to any quantity of hydroquinine. The details will be found in the experimental part.

As derivatives of the levorotatory alkaloid hydroquinine both hydrocupreine and its ethyl ether rotate the plane of polarized light to the left. It seemed, therefore, of interest to study the corresponding dextrorotatory stereoisomers, derivatives of hydroquinidine. We have been unable to find any description of these alkaloids, which we have named hydrocupreidine and ethylhydrocupreidine, although the former was evidently in the hands of Forst and Böhringer,[2] who heated hydroquinidine 6–8 hours at 140–50° with hydrochloric acid (sp. gr. 1.125) in a sealed tube and noted the evolution of methyl chloride and the presence in the tube of a mass of crystals from which a crystalline base could be isolated. No further description is given, however. We have found that hydrocupreidine is readily isolated by the method used for the preparation of its levorotatory isomer hydrocupreine, and that it may be converted without difficulty into its ethyl ether by means of diethyl sulfate and alcoholic alkali as described for the case of ethylhydrocupreine in German patent 254,712.

Another alkaloid selected for study was quinicine (quinotoxine). Quinidine was accordingly isomerized according to the specific instructions given by v. Miller, Rohde, and Fussenegger[3] for Pasteur's[4] original method. The first preparation was worked up in the usual manner as the oxalate, but subsequently the quinicine was isolated in good yield and without difficulty as the monohydrochloride, a salt which other workers have stated they were unable to obtain.

Finally, the preparation of isooctylhydrocupreine dihydrochloride was undertaken, this substance having been introduced in Germany during the war as "Vuzin"[5] and recommended for the treatment of infected wounds.

Experimental.

All of the values given for the optical rotation of the bases and salts were calculated by means of the formula $[\alpha] = \alpha \times 100/l \times c$, taking c as grams of substance per 100 cc. *solvent*, a close approximation for low concentrations.

[1] *Monatsh.*, **16**, 73 (1895).

[2] *Ber.*, **15**, 1658 (1882).

[3] *Ibid.*, **33**, 3228 (1900).

[4] *Compt. rend.*, **37**, 110 (1853).

[5] The original references, Morgenroth and Tugendreich, *Biochem. Z.*, **79**, 257 (1917) and *Berl. klin. Wochschr.*, **1916**, No. 29, are not available at the present writing.

Cinchonine Hydrochloride.—The base was suspended in hot water containing a few drops of alcohol and carefully neutralized to litmus on the water bath with hydrochloric acid. The salt separated from the filtered solution as spheres of woolly needles containing water of crystallization, part of which was slowly lost on air-drying. After coming to constant weight the crystals contained somewhat less than one molecule of water of crystallization. When rapidly heated to 215°, then slowly, the anhydrous salt softens at about 175° and melts at 217–8° with slow decomposition. In water $[\alpha]_D^{20.5} = +177.4°$, $c = 1.083$.

Subs., 0.6019: loss 0.0224 at 100° *in vacuo* over H_2SO_4.
Calc. for $C_{19}H_{22}ON_2.HCl.H_2O$: H_2O, 5.17. Found: 3.72.
Subs., (anhydrous); 0.2442: AgCl, 0.1064.
Calc. for $C_{19}H_{22}ON_2.HCl$: Cl, 10.72. Found: 10.78.

Cinchonidine Hydrochloride.—The alkaloid was dissolved in boiling alcohol, neutralized to litmus with hydrochloric acid, and the solution concentrated to dryness *in vacuo*. The residue was taken up in hot absolute alcohol and treated with several volumes of dry ether, the salt separating on rubbing as radiating masses of needles which contained one molecule of water of crystallization when air-dry. When rapidly heated to 240°, then slowly, the anhydrous compound softens at about 160–70° and melts with slow decomposition at 242°. In water $[\alpha]_D^{20} = -117.6°$, $c = 1.214$.

Subs., 0.7664: loss 0.0400 at 100° *in vacuo* over H_2SO_4.
Calc. for $C_{19}H_{22}ON_2.HCl.H_2O$: H_2O, 5.17. Found: 5.22.
Subs., (anhydrous): 0.2875; AgCl, 0.1233.
Calc. for $C_{19}H_{22}ON_2.HCl$: Cl, 10.72. Found: 10.61.

Quinine Hydrochloride.—Quinine was dissolved in alcohol, neutralized to litmus with hydrochloric acid, and the solution concentrated to dryness *in vacuo*. After recrystallization from water the salt showed the properties given by Hesse,[1] separating with 1.5 molecules of water of crystallization, melting to a jelly at 154–60° when anhydrous, and then also showing $[\alpha]_D^{20} = -149.8°$ in water, $c = 1.322$.

Quinidine Hydrochloride.—Our sample of the salt, prepared as in the case of the quinine hydrochloride, contained one molecule of water of crystallization as stated by Hesse.[2] The anhydrous salt gave $[\alpha]_D^{20} = +200.8°$ in water, $c = 1.3$, and when rapidly heated to 255°, then slowly, melted with decomposition at 258–9°, with preliminary darkening and sintering.

Levorotatory Hydrogenated Cinchona Derivatives.

Hydroquinine.—As stated in the introduction this substance was prepared according to the second method given in German patent 252,136. 40 g. of U. S. P. quinine were dissolved in 180 g. of 10% aqueous sulfuric

[1] *Ann.*, **267**, 143 (1892).
[2] *Ibid.*, 176, 225 (1875).

acid and the solution was filtered and treated with 8–10 cc. of a 2% solution of palladious chloride, shaking until the precipitate first formed redissolved. The clear solution was then rinsed into a shaking apparatus, the air displaced by hydrogen, and the whole then shaken with free access of hydrogen under pressure of a column of water varying from about 25 to 60 cm. The reaction proceeded slowly until the palladium was entirely reduced, after which the absorption of hydrogen was quite rapid until almost the calculated amount had been absorbed. At the end the mixture was allowed to stand until the palladium had settled, after which the supernatant liquid was carefully decanted off and the palladium used again until its catalytic activity diminished. Ordinarily 8–10 cc. of the palladium chloride solution are sufficient for 5 or 6 reductions, after which the reduction proceeds so slowly that it is best to start with a new portion. The combined solutions from a number of reductions are filtered if necessary, diluted with a large volume of water, and rapidly made alkaline with sodium hydroxide. If the addition of alkali is too slow the neutral sulfate of hydroquinine is apt to crystallize out and contaminate the base. The amorphous precipitate of hydroquinine is filtered off on a large Büchner funnel, washed well with water, sucked as dry as possible, and then spread out to dry in the air. As so obtained the crude base contains about 5.5% of moisture, and, being stable to permanganate in sulfuric acid solution, is sufficiently pure for use in the preparation of hydrocupreine. The crude alkaloid may, if desired, be advantageously recrystallized from dry acetone, in which the amorphous substance is quite soluble and the crystalline form much less so. The dry, purified substance melts at 171–2°, as given in the literature for the natural alkaloid.

Hydroquinine Hydrochloride.—10 g. of commercial hydroquinine hydrochloride (purchased before the war) were dissolved in dry acetone, filtered from dirt, and treated with several volumes of dry ether. Crystallization was induced by rubbing, the salt separating as rhombic prisms. After air-drying the salt contained 0.5 molecule of water of crystallization. When rapidly heated to 200°, then slowly, the anhydrous salt melts with preliminary softening at 206–8° to a liquid filled with bubbles. It dissolves readily in water, alcohol, methyl alcohol, or acetone. $[\alpha]_D^{21}$ of the dried salt is —123.9° in water, $c = 1.113$. Hesse,[1] who prepared the salt from the sulfate and barium chloride describes it as long, flat prisms with two molecules of water of crystallization.

Subs., 0.7705: Loss, 0.0177, *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{20}H_{26}O_2N_2.HCl.{}^1/_2H_2O$: H_2O, 2.42. Found: 2.30.
Subs., (anhydrous): 0.2630; AgCl, 0.1045.
Calc. for $C_{20}H_{26}O_2N_2.HCl$: Cl, 9.78. Found: 9.83.

Hydrocinchonidine Hydrochloride.—The reduction of cinchonidine was

[1] *Ann.*, **241**, 261 (1887).

carried out in the same way as that of hydroquinine, the yield being practically quantitative after recrystallization of the crude material from 50% alcohol. Ten g. of the base were suspended in hot water and neutralized with hydrochloric acid. The mixture was filtered, concentrated to dryness *in vacuo* and then redissolved in absolute alcohol and again concentrated as before, repeating this treatment in order to remove all of the water present. The residue was taken up in 50 cc. of absolute alcohol and cautiously treated with dry ether. The salt started to crystallize on rubbing and ligroin was then added in small amounts, with frequent rubbing, the salt gradually depositing as flat, microscopic needles and long, thin plates which were filtered off and washed with ligroin. The yield was 8 g. The salt contains no water, and when rapidly heated to 195°, then slowly, it melts at 202–3° with slight preliminary softening. $[\alpha]_D^{26} = -89.4°$ in water, $c = 1.197$. According to Hesse,[1] who probably obtained the salt by evaporation of an aqueous solution, it contains two molecules of water of crystallization, and, air-dry, shows $[\alpha]_D^{20} = -80.4°$. In addition to the solubilities reported by Hesse it may be mentioned that the salt dissolves easily in dry chloroform and is somewhat less soluble in dry acetone.

Subs., 0.1541: $AgNO_3$ soln. 9.13 cc. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{19}H_{24}ON_2.HCl$: Cl, 10.66. Found: 10.73.

Hydrocupreine.—As stated in the introduction the use of either hydrochloric or hydriodic acid for the demethylation of hydroquinine seemed scarcely suitable for preparative purposes, so the following method was adopted: 200 g. of crude hydroquinine were boiled 4 hours with 800 cc. of commercial aqueous hydrobromic acid (sp. gr. 1.49). If it is desired to collect the methyl bromide formed an air condenser may be used, connected with tubes leading into a freezing mixture. Otherwise it is advantageous to let the water liberated by the weakening of the acid boil off and attach the condenser only when the temperature of the boiling liquid has again reached 122–3°. The final dark brown solution is cooled and let stand overnight in the ice box, filtering off the heavy, crystalline precipitate of hydrocupreine dihydrobromide on cloth, washing with a little conc. hydrobromic acid, and distilling the filtrate down to about $1/3$ of its original volume, a process requiring several hours and effecting the conversion of any unchanged hydroquinine present. The crop of crystals collected after cooling the concentrated liquid is filtered off and added to the first fraction, while the filtrate, in our experiments, was added to the hydrobromic acid used for the next preparation, instead of being worked up for the relatively small amount of hydrocupreine it contained. In this way the yield of subsequent preparations averages somewhat higher than that of the first. The combined fractions of the dihydrobromide are dis-

[1] *Ann.*, **214**, 7, 15 (1882).

solved in about 8 liters of warm water, cooled, and cautiously treated with 10% sodium hydroxide solution until the localized precipitate first formed begins to dissolve slowly. Addition of sodium hydroxide is then continued rapidly, with vigorous stirring, until the copious precipitate of the base just redissolves in the excess of alkali. In this way the separation of a portion of the hydrocupreine as a gum is avoided, the gummy material dissolving in excess alkali only with the greatest difficulty. Bone-black is next added to collect a trace of gelatinous precipitate, and the solution is filtered, precipitating the hydrocupreine from the clear, yellow filtrate by the addition of an excess of saturated ammonium chloride solution. The amorphous base is filtered off on a large Büchner funnel, sucked as dry as possible, and added to about 750 cc. of boiling 95% alcohol. Most of the material dissolves before crystals begin to separate. At this point the solution is rapidly decanted from undissolved substance and this dissolved in the minimum amount of boiling alcohol and added to the rest. The mixture is then diluted with about 100 cc. of water, allowed to cool, and let stand overnight in the ice box, yielding 93 g. of crystalline hydrocupreine of a sufficiently high degree of purity for use in further work. On concentration of the mother liquors and washings to about $^1/_2$ volume *in vacuo* and addition of about $^1/_4$ volume of warm water a further crop of 21 g. was obtained, melting a few degrees below the main fraction. The ammoniacal filtrate from the crude base was shaken out with chloroform, the solvent removed, and the residue taken up in hot alcohol and cautiously diluted with water, yielding an additional 8.8 g. of hydrocupreine. The total yield was thus 67% of the theory, calculating both the hydroquinine and hydrocupreine to the anhydrous basis. A portion of the main fraction, recrystallized from 85% alcohol, separated as compact aggregates of thick, minute, barely cream-colored plates which contain no water of crystallization. The substance swells and evolves gas at 185–90°, with preliminary softening, forming a glassy mass which adheres to the walls of the tube and only liquefies completely at 230°, with simultaneous darkening. A solution of the base in absolute alcohol is practically colorless and turns yellow when water is added. An aqueous suspension gives a rather weak brown color with ferric chloride. $[\alpha]_D^{23}$ in absolute alcohol is —148.7°, $c = 1.13$.

Subs., 0.1708: N, 13.6 cc. (24.0°, 761 mm.).
Calc. for $C_{19}H_{24}O_2N_2$: N, 8.97. Found: N, 9.17.

According to Hesse[1] hydrocupreine separates with two molecules of water of crystallization, melts at 168–70°, and gives a dark brown color with ferric chloride. Pum[1] gives the melting point as 170°, while Giemsa and Halberkann,[2] who obtained the base by the catalytic reduction of

[1] *Loc. cit.*
[2] *Ber.*, **51**, 1329 (1918).

cupreine, describe it as forming needles melting at 204°, with $[\alpha]_D^{20} = -154.8°$ in absolute alcohol, $c = 1.0044$.

Hydrocupreine Hydrochloride, $C_{19}H_{24}O_2N_2.HCl$.—As far as we have been able to find, this salt has never been described. Hydrocupreine was suspended in hot water and neutralized at the boiling point with 10% hydrochloric acid. The resulting mixture was filtered, cooled, and the precipitate recrystallized from boiling water containing a few drops of dilute hydrochloric acid to drive back the slight dissociation which otherwise occurred. The salt separated slowly as radiating masses of needles which did not contain water of crystallization. When rapidly heated the compound blackens above 255° and melts and decomposes at about 280°. In absolute alcohol $[\alpha]_D^{22.5} = -132.3°$, $c = 0.945$. The salt is difficultly soluble in cold water, acetone, or chloroform, but dissolves more readily in alcohol and still more easily in methyl alcohol. The aqueous solution is yellow, as was found by Hesse[1] for the other neutral salts.

Subst., 0.1515: $AgNO_3$ soln. 8.49 cc. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{19}H_{24}O_2N_2HCl$: Cl, 10.17. Found: 10.15.

Hydrocupreine Dihydrobromide.—A portion of the first crop of crude hydrocupreine dihydrobromide obtained in the preparation of the alkaloid (see above) was dissolved in boiling water containing a little hydrobromic acid, boneblacked, and filtered. From the faintly yellow, supersaturated solution obtained on cooling the salt separates after seeding as leaf-like aggregates of irregular prisms which contain two molecules of water of crystallization when air-dry. The anhydrous salt turns yellow and softens to a jelly at about 180–90°, gradually becoming fluid as the temperature is further raised.

Subs., (air-dry) 0.7565: Loss, 0.0533 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{19}H_{24}O_2N_2.2HBr.2H_2O$: H_2O, 7.06. Found: 7.05.
Subs., (anhydrous), 0.1144: AgBr, 0.0904.
Calc. for $C_{19}H_{24}O_2N_2.2HBr$: Br, 33.73. Found: 33.62.

The air-dry salt is fairly easily soluble in water, while the anhydrous substance dissolves readily in absolute alcohol or methyl alcohol and is practically insoluble in chloroform or dry acetone.

Hydrocupreine Nitrate, $C_{19}H_{24}O_2N_2.HNO_3$.—Five g. of hydrocupreine were suspended in a little dil. alcohol and neutralized to litmus with dil. nitric acid, finally warming on the water bath to dissolve all of the base. The solution was concentrated to dryness *in vacuo* and the residue dried in a vacuum desiccator. After dissolving in warm, dry acetone and filtering, the solution was seeded with crystals obtained by letting some of the crude product stand overnight in dry acetone. The salt was deposited slowly as a hard crust of rosets of flat needles which were anhydrous when air-dried. The yield was 3.2 g. When rapidly heated to 215°,

[1] *Loc. cit.*

then slowly, the compound melts to a dark liquid at 220–2°. It turns pink on exposure to direct sunlight, is quite freely soluble in water, and dissolves readily in alcohol or methyl alcohol, less easily in dry acetone, and very sparingly in dry chloroform or benzene.

Subs., 0.1195: N, 11.6 cc. (22.0°, 754 mm.).
Calc. for $C_{19}H_{24}O_2N_2.HNO_3$: N, 11.20. Found: 11.15.

Ethylhydrocupreine Hydrochloride, $C_{21}H_{28}O_2N_2.HCl$.—The ethylhydrocupreine and amorphous ethylhydrocupreine hydrochloride used in the preparation of the 4 derivatives of "optochin" here recorded were purchased in the open market before the war. As stated by Giemsa and Halberkann[1] the hydrochloride on the market is amorphous, but these authors found that if dissolved in water or alcohol and evaporated it was left behind as radiating needles. We have found it a simple matter to obtain the pure, crystalline salt as follows: The commercial hydrochloride is dissolved in boiling, dry acetone, filtered from dirt, and the solution treated with several volumes of dry ether. The salt separates on scratching as rhombic crystals which are anhydrous when air-dried. It melts at 252–4° to a brown, turbid liquid which rapidly clears, and in water shows $[\alpha]_D^{21} = -123.6°$, $c = 0.959$. The salt dissolves readily in water, alcohol, or methyl alcohol, less easily in dry acetone.

Subs., 0.2434: AgCl, 0.0935.
Calc. for $C_{21}H_{28}O_2N_2.HCl$: Cl, 9.41. Found: 9.50.

Ethylhydrocupreine Hydrobromide.—The commercial hydrochloride was dissolved in a little hot water and treated with conc. potassium bromide solution until a faint turbidity just persisted. On cooling and letting stand part of the hydrobromide separated as an oil which gradually crystallized, the process being accelerated by rubbing. The crystals were filtered off, washed with a little ice-cold water, and recrystallized from water, separating slowly on seeding and letting stand at 0° as aggregates of rhombs which contain no water of crystallization. When rapidly heated to 255°, then slowly, the salt melts to a dark liquid at 258–9°, with slight preliminary darkening and sintering. It dissolves sparingly in cold water, readily on boiling, and is also easily soluble in methyl or ethyl alcohol or chloroform.

Subs., 0.1196: $AgNO_3$ soln. 5.65 cc. (1 cc. = 0.004043 g. Br).
Calc. for $C_{21}H_{28}O_2N_2.HBr$: Br, 18.96. Found: 19.11.

Ethylhydrocupreine Dihydrobromide.—One g. of ethylhydrocupreine was dissolved in a little water with the aid of enough conc. hydrobromic acid to give a strong blue color with congo-red. The solution was bone-blacked to remove a slight turbidity and set in the ice box, with occasional rubbing. The salt separated slowly as pale greenish yellow crusts of rhombic crystals containing 0.5 molecule of water of crystallization.

[1] *Loc. cit.*

Subs., 0.8541 g.: loss 0.0157 *in vacuo* at room temp. over H_2SO_4 + NaOH.
Calc. for $C_{21}H_{28}O_2N_2.2HBr.{}^1/_2H_2O$: H_2O, 1.76. Found: 1.84.
Subs., anhydrous: 0.1221; AgBr, 0.0905.
Calc. for $C_{21}H_{28}O_2N_2.2HBr$: Br, 31.85. Found: 31.55.

Ethylhydrocupreine Methiodide, $C_{21}H_{28}O_2N_2.CH_3I$.—17 g. of ethylhydrocupreine were dissolved in acetone and treated with 7.2 g. of methyl iodide. Heat was evolved and the quaternary salt separated almost immediately as glistening crystals. After standing overnight the methiodide was filtered off and washed with acetone. The yield was 21.5 g. A portion was recrystallized from absolute alcohol, adding a little dry ether to the warm solution before crystallization commenced. The methiodide forms glistening platelets with a faint yellow tinge and melts at 195–6° to a yellow-brown liquid. $[\alpha]_D^{21.5}$ in absolute alcohol is —113.0°, c = 0.992. The compound dissolves somewhat sparingly in water, more easily in absolute alcohol, and very readily in methyl alcohol or chloroform.

Subs., 0.2465: AgI, 0.1200.
Calc. for $C_{22}H_{31}O_2N_2I$: I, 26.32. Found: 26.31.

Sec.-Octylhydrocupreine Dihydrochloride ("Vuzin").—10.4 g. of hydrocupreine were suspended in 35 cc. of absolute alcohol and treated with 3.8 g. of 50% potassium hydroxide solution. The mixture was warmed until clear, cooled in ice-water, and then treated with 8 g. secondary octyl iodide, $C_6H_{13}(CH_3)CHI$, the general procedure being one of the alternatives outlined in German patent 254,712. The solution was allowed to stand at the temperature of a warm room for a month and was then chilled to 0° and filtered, 3.3 g. of potassium iodide remaining on the filter. The filtrate was diluted with an excess of dil. hydrochloric acid and shaken out with ether to remove isooctyl iodide and isooctyl alcohol, after which the aqueous liquid was made strongly alkaline with sodium hydroxide and again shaken out with ether. The ethereal extract was allowed to stand for several days, being then poured from a few drops of a dark, aqueous solution that had separated and extracted with 5% hydrochloric acid. The acid extract was partially concentrated *in vacuo* but the concentration could not be carried far owing to gelatinization of the solution. On standing overnight the dihydrochloride began to crystallize, and the transformation from the gelatinous into the crystalline form was completed by letting stand for several days in a warm place and finally cooling to room temperature. The salt was filtered off, washed with a little very dil. hydrochloric acid, and recrystallized from water, adding a few drops of conc. hydrochloric acid after cooling. The salt forms faintly yellow sheaves and rosets of delicate needles which contain two molecules of water of crystallization when air-dry. The yield was 6 g. The anhydrous salt softens slightly above 140°, melts to a pale yellow jelly at 157–60°, and

liquefies completely at 190–5°, with slight gas evolution. It dissolves readily in cold absolute alcohol, methyl alcohol, or dry chloroform, sparingly in cold dry acetone, more easily on boiling, and gelatinizes with a little benzene. The air-dry salt dissolves rather sparingly in cold water, readily on warming. The solution has a salty taste and gives precipitates with potassium dichromate and picric acid. A clear, warm, dilute aqueous solution soon becomes turbid, presumably owing to the separation of the monohydrochloride, as it clears again on heating. A dilute solution, treated with a few drops of aqueous hydrobromic acid, deposits the dihydrobromide on rubbing as spherical aggregates of microscopic needles.

Subs., (air-dry) 0.7612: Loss, 0.0467, *in vacuo* at room temp. over H_2SO_4.
Calc. for $C_{27}H_{40}O_2N_2.2HCl.2H_2O$: H_2O, 6.76. Found: 6.14.
Subs., (anhydrous), 0.1421: N, 7.1 cc. (21.0°, 750 mm.).
Subs., 0.1359: $AgNO_3$ soln. 10.9 cc. (1 cc. = 0.001794 g. Cl).
Calc. for $C_{27}H_{40}O_2N_2.2HCl$: N, 5.63; Cl, 14.26. Found: N, 5.73; Cl, 14.38.

Dextrorotatory Hydrogenated Cinchona Derivatives.

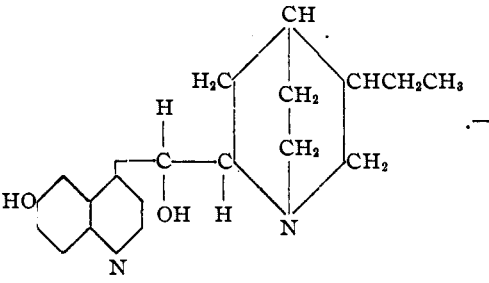
Hydrocinchonine Hydrochloride.—Two samples of this salt were prepared by neutralizing the base with hydrochloric acid in boiling water suspension; one from the naturally occurring alkaloid recovered as a by-product in the oxidation of commercial cinchonine to cinchotenine,[1] and the other from hydrocinchonine prepared from cinchonine by reduction with palladium and hydrogen as in the case of hydroquinine. Both samples gave good analyses, and conformed to the description given by Forst and Böhringer,[2] forming delicate needles containing two molecules of water of crystallization. The anhydrous hydrochloride prepared from the natural alkaloid darkened above 180°, melted at 220–1° to a dark liquid, and showed $[\alpha]_D^{23} = +155.2°$ in water, $c = 0.796$, while the anhydrous salt from the synthetic base darkened slightly above 200°, melted at 221–3° to a dark liquid, with slight gas evolution, and showed $[\alpha]_D^{25} = +159.3°$ in water, $c = 0.741$. A mixed melting-point determination showed no material depression, so it appears certain that the two preparations represent one and the same substance, as was to be expected.[3] v. Arlt[4] gives the melting point of hydrocinchonine hydrochloride as 216°.

Hydroquinidine Hydrochloride.—The salt was prepared from catalytically reduced quinidine, neutralized with hydrochloric acid in 50% alcoholic suspension, concentrated to dryness *in vacuo*, and recrystallized from water, separating as rhombic crystals which contained no water of crystallization. The salt was first described by Forst and Böhringer,[5] to

[1] *Loc. cit.*
[2] *Ber.*, 14, 437 (1881).
[3] *D. R. P.* 234,137.
[4] *Monatsh.*, 20, 431 (1899).
[5] *Ber.*, 15, 1657 (1882).

whose description the following data are added: It darkens at about 270° and decomposes at 273–4°. $[\alpha]_D^{26}$ in water is +183.9°, c = 1.278. The salt dissolves easily in cold methyl alcohol or chloroform, less readily in water or absolute alcohol, and difficultly in dry acetone.

Subs., 0.1538: $AgNO_3$ soln., 8.40 cc. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{20}H_{26}O_2N_2.HCl$: Cl, 9.78. Found: 9.90.

Hydrocupreidine,  .—The crude hydroquinidine used for the preparation of this alkaloid was obtained in precisely the same way as the hydroquinine used in the preparation of hydrocupreine, the levorotatory stereoisomer of hydrocupreidine. 77 g. of the crude hydroquinidine were dissolved in 320 cc. of commercial 40% hydrobromic acid. The solution was boiled until the temperature of the liquid had reached 125° before attaching an air-condenser to the flask. After another three-quarters of an hour a heavy precipitate of hydrocupreidine dihydrobromide suddenly separated. After cooling the product was filtered off, washed with several small portions of 40% hydrobromic acid and the filtrate and washings distilled until a second crop separated. This was filtered off and washed as in the case of the first crop, and the filtrate again concentrated to about $^1/_2$ volume, when a further amount of the salt was obtained on cooling and seeding. The combined fractions of the dihydrobromide were then dissolved in 3–4 liters of water, made alkaline with an excess of sodium hydroxide, and the base precipitated with ammonium chloride solution, using the same precautions as in the case of hydrocupreine. The crude base began to crystallize spontaneously on letting stand overnight and was recrystallized by dissolving in hot 95% alcohol and adding water until the initial turbidity just redissolved. In this way a first crop of 36.5 g. was obtained, while dilution of the mother liquors yielded further amounts which, when recrystallized as above, totaled 15.3 g., making the entire yield of purified base 51.8 g. For characterization a portion of the substance was converted into the hydrochloride (see below) and a part of this dissolved in warm water, precipitated with a slight excess of aqueous ammonia, and recrystallized from 50% alcohol, forming glistening, cream-colored, hexagonal plates which were air-dried and then contained between 0.5 and 1.0 molecule of water of crystallization. The anhydrous alkaloid

does not melt sharply, softening to a jelly above 170° and becoming completely fluid at about 195°. It is readily soluble in cold absolute alcohol or methyl alcohol, sparingly in the cold in dry acetone or chloroform, more easily on heating, and is quite difficultly soluble in dry ether. $[\alpha]_D^{19.5}$ of the anhydrous base in absolute alcohol is +253.4°, c = 1.422. In all its chemical properties the alkaloid shows a strict analogy to its levorotatory stereoisomer, hydrocupreine. Like this, its absolute alcoholic solution is practically colorless and turns yellow on adding water. An aqueous suspension also gives a rather weak brown color with ferric chloride.

Subs. (air-dry) 0.1052: Loss, 0.0048, *in vacuo* at 110° over H_2SO_4.
Calc. for $C_{19}H_{24}O_2N_2.H_2O$: H_2O, 5.45. Found: 4.56.
Subs., (anhydrous), 0.1004: CO_2, 0.2700; H_2O, 0.0678.
Subs., (anhydrous), 0.1353: N, 10.7 cc. (20.0° and 741 mm.).
Calc. for $C_{19}H_{24}O_2N_2$: C, 73.03; H, 7.75; N, 8.97. Found: C, 73.34; H, 7.56; N, 8.99.

Hydrocupreidine Hydrochloride, $C_{19}H_{24}O_2N_2.HCl.H_2O$.—9.5 g. of crystalline hydrocupreidine were suspended in about 50 cc. of 50% alcohol and neutralized with dil. hydrochloric acid, finally warming on the water bath. The hydrochloride, which separated on cooling, was filtered off and recrystallized from 50% alcohol, separating slowly as rosets and sheaves of prismatic needles containing one molecule of water of crystallization. The yield was 7.7 g. When rapidly heated to 230°, then slowly, the anhydrous salt melts at 231–3°, with darkening. $[\alpha]_D^{24}$ in water is +194.2°, c = 0.618. It dissolves rather sparingly in dry acetone or chloroform and in cold absolute alcohol or water, but dissolves in the last solvents on warming. The aqueous solution is yellow, like the solutions of the neutral salts of hydrocupreine. 1.8 g. were recovered from the mother liquors of the recrystallization by adding saturated sodium chloride solution.

Subs. (air-dry) 0.6133: Loss, 0.0291 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{19}H_{24}O_2N_2.HCl.H_2O$: H_2O, 4.91. Found: 4.75.
Subs., (anhydrous), 0.2109: AgCl, 0.0855.
Calc. for $C_{19}H_{24}O_2N_2.HCl$: Cl, 10.17. Found: 10.03.

Hydrocupreidine Dihydrobromide.—A portion of the first fraction of this salt obtained in the preparation of hydrocupreidine (see above) was recrystallized from water, adding about ½ volume of 40% hydrobromic acid to the cooled, filtered solution. The dihydrobromide separated after seeding as faintly yellow, glistening plates which contained no water of crystallization. When heated the salt turns yellow, but does not melt below 275°. It is quite freely soluble in cold water, rather difficultly in boiling absolute alcohol, and apparently insoluble in dry acetone or chloroform.

Subs., 0.1302: AgBr, 0.1030.
Calc. for $C_{19}H_{24}O_2N_2.2HBr$: Br, 33.73. Found: 33.67.

Hydrocupreidine Hydriodide.—1.8 g. of hydrocupreidine hydrochloride were dissolved in hot water and treated with several grams of sodium iodide. The hydriodide separated on cooling and scratching and was recrystallized from water, forming faintly pinkish rhombic plates and prisms containing one molecule of water of crystallization. The anhydrous salt melts at 209–12° to a brown liquid which slowly decomposes. It dissolves sparingly in boiling water with a yellow color, more easily in boiling absolute alcohol, separating on cooling as rhombic prisms, and also dissolves in the cold in dry acetone with a bright yellow color.

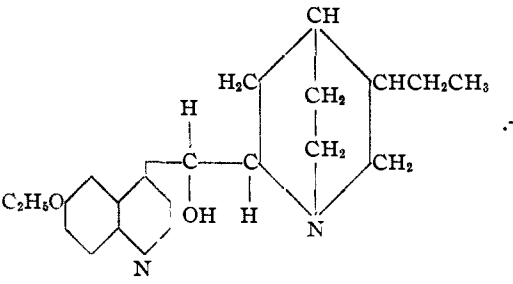
Subs. (air-dry) 0.9327: Loss, 0.0367 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{19}H_{24}O_2N_2.HI.H_2O$: H_2O, 3.93. Found: 3.93.
Subs., (anhydrous), 0.1823: AgI, 0.0961.
Calc. for $C_{19}H_{24}O_2N_2.HI$: I, 28.84. Found: 28.49.

Hydrocupreidine Nitrate.—The base was dissolved in a small volume of 95% alcohol, cooled, diluted with a little water, and neutralized to litmus with 10% aqueous nitric acid, adding a little water from time to time until the final strength of the alcohol present was about 33%. The salt crystallized on rubbing and was filtered off after standing in the ice box, washed with a little 33% alcohol, and recrystallized from 50% alcohol, separating slowly on cooling as cream-colored rhombs containing one molecule of water of crystallization. The air-dry salt dissolves in boiling water with a yellow color but is only sparingly soluble in the cold, while the anhydrous nitrate is readily soluble in absolute alcohol or methyl alcohol and very sparingly so in dry chloroform, acetone, or benzene. When rapidly heated to 150°, then slowly, it turns yellow and gradually softens, forming a jelly at about 160° and liquefying completely at 175–80°.

Subs. (air-dry) 0.6215: Loss, 0.0287, *in vacuo* at 80° over H_2SO_4.
Calc. for $C_{19}H_{24}O_2N_2.HNO_3.H_2O$: H_2O, 4.58. Found: 4.62.
Subs., anhydrous, 0.1271: N, 12.2 cc. (23.0°, 758 mm.).
Calc. for $C_{19}H_{24}O_2N_2.HNO_3$: N, 11.20. Found: 11.03.

Hydrocupreidine Methiodide, $C_{19}H_{24}O_2N_2.CH_3I$.—1.6 g. of crystalline hydrocupreidine were dissolved in warm absolute alcohol, cooled, and treated with 0.8 g. of methyl iodide. The solution was allowed to stand for 5 days in a dark place, after which the deposit of 2.0 g. of yellow, rhombic crystals of the methiodide was filtered off and washed with a little absolute alcohol. A portion was pulverized and dissolved in boiling water, in which it is difficultly soluble, separating on cooling as glistening prisms which darken slightly when rapidly heated and melt and decompose at about 295° only when left in the hot bath for a few moments. The methiodide is more soluble in 50% alcohol than in water or absolute alcohol, and also dissolves in methyl alcohol. $[\alpha]_D^{20}$ in 50% alcohol is $+202.6$, $c = 0.555$.

Subs., 0.2009: AgI, 0.1034.
Calc. for $C_{20}H_{27}O_2N_2I$: I, 27.94. Found: 27.82.

Ethylhydrocupreidine,  .—As

stated in the introduction, hydrocupreidine was converted into its ethyl ether by one of the alternative methods given in German patent 254,712. 32 g. of air-dry hydrocupreidine (+ 1 H_2O) were suspended in 90 cc. of absolute alcohol and treated with 11.5 g. of 50% aqueous potassium hydroxide solution. After stirring until clear and chilling in ice-water 13.5 cc. of washed diethyl sulfate were added and the solution placed in the ice box. The gelatinous mass first formed gradually changed over into crystals of the ethylhydrocupreidine. After 9 days the new alkaloid was filtered off, washed with a little cold alcohol, let stand for several hours with 50% alcohol containing sodium hydroxide solution, and finally washed with 50% alcohol and water. The yield was 12.7 g. The combined filtrates were made strongly alkaline and shaken out with ether, yielding only an additional trace of ethylhydrocupreidine, but on adding saturated ammonium chloride solution to the aqueous layer and shaking out the precipitated gum with ether 3 g. of hydrocupreidine was recovered. Deducting for water and recovered hydrocupreidine, the yield of the ethyl ether is 42.3% of the theory. A portion of the base was recrystallized twice from 50% alcohol and then from benzene, separating as rosets and sheaves of delicate needles which melt constantly at 197.5–8.0° with slight preliminary softening, resolidifying again a few degrees below the melting point. It dissolves quite freely in cold chloroform or methyl alcohol, rather sparingly in the cold in absolute alcohol, benzene, or ethyl acetate, easily on boiling, and is less soluble in dry acetone. $[\alpha]_D^{23.5}$ in absolute alcohol is +212.8, c = 1.008.

Subs., 0.1151: CO_2, 0.3147; H_2O, 0.0849.
Subs., 0.1399: N, 10.2 cc. (23.0°, 763 mm.).
Calc. for $C_{21}H_{28}O_2N_2$: C, 74.07; H, 8.29; N, 8.24. Found: C, 74.57; H, 8.25; N, 8.45.

Ethylhydrocupreidine Hydrochloride.—Four g. of crystalline ethylhydrocupreidine were suspended in boiling water, treated with dil. hydrochloric acid until neutral to litmus, filtered from a small amount of insoluble material, and rapidly cooled. The hydrochloride which separated was collected and recrystallized from a small volume of 50% alcohol,

separating after seeding and standing in the ice box as nacreous aggregates of flat needles and long, narrow plates. The yield was 3.5 g. The air-dry salt contains 4 molecules of water of crystallization and has a not very pronounced, bitter taste. After drying $[\alpha]_D^{22}$ is $+183.3°$ in water, $c = 0.592$, and when rapidly heated it sinters to a jelly at 140–55° and melts at 258–60° to a red-brown liquid. The dried salt dissolves very easily in absolute alcohol, methyl alcohol, or dry chloroform, difficultly in dry acetone, and sparingly in cold benzene, but quite easily on warming. It also dissolves fairly readily in cold water, the hydrate soon separating. A dilute aqueous solution gives precipitates with picric acid and potassium dichromate. When the salt is recrystallized from water it separates slowly as rhombic crystals.

Subs. (air-dry) 0.7177: Loss, 0.1150, *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{21}H_{28}O_2N_2.HCl.4H_2O$: H_2O, 16.05. Found: 16.03.
Subs., (anhydrous), 0.1387: N, 9.1 cc. (23.0°, 762 mm.).
Subs., (anhydrous), 0.1242: $AgNO_3$ soln., 6.53 cc. (1 cc. = 0.001794 g. Cl).
Calc. for $C_{21}H_{28}O_2N_2.HCl$: N, 7.44; Cl, 9.41. Found: N, 7.59; Cl, 9.43.

Ehylhydrocupreidine Hydrobromide.—0.7 g. of the hydrochloride was dissolved in hot water and treated with about 2 g. of potassium bromide. 0.5 g. of the hydrobromide separated from the still hot solution on rubbing as rhombic crystals containing no water of crystallization. When rapidly heated to 248°, then slowly, the salt melts at 250.5–3° with slow decomposition. It dissolves readily in cold, dry chloroform or methyl alcohol, less easily in absolute alcohol, and very sparingly in cold water, more readily on boiling.

Subs., 0.1198: $AgNO_3$ soln., 5.70 cc. (1 cc. = 0.004043 g. Br).
Calc. for $C_{21}H_{28}O_2N_2.HBr$: Br, 18.96. Found: 19.23.

Ethylhydrocupreidine Dihydrobromide.—1.5 g. of crystalline base were dissolved in water with the aid of an excess of hydrobromic acid. Crystallization soon started, and the collected salt was recrystallized from water, adding about $1/3$ volume of 40% hydrobromic acid after cooling. When seeded the solution rapidly deposited the dihydrobromide as radiating masses of delicate, silky needles containing 0.5 molecule of water of crystallization. The yield was 1.3 g. The dried salt gradually turns yellow above 130°, melts to a jelly at about 175–85°, and swells and evolves gas at 200–5°. It dissolves readily in water, alcohol, or methyl alcohol, is somewhat soluble in boiling dry chloroform, and is practically insoluble in dry acetone.

Subs., 1.4083: Loss, 0.0292, *in vacuo* at room temp. over H_2SO_4 and NaOH.
Calc. for $C_{21}H_{28}O_2N_2.2HBr.{}^1/_2H_2O$: H_2O, 1.76. Found: 2.07.
Subs., (anhydrous), 0.1246: AgBr, 0.0921.
Calc. for $C_{21}H_{28}O_2N_2.2HBr$: Br, 31.85. Found: 31.45.

Ethylhydrocupreidine Methiodide.—0.6 g. of the crystalline alkaloid was dissolved in warm alcohol, cooled, and treated with 0.3 g. of methyl

iodide. After letting stand overnight the solution was diluted with water, but as no precipitation occurred the solution was concentrated on the water bath until most of the alcohol had escaped. The crystals obtained on cooling were filtered off, washed with a little water, and recrystallized, with boneblacking, from 50% alcohol, separating as rhombs and prisms showing $[\alpha]_D^{22} = +189.6°$ in methyl alcohol, $c = 1.131$. When rapidly heated to 252°, then slowly, the methiodide decomposes at 253–5°. It dissolves rather sparingly in boiling water, more easily in boiling alcohol or cold methyl alcohol, and is practically insoluble in boiling dry acetone.

Subs., 0.1365: $AgNO_3$ soln., 5.6 cc. (1 cc. = 0.006421 g. I).
Calc. for $C_{22}H_{31}O_2N_2I$: I, 26.32. Found: 26.34.

Quinicine Hydrochloride, $C_{20}H_{24}O_2N_2.HCl$.—This salt has apparently never been prepared, but as will be set forth below, it may be isolated so easily and in such good yield that the customary isolation of quinicine as the sparingly soluble oxalate would seem unnecessary, especially as the oxalic acid present must often be removed before the alkaloid can be used in subsequent operations. Our first sample of the hydrochloride was prepared from quinicine oxalate[1] as follows: The salt was dissolved in hot water, treated with a slight excess of calcium chloride, and boneblacked and filtered. After concentrating to dryness *in vacuo* the residue was taken up in absolute alcohol and again concentrated as before. The deposit of crystals was taken up in hot absolute alcohol, filtered from a trace of precipitate which was collected with the aid of boneblack, and dry ether added to the filtrate until the initial turbidity dissolved with difficulty. The salt separated on seeding and rubbing as arborescent aggregates of minute leaflets which melted at 179–80° and showed $[\alpha]_D^{20} = +16.26°$ in water, $c = 0.80$. A subsequent preparation was obtained directly as follows:

112 g. of quinidine (100 g., calculated to the anhydrous basis) were converted into quinicine according to the method of v. Miller, Rohde, and Fussenegger,[1] and the crude, viscous base taken up without further treatment in about 3 volumes of absolute alcohol and neutralized with absolute alcoholic hydrochloric acid until a test drop proved neutral on wet litmus paper. After seeding with a few crystals of the preparation obtained through the oxalate the hydrochloride separated rapidly on rubbing and letting stand in the ice box. 74 g. were obtained after washing with a little absolute alcohol. A portion, recrystallized from absolute alcohol, separated in the form given above and did not contain water of crystallization. It melted with decomposition at 180–2° and showed $[\alpha]_D^{20} = +13.7°$ in water, $c = 1.861$. It dissolves readily in water

[1] *Loc. cit.*

or methyl alcohol, less easily in absolute alcohol, and is practically insoluble in dry acetone.

Subs., 0.1395: N, 9.4 cc. (21.5°, 770 mm.).
Subs., 0.1817: AgCl, 0.0717.
Calc. for $C_{20}H_{24}O_2N_2.HCl$: N, 7.77; Cl, 9.83. Found: N, 7.91; Cl, 9.76.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA.]

THE HALOGENATION OF JUGLONE: A NEW TYPE OF NAPHTHALENE DYES.[1]

BY A. S. WHEELER AND J. W. SCOTT.

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Previous to the work of Wheeler and Edwards[2] the study of the behavior of the hydroxy-naphthoquinones under direct halogenation seems to have been almost overlooked. In the monohydroxy-naphthoquinone series the only halogen derivatives obtained in this way are the 3-bromo-2-hydroxy-naphthoquinone by Diehl and Merz,[3] and the analogous iodo compound by Kehrmann and Mascioni.[4] The 4 known chloro derivatives were obtained by indirect means. In the dihydroxy-naphthoquinone series two chloro derivatives of naphthazarine have been described by Zincke and Schmidt,[5] the addition compound called the dichloride and the 2-chloro-naphthazarine. This appears to cover the ground up to 1917 when Wheeler and Edwards published their investigation of the bromination of naphthazarine and of 1,4,5,6-tetrahydroxy-naphthalene, in which they showed that the bromination of naphthazarine proceeded analogously to its chlorination and that the bromination of the tetrahydroxy-naphthalene gave isomeric compounds, explained by their earlier discovery that 1,4,5,6-tetrahydroxy-naphthalene is a case of tautomerism,[6] since it exists in the keto-enol forms. Hence a halogenated quinone would be at least one product of its halogenation.

In this paper we present the initial work upon the chlorination and the bromination of juglone or 5-hydroxy-1,4-naphthoquinone. When juglone in acetic acid solution is treated in the cold with chlorine or bromine, addition products B and G (see chart), are obtained, which lose a mole-

[1] This paper forms part of a thesis submitted by J. W. Scott in partial fulfilment of the requirements for the degree of Doctor of Philosophy in the University of North Carolina. Mr. Scott succumbed to influenza last October one week after assuming his duties as research chemist with the du Pont Company.

[2] THIS JOURNAL, **39**, 2460 (1917).

[3] *Ber.*, **11**, 1066 (1878).

[4] *Ibid.*, **28**, 345 (1895).

[5] *Ann.*, **286**, 41 (1895).

[6] THIS JOURNAL, **38**, 387 (1916).