ting masses of pale yellow, delicate needles which retain 3.5 molecules of water of crystallization when dried to constant weight in a desiccator over water. When dried in the air, water is lost and the substance sinters to a gum. The hydrate begins to soften above 60° and melts to a turbid liquid at 67.5–9°. It dissolves readily in alcohol, acetone, or chloroform, and rather less easily in ether. It does not give the thalleoquinine test. $[\alpha]_D^{22}$ is +80.2° in 95% alcohol; $c = 1.059$.

Air-dry: Subs., 0.4842: loss, 0.0717 *in vacuo* at 80° over H_2SO_4. Subs., 0.1218: 10.8 cc. N (23.5°, 757 mm.).

Calc. for $C_{20}H_{25}O_3N_3.3.5H_2O$: H_2O, 15.07; N, 10.04. Found: H_2O, 14.80; N, 10.17.

An attempt to reduce this substance failed owing to the insolubility of its tin double salt.

Summary.

Improved methods are given for the preparation of 5-nitro- and 5-amino-dihydro-quinine, and it is shown that under the usual conditions of nitration with nitric and sulfuric acids sulfonation also occurs, and 5-nitro-dihydro-quinine sulfonic acid is formed as a by-product. The extension of the methods of nitration and reduction to ethyl-dihydro-cupreine (optochin), dihydro-quinidine and ethyl-dihydro-cupreidine led to the formation of the nitro and amino derivatives of these alkaloids, and descriptions of these new substances are given. 5-Nitro-dihydro-quinane (see next paper) is also described.

NEW YORK, N. Y.

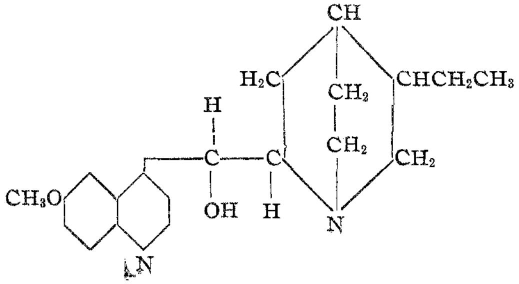
[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

SYNTHESES IN THE CINCHONA SERIES. V. DIHYDRO-DESOXY-QUININE AND DIHYDRO-DESOXY-QUINIDINE AND THEIR DERIVATIVES.

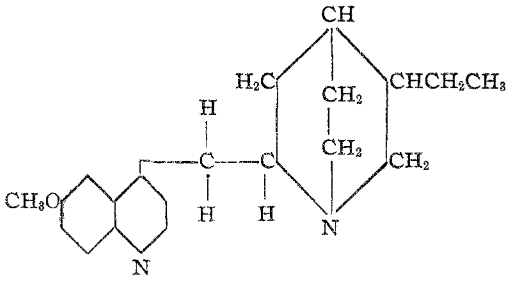
BY MICHAEL HEIDELBERGER AND WALTER A. JACOBS.

Received May 4, 1920.

As a part of our studies on the cinchona alkaloids it became of interest to examine the biological properties of the so-called "desoxy" compounds, in which the secondary alcoholic group of the parent bases

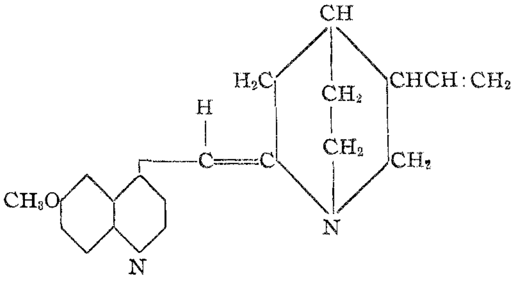


has been replaced by the hydrogen atom.

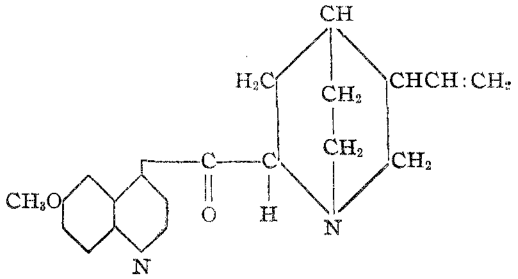


While several of these modified alkaloids have been prepared and studied chemically by Koenigs[1] and Rabe[2] and their co-workers, we are unaware of any previous publications on the desoxy compounds of dihydro-quinine and dihydro-quinidine or their immediate derivatives.

In reporting this work we have adopted a slight modification of the terminology hitherto used in this series, a modification which we believe will avoid the use of unwieldy combinations and take care of any further expansion in this field. Using as a basis Koenigs' adoption of the term "quinene" for



and Rabe's use of the term "quininone" for



we have employed the suffix "-ane" to indicate "desoxy-." "Desoxyquinine" and its stereoisomer would then become "quinane" and "quinidane," while the awkward dihydro-desoxy-quinine and dihydro-desoxy-

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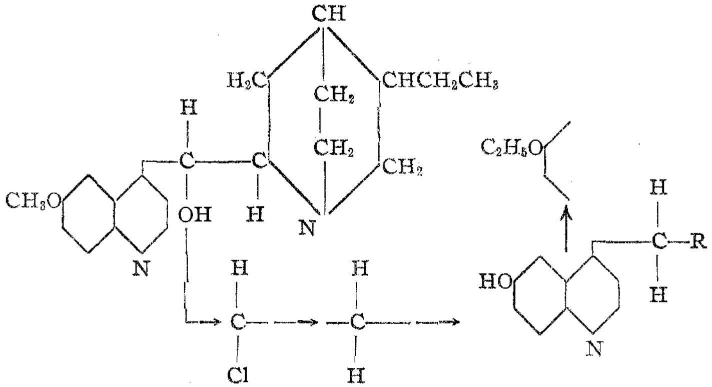
[1] Koenigs, *Ber.*, 28, 3147 (1895); 29, 372 (1896).

[2] Rabe, *Ann.*, 373, 107 (1910).

quinidine become dihydro-quinane and dihydro-quinidane. Similarly, the terms "cinchonane" and "dihydro-cupreane" seem preferable to desoxy-cinchonine and dihydro-desoxy-cupreine.

Adopting this terminology then, the following series was studied, dihydro-quinine ⟶ chloro-dihydro-quinine ⟶ dihydro-quinane ⟶ dihydro-cupreane ⟶ ethyl-dihydro-cupreane; or, graphically.



While it would no doubt have been possible to complete the corresponding series starting with the dextrorotatory dihydro-quinidine, we have carried our chemical studies with the entire group only as far as was necessary to establish the fact that these compounds are less bactericidal for the pneumococcus than the corresponding parent alkaloids.

The methods used for the preparation of the chloro- compounds and the "quinanes" were essentially those employed by Koenigs and Rabe for the corresponding non-hydrogenated derivatives, with the exception that the "quinanes" were isolated directly from the reaction mixture as the picrates. The demethylation of dihydro-quinane and dihydro-quinidane was accomplished by boiling with hydrobromic acid (sp. gr. 1.49).[1]

With the exception of ethyl-dihydro-cupreane all of the new bases crystallized fairly readily, and were further characterized by the preparation of crystalline mono-acid and di-acid salts. Dihydro-quinane and its stereoisomer could be crystallized, however, only in the form of hydrates, a property already noted by Koenigs in the case of quinane and quinidane. The 2 phenolic alkaloids, dihydro-cupreane and dihydro-cupreidane showed themselves entirely analogous in their properties to dihydro-cupreine and dihydro-cupreidine.

A. Derivatives of Dihydro-Quinine.

Chloro-dihydro-quinine.—133 g. of anhydrous dihydro-quinine dihydrochloride were worked up into a smooth, thin paste with dry chloroform and poured into a suspension of 200 g. of phosphorus pentachloride

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[1] Cf. This Journal, 41, 821 (1919).

in dry chloroform, checking the first evolution of heat by immersion in a freezing mixture. A voluminous, pale yellow precipitate formed, and there was a steady evolution of hydrogen chloride as the mixture came up to room temperature. During the next 4 or 5 days the mixture was heated in a water bath at 45–55° with frequent shaking, and was then cooled and treated with ice until no further evolution of heat was apparent. The base was precipitated from the aqueous layer by means of sodium hydroxide, taken up with ether, dried over sodium sulfate, and the solvent distilled off. The crystalline residue was taken up in boiling benzene and the solution treated with several volumes of ligroin (b. p. 80–90°), the chloro-dihydro-quinine separating on seeding as cream-colored rhombs. The yield was 67 g. Recrystallized first from dil. alcohol, then from ligroin, it forms large rhombic aggregates which melt slowly at 143–4° with slight preliminary softening. The substance dissolves readily in alcohol, acetone, chloroform, or benzene, less readily in ether, and is very sparingly soluble in cold ligroin but fairly readily so at the boiling point. It gives a pale yellow, non-fluorescent solution in dil. sulfuric acid. $[\alpha]_D^{21.5}$ is +42.1° in absolute alcohol; $c = 1.365$.

Subs., 0.1869: 13.4 cc. N (22.0°, 757 mm.).
Subs., 0.1534: (Carius) AgCl, 0.0635.
Calc. for $C_{20}H_{25}ON_2Cl$: N, 8.13; Cl, 10.28. Found: N, 8.27; Cl, 10.24.

The Hydrochloride.—A solution of the base in dil. hydrochloric acid was neutralized to litmus and treated with sodium chloride until the initial turbidity just redissolved on shaking. The salt gradually separated, and was recrystallized from 50% alcohol, separating on seeding and letting stand in the ice-box as aggregates of narrow plates which are anhydrous and dissolve rather sparingly in cold water or alcohol, more easily on heating. The aqueous solution is colorless, but turns a pale yellow when excess acid is added. The hydrochloride begins to darken and decomposes at 230°, melting with decomposition at 232–3°. $[\alpha]_D^{20.5}$ is —2.9° in water; $c = 1.197$.

Subs., 0.1387: 8.8 cc. N (20.0°, 760 mm.).
Subs., 0.1700: 8.89 cc. $AgNO_3$ sol. (1 cc. = 0.001794 g. Cl).
Calc. for $C_{20}H_{25}ON_2Cl.HCl$: N, 7.35; Cl^-, 9.31. Found: N, 7.40; Cl^-, 9.38.

Dihydro-quinane (Dihydro-desoxy-quinine). — Chloro-dihydro-quinine was reduced with iron filings and dil. sulfuric acid according to the method of Rabe *et al.*[1] for the formation of similar desoxy compounds. Instead of extracting the base from the dried precipitate of iron hydroxides, we found it less time-consuming to filter, dilute the solution with an equal volume of water, and precipitate the alkaloid with an excess of 4% sodium picrate solution, making sure that the reaction remained acid to Congo red. The picrate, which filters readily, was washed with 1%

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[1] *Ann.*, 373, 107 (1910).

sulfuric acid, ground to a thin paste with water, the mixture diluted, and then made strongly alkaline with sodium hydroxide. The base was shaken out with ether, the latter dried over sodium hydroxide, and concentrated. The residue, taken up in acetone and precipitated with water, crystallized on rubbing, owing to the formation of the *trihydrate*, the yield being 85% of the amount of chloro compound used. Recrystallized twice by dissolving in acetone, diluting with water to incipient turbidity, and rubbing, the trihydrate separated as silky needles which were brought to equilibrium for analysis in a desiccator containing only a beaker of water. When exposed to the air the crystals gradually lose their water, forming the oily, anhydrous base which could not be crystallized from dry solvents. The trihydrate dissolves readily in the usual organic solvents. A solution in dil. sulfuric acid shows a strong bluish fluorescence and is also relatively stable to permanganate. The base also gives a typical thalleoquinine test. $[\alpha]_{\mathrm{D}}^{24}$ of the trihydrate is —77.5° in absolute alcohol; c = 1.244.

Subs., 0.4048: loss, 0.0606 *in vacuo* at 100° over H_2SO_4.
Subs., 0.1142: CO_2, 0.2761; H, 0.0889.
Subs., 0.1181: 8.4 cc. N (23.0°, 764 mm.).
Subs., 0.1613: (Kjeldahl) 12.45 cc. 0.0714 *N* HCl.

Calc. for $C_{20}H_{26}ON_2.3H_2O$: C, 65.88; H, 8.86; N, 7.69; H_2O, 14.83. Found: C, 65.94; H, 8.71; N, 8.25; 7.72, H_2O, 14.97.

The Hydrochloride.—Dihydro-quinane was neutralized in alcoholic solution with hydrochloric acid, concentrated to dryness *in vacuo*, and the residue again taken down to dryness *in vacuo* after the addition of absolute alcohol. On adding dry acetone the salt soon crystallized as delicate needles which are anhydrous when air dried and melt at 179–80°. $[\alpha]_{\mathrm{D}}^{22.5}$ is —6.8° in water; c = 1.034. It dissolves readily in water, alcohol, chloroform, or methyl alcohol, and only difficultly in the cold in dry acetone or benzene, more easily on warming.

Subs., 0.1237: 9.0 cc. N (22.5°, 753 mm.).
Subs., 0.1293: 7.40 cc. $AgNO_3$ sol. (1 cc. = 0.00176 g. Cl).
Calc. for $C_{20}H_{26}ON_2.HCl$: N, 8.08; Cl, 10.22. Found: N, 8.33; Cl, 10.07.

The Dihydrochloride.—The base was treated with a slight excess of absolute alcoholic hydrochloric acid and then with dry acetone to initial turbidity. The salt crystallized on seeding with a test portion which was precipitated with dry acetone, decanted off, and let stand under dry acetone. Recrystallized by dissolving in absolute alcohol, adding a few drops of dry alcoholic hydrochloric acid, then about two volumes of dry acetone, followed by dry ether to incipient turbidity, the salt separated on seeding as faintly yellow, radiating masses of hair-like, felted needles which come to equilibrium in the air with solvent equivalent to 1.5 molecules of water of crystallization. When rapidly heated to 155°, then slowly, the salt softens to a jelly at 158–62°, gradually swelling and evolving gas, and becoming entirely fluid at about 210°. It dissolves readily in alcohol or chloroform, and very easily in water, yielding a non-fluorescent solution. When treated with a slight excess of hydrobromic acid (sp. gr. 1.49), then with acetone to incipient turbidity, a dihydrobromide separates on standing as long, delicate needles.

Air dry: Subs., 0.5360: loss, 0.0380 *in vacuo* at room temp. over H_2SO_4.
Calc. for $C_{20}H_{26}ON_2.2HCl.1.5H_2O$: H_2O, 6.59. Found: 7.09.
Anhydrous: Subs., 0.1241: 8.05 cc. N (24.0°, 753 mm.).
Subs., 0.1232: 12.95 cc. $AgNO_3$ sol. (1 cc. = 0.00176 g. Cl).
Calc. for $C_{20}H_{26}ON_2.2HCl$: N, 7.31; Cl, 18.50. Found: N, 7.39; Cl, 18.50.

Dihydro-quinane Methiodide.—After several hours the solution of the components in dry acetone was diluted with water, the salt separating slowly on rubbing and letting the solution stand. Recrystallized from 25% alcohol it separates on seeding as faintly yellow, glistening platelets and prisms which contain one molecule of water of crystallization and dissolve with difficulty in cold water and very easily on boiling. The anhydrous substance begins to sinter above 110°, forms a pale yellow jelly at 119–24°, and is completely fluid at about 145°. $[\alpha]_D^{21}$ is —7.4° in absolute alcohol; *c* = 1.145. It dissolves very easily in dry chloroform, somewhat less readily in dry methyl or ethyl alcohol, and is almost insoluble in dry acetone.

Air dry: Subs., 0.7350: loss, 0.0286 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{21}H_{29}ON_2I.H_2O$: H_2O, 3.83. Found: 3.89.
Anhydrous: Subs., 0.1486: 8.1 cc. N (23.5°, 762 mm.).
Subs., 0.1104: 4.85 cc. $AgNO_3$ sol. (1 cc. = 0.00642 g. I).
Calc. for $C_{21}H_{29}ON_2I$: N, 6.20; I, 28.07. Found: N, 6.29; I, 28.22.

Dihydro-cupreane (Dihydro-desoxy-cupreine).—25 g. of dihydroquinane trihydrate were boiled with 100 cc. of hydrobromic acid (sp. gr. 1.49) until the temperature reached 125°, after which an air condenser was attached and the boiling continued for 3 hours.[1] The solution was then concentrated *in vacuo*, taken up in about 1.5 liters of water, and treated with 10% sodium hydroxide solution until all but a little gummy material had dissolved. This was redissolved in dil. hydrochloric acid and again made alkaline with sodium hydroxide, whereupon it all redissolved. The combined solutions were treated with boneblack and filtered to remove an almost negligible turbidity, and the filtrate treated with ammonium chloride solution. The resulting precipitate, and an additional portion obtained by shaking out the filtrate with chloroform, were dried and boiled with dry acetone, crystallization soon being complete. The yield was 15.8 g. Recrystallized from ethyl acetate, it separates on seeding as minute, delicate needles which melt at 191–1.5° to a yellow liquid filled with bubbles. It is very slightly soluble, with a faint yellow color, in boiling water, but dissolves readily in methyl or ethyl alcohol, or chloro-

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[1] *Loc. cit.*

form. It is sparingly soluble in cold benzene, but dissolves on warming. The base separates from methyl ethyl ketone as crusts of minute, thin, narrow platelets. $[\alpha]_D^{21}$ is —77.1° in absolute alcohol; c = 0.973. Like dihydro-cupreine and dihydro-cupreidine[1] it couples readily in alkaline solution with diazotized aromatic amines and does not give the thalleoquinine reaction.

Subs., 0.1123: CO_2, 0.3165; H_2O, 0.0800.

Subs., 0.1175: 10.0 cc. N (28.0°, 748 mm.).

Calc. for $C_{19}H_{24}ON_2$: C, 76.97; H, 8.17; N, 9.46. Found: C, 76.86; H, 7.97; N, 9.50.

The Hydrochloride.—Dihydro-cupreane was dissolved in a little absolute alcohol and neutralized to wet litmus with absolute alcoholic hydrochloric acid. The salt soon crystallizes if water has been excluded. Recrystallized from absolute alcohol, filtering the cooled solution from a slight turbidity, it separates on standing in the cold as thin, glistening platelets which melt at about 210° with slight decomposition. $[\alpha]_D^{23}$ = +1.5° in water, c = 0.999. It dissolves readily in water with a greenish yellow color, the solution giving a brown color with ferric chloride and becoming almost colorless with an excess of hydrochloric acid. It also dissolves readily in dry methyl alcohol without color, changing to yellow on adding water. It is very difficultly soluble in boiling dry acetone or chloroform.

Subs., 0.1229: 9.1 cc. N (26.0°, 764 mm.).

Subs., 0.1227: 7.4 cc. $AgNO_3$ sol. (1 cc. = 0.00176 g. Cl).

Calc. for $C_{19}H_{24}ON_2.HCl$: N, 8.42; Cl, 10.66. Found: N, 8.50; Cl, 10.62.

The Dihydrobromide.—In another preparation of dihydro-cupreane the hydrobromic acid solution was concentrated as far as possible *in vacuo*, finally in a boiling water bath, taken up in a small volume of absolute alcohol, and allowed to stand overnight in the cold. The crude salt was recrystallized from 20% aqueous hydrobromic acid, after seeding with a test portion. It forms delicate, radiating needles which contain one molecule of water of crystallization and dissolve readily in water. The anhydrous salt slowly liquefies to a yellow fluid filled with bubbles at 225–7°. It dissolves in dry methyl alcohol, less readily in absolute alcohol, and very difficultly in boiling dry acetone or chloroform.

Air dry: Subs., 0.7651: loss, 0.0266 *in vacuo* at room temp. over H_2SO_4.

Calc. for $C_{19}H_{24}ON_2.2HBr.H_2O$: H_2O, 3.78. Found: 3.48.

Subs., 0.1239: 10.85 cc. $AgNO_3$ sol. (1 cc. = 0.00396 g. Br).

Calc. for $C_{19}H_{24}ON_2.2HBr$: Br, 34.89. Found: 34.70.

Dihydro-cupreane Methiodide.—The salt separated from chloroform solution. Recrystallized twice from absolute alcohol it forms thin, nacreous, faintly yellow platelets which dissolve in the cold in water, 50% alcohol, or methyl alcohol, and only sparingly in absolute alcohol but more

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[1] Cf. This Journal, 41, 827 (1919).

easily on boiling. It is difficultly soluble in boiling dry acetone, chloroform, or benzene. $[\alpha]_D^{22}$ is —37.6° in 50% alcohol, c = 1.050. When rapidly heated to 160°, then slowly, it melts to a jelly at 160–5° and becomes completely fluid at 165–7°.

Subs., 0.1452: AgI, 0.0766.
Calc. for $C_{20}H_{27}ON_2I$: I, 28.97. Found: 28.52.

Ethyl-dihydro-cupreane (Dihydro-cupreane Ethyl Ether) Hydrochloride.—Equimolecular amounts of dihydro-cupreane, 50% aqueous potassium hydroxide, and washed diethyl sulfate were allowed to stand in the cold in absolute alcoholic solution for 10 days.[1] The mixture was then treated with water and sodium hydroxide, shaken out with ether, and this dried over potassium hydroxide and concentrated. As the free base showed no tendency to crystallize it was neutralized to wet litmus with absolute alcoholic hydrochloric acid, treated with several volumes of dry ether, and seeded with crystals obtained from a similar test portion on long standing. The hydrochloride forms delicate needles which melt at 185–6° and dissolve readily in water, methyl or ethyl alcohol, acetone, or chloroform. The yield was poor. $[\alpha]_D^{23}$ is —9.0° in water, c = 0.722. It gives the thalleoquinine test, and fluorences strongly in aqueous solution on addition of a drop of dil. sulfuric acid.

Subs., 0.1193: 8.4 cc. N (22.5°, 753 mm.).
Subs., 0.1158: 6.28 cc. $AgNO_3$ sol. (1 cc. = 0.00176 g. Cl).
Calc. for $C_{21}H_{28}ON_2.HCl$: N, 7.77; Cl, 9.83. Found: N, 8.06; Cl, 9.55.

Bromo-dihydro-cupreine Dihydrobromide.—8 g. of chloro-dihydroquinine were demethylated in the same way as was dihydro-quinane. During the concentration of the hydrobromic acid solution *in vacuo* the dihydrobromide crystallized and was filtered off after cooling and the concentration continued, an additional amount being obtained from the residue on taking up in water and seeding. The total yield was 10.6 g. Recrystallized from water containing a little hydrobromic acid it separates as glistening, cream-colored plates containing one molecule of water of crystallization. Analysis showed that the chlorine of the chloro-dihydro quinine had been substituted by bromine. The salt dissolves in water with a pale yellow color, and after neutralization with sodium hydroxide gives a pale brown color with ferric chloride. $[\alpha]_D^{24}$ of the anhydrous salt is —69.1° in water, c = 1.005. When rapidly heated to 195°, then slowly, the yellowish anhydrous salt turns a deeper yellow and melts with gas evolution at 196–7°. It is soluble in absolute alcohol, especially on warming, and is almost insoluble in boiling dry acetone or chloroform.

Air dry: Subs., 0.5990: loss, 0.0201 *in vacuo* at room temp. over H_2SO_4.
Calc. for $C_{19}H_{23}ON_2Br.2HBr.H_2O$: H_2O, 3.25. Found: 3.36.
Anhydrous: Subs., 0.1367: 6.6 cc. N (26.0°, 752 mm.).
Subs., 0.1423: 10.71 cc. $AgNO_3$ sol. (1 cc. = 0.00396 g. Br).
Calc. for $C_{19}H_{23}ON_2Br.2HBr$: N, 5.22; Br^-, 29.76. Found: N, 5.45; Br^-, 29.81.

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[1] Cf. Ger. pat 254,712; THIS JOURNAL, 41, 830 (1919).

The free base was found to be quite unstable. It is precipitated from aqueous solution by sodium carbonate or bicarbonate as pale yellow, amorphous flocks, but on extracting with chloroform red decomposition products are rapidly formed, and while crystals could be obtained by taking up in dry acetone the residue from the evaporation of the chloroform *in vacuo,* satisfactory analytical values could not be realized. It was also noted that the product contained ionizable halogen. Solution of the dihydrobromide in excess alkali resulted in the rapid development of an orange color, and the base recovered on adding ammonium chloride was found to be halogen-free.

B. Derivatives of Dihydro-quinidine.

Chloro-dihydro-quinidine.—133 g. of dihydro-quinidine dihydrochloride (anhydrous) were dissolved in about 10 volumes of dry chloroform and converted into chloro-dihydro-quinidine exactly as in the case of the dihydro-quinine derivative. The crude base was dissolved in several volumes of hot ligroin, filtered with the aid of boneblack from a small amount of insoluble material, and seeded while still warm with crystals obtained by dissolving a test portion in ligroin and letting stand. 44.6 g. of the crystalline base were obtained by keeping the solution warm until most of the base had crystallized and then allowing to cool slowly to room temperature. The filtrate was treated with absolute alcohol and neutralized to litmus with alcoholic hydrochloric acid, an additional 21 g. of the hydrochloride separating in this way as delicate, voluminous needles. Recrystallized twice from ligroin as above, the base forms hard, compact, cream-colored aggregates of minute plates which melt at 93.5–5° with preliminary softening and show $[\alpha]_D^{22}$ +20.0° in absolute alcohol, $c = 0.600$. It gives the thalleoquinine reaction and is very easily soluble in alcohol, acetone, chloroform, benzene, or ether.

Subs., 0.1280: 9.4 cc. N (24.0°, 770 mm.).
Subs., 0.1742: (Carius) AgCl, 0.0717.
Calc. for $C_{20}H_{25}ON_2Cl$: N, 8.13; Cl, 10.28. Found: N, 8.55; Cl, 10.18.

The Hydrochloride.—The base was dissolved in a little absolute alcohol and neutralized to wet litmus with dry alcoholic hydrochloric acid. The salt which separated was recrystallized from absolute alcohol, forming sheaves and rosets of delicate needles. After drying *in vacuo* $[\alpha]_D^{25}$ was +39.7° in water; $c = 0.795$. The salt turns yellow and softens above 205° and blackens and melts at 208–9°. It is quite soluble in cold water and dissolves readily in dry methyl alcohol, less easily in dry alcohol or chloroform, and only with difficulty in boiling dry acetone.

Subs., 0.1191: 6.25 cc. $AgNO_3$ sol. (1 cc. = 0.00176 g. Cl).
Calc. for $C_{20}H_{25}ON_2Cl.HCl$: Cl^-, 9.31. Found: 9.24.

Dihydro-quinidane (Dihydro-desoxy-quinidine).—40 g. of chlorodihydro-quinidine were reduced to dihydro-quinidane and isolated exactly as in the case of the corresponding quinine derivatives. The oily base was dissolved in alcohol, diluted with water to incipient turbidity, and seeded with crystals obtained from a test portion dissolved in a little ligroin and allowed to evaporate spontaneously. The dihydrate separated as glistening rhombs, the amount being increased by the cautious addition of small quantities of water. The yield was 28.7 g. Recrystallized twice from 60% alcohol the dihydrate separates as rhombs and prisms which show $[\alpha]_D^{22.5} = +167.3°$ in absolute alcohol, $c = 1.124$, and melt at 81–3° with marked preliminary softening to a turbid liquid which clears at 88°. It dissolves readily in alcohol, acetone, chloroform, or benzene, less easily in ether, exhibits a marked purplish fluorescence in dil. sulfuric acid solution, and gives the thalleoquinine test. The anhydrous alkaloid melts at 68.5–70° with preliminary softening.

Air dry: Subs., 0.4798: loss, 0.0496 *in vacuo* at room temp. over H_2SO_4.

Subs., 0.1242: CO_2, 0.3159; H_2O, 0.0980.

Subs., 0.1255: 9.6 cc. N (23.0°, 760 mm.).

Subs., 0.1554: (Kjeldahl) 9.05 cc. 0.1 *N* HCl.

Calc. for $C_{20}H_{26}ON_2.2H_2O$: C, 69.31; H, 8.73; N, 8.09; H_2O, 10.40. Found: C, 69.37; H, 8.83; N, 8.82, 8.17; H_2O, 10.33.

The Hydrobromide.—The dihydrate was suspended in a little 50% alcohol and neutralized hot with 40% aqueous hydrobromic acid. The salt separated on chilling and rubbing and was recrystallized twice from 50% alcohol, separating as prismatic needles containing one molecule of water of crystallization, dissolving rather sparingly in cold water but readily in cold alcohol, and showing $[\alpha]_D^{24} = +64.5°$ in water, $c = 1.063$. The anhydrous salt melts slowly at 151–2° with very slight gas evolution and dissolves readily in methyl or ethyl alcohol, acetone, or chloroform and difficultly in cold benzene but easily on warming.

Subs., 0.4948: loss, 0.0222 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{20}H_{26}ON_2.HBr.H_2O$: H_2O, 4.40. Found: 4.49.

Anhydrous: Subs., 0.1177: 7.5 cc. N (26.0°, 756 mm.).

Subs., 0.1048: 5.45 cc. $AgNO_3$ sol. (1 cc. = 0.00396 g. Br).

Calc. for $C_{20}H_{26}ON_2.HBr$: N, 7.16; Br, 20.42. Found: N, 7.24; Br, 20.59.

The Dihydrobromide.—Dihydro-quinidane dihydrate was dissolved in absolute alcohol and treated with hydrobromic acid (sp. gr. 1.49) until acid to wet Congo red paper. Dry ether was then added to incipient turbidity and the solution seeded with crystals obtained by precipitating a test portion with dry ether and taking up the product in dry acetone. The collected salt was suspended in a little boiling absolute alcohol containing a few drops of hydrobromic acid and treated on the water bath with small portions of 95% alcohol until clear. The dihydrobromide separated slowly on cooling and seeding as faintly yellow, glistening rhombs which were white when powdered and contained no solvent of crystallization. It begins to turn yellow above 180°, softens at about

210°, and is completely fluid, with slow gas evolution, at about 225°. The salt dissolves readily in water and very difficultly in boiling dry acetone or chloroform.

Subs., 0.1051: 8.91 cc. $AgNO_3$ sol. (1 cc. = 0.00396 g. Br).
Calc. for $C_{20}H_{26}ON_2.2HBr$: Br, 33.86. Found: 33.59.

Dihydro-quinidane Methiodide.—The salt separates in quantitative yield from a solution of the components in dry acetone. Recrystallized twice from absolute alcohol it forms faintly yellow, warty masses of short needles which dissolve appreciably in cold water, readily on heating. When rapidly heated to 160°, then slowly, it melts at 163–4° with slight preliminary softening to a yellow liquid. It dissolves readily in methyl alcohol or chloroform.

Subs., 0.1020: 4.47 cc. $AgNO_3$ sol. (1 cc. = 0.00629 g. I).
Calc. for $C_{21}H_{29}ON_2I$: I, 28.07. Found: 27.57.

Dihydro-cupreidane (Dihydro-desoxy-cupreidine).—25 g. of dihydroquinidane were demethylated as in the case of the quinine analog. The residue from the concentration *in vacuo* crystallized on standing overnight, and was dissolved in much water, the solution made alkaline and then treated with saturated ammonium chloride solution. The gummy alkaloid was filtered off, dried, and combined with a further amount obtained by extracting the filtrate with ether. A crystalline product was rapidly formed on rubbing with dry acetone, the yield being 16.1 g. after washing with dry acetone. Recrystallized from toluene, in which it is quite soluble at the boiling point, but sparingly so at even a few degrees less, it forms a crust of cream-colored rosets of microcrystals which melt slowly at 183–3.5° to a straw-colored liquid. $[\alpha]_D^{24}$ is +183.7° in absolute alcohol, c = 0.991. It dissolves readily in methyl or ethyl alcohol or chloroform, and very difficultly in boiling benzene. In its chemical reactions it behaves like its stereoisomer, dihydrocupreane.

Subs., 0.1033: CO_2, 0.2912; H_2O, 0.0762.
Subs., 0.1428: 11.75 cc. N (23.5°, 764 mm.).
Calc. for $C_{19}H_{24}ON_2$: C, 76.97; H, 8.17; N, 9.46. Found: C, 76.88; H, 8.25; N, 9.52.

The Hydrochloride.—The base was dissolved in a slight excess of *N* hydrochloric acid, neutralized, and the solution treated with saturated sodium chloride solution. It soon solidified, and the collected salt was recrystallized from water, separating on seeding as short, slightly brownish, glistening needles which contain 2 molecules of water of crystallization when air dry, but appear to separate with more water, as the air dry salt first dissolves freely in water and then quickly crystallizes again. The solution gives a brownish color with ferric chloride. The anhydrous salt gradually softens to a jelly at 125–45°, and forms a yellow fluid at about 200°. It dissolves readily in dry methyl or ethyl alcohol or chloroform, the colorless solutions in the first two turning yellow on adding water. $[\alpha]_D^{22}$ of the anhydrous salt is +76.8° in water, $c = 0.436$.

Air dry: Subs., 0.5424: loss, 0.0547 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{19}H_{24}ON_2.HCl.2H_2O$: H_2O, 9.77. Found: 10.08.
Anhydrous: Subs., 0.1244: 9.2 cc. N (22.5°, 763 mm.).
Subs., 0.1530: 9.18 cc. $AgNO_3$ sol. (1 cc. = 0.00176 g. Cl).
Calc. for $C_{19}H_{24}ON_2.HCl$: N, 8.42; Cl. 10.66. Found: N, 8.57; Cl, 10.56.

The Dihydrobromide.—The salt separates from a small volume of chilled, dil. hydrobromic acid as faintly yellow aggregates of hexagonal plates containing 2 molecules of water of crystallization and dissolving quite readily in water at room temperature, less easily at 0°. The anhydrous salt softens and turns yellow above 140°, forming a jelly by the time 175° is reached and becoming completely fluid at about 205°. It forms a gum under dry methyl or ethyl alcohol, dissolving on shaking, and also gums under dry chloroform but does not dissolve completely.

Air dry: Subs., 0.5211: loss, 0.0414 *in vacuo* at room temp. over H_2SO_4.
Calc. for $C_{19}H_{24}ON_2.2HBr.2H_2O$: H_2O, 7.29. Found: 7.95.
Anhydrous: Subs., 0.1225: 10.68 cc. $AgNO_3$ sol. (1 cc. = 0.00396 g. Br).
Calc. for $C_{19}H_{24}ON_2.2HBr$: Br, 34.89. Found: 34.54.

Dihydrocupreidane Methiodide.—The salt soon separated from a solution of the components in absolute alcohol. Recrystallized from 25% alcohol it forms short, slightly brownish, prismatic rods which contain no water of crystallization and are difficultly soluble in cold water but readily on heating. It is quite soluble in methyl alcohol or 50% alcohol and almost insoluble in boiling dry acetone or chloroform. $[\alpha]_D^{23}$ is +95.0° in 50% alcohol, $c = 1.105$.

Subs., 0.1369: 6.25 cc. $AgNO_3$ sol. (1 cc. = 0.00629 g. I).
Calc. for $C_{20}H_{27}ON_2I$: I, 28.97. Found: 28.71.

Bromo-dihydro-cupreidine Dihydrobromide. — Chloro-dihydro-quinidine hydrochloride was demethylated as in the case of chloro-dihydro-quinine. In less than 2 hours the dihydrobromide separated from the boiling solution and the mixture was accordingly cooled and the salt filtered off, an additional amount being recovered on concentrating the filtrate to small bulk. Recrystallized from water containing a little hydrobromic acid it separates as sheaves of pale yellow, delicate needles which are anhydrous and decompose at about 255–6° with slight preliminary softening and darkening. $[\alpha]_D^{24}$ is —47.7° in water, $c = 1.141$. A neutralized aqueous solution gives a brown color with ferric chloride. The salt is sparingly soluble in boiling absolute alcohol, but dissolves somewhat more readily in boiling dry methyl alcohol, and behaves in the same way as its stereoisomer with carbonates and alkalies, the free base being equally unstable.

Subs., 0.1620: 7.40 cc. N (23.0°, 755 mm.).
Subs., 0.1200: 9.0 cc. $AgNO_3$ sol. (1 cc. = 0.00396 g. Br).
Calc. for $C_{19}H_{23}ON_2Br.2HBr$: N, 5.22; Br^-, 29.76. Found: N, 5.23; Br^-, 29.70.

If a warm, fairly concentrated solution in water is nearly neutralized with sodium hydroxide, the monohydrobromide separates on rubbing as diamond shaped, microscopic platelets.

C. Derivatives of Quinidine.

Chloroquinidine Hydrochloride.—Chloroquinidine, prepared essentially according to Comstock and Koenigs,[1] was neutralized in dil. alcohol with hydrochloric acid. The solution, after boiling with boneblack and filtering, was concentrated to dryness *in vacuo* and the residue taken up in boiling absolute alcohol. The hydrochloride was deposited on cooling and was recrystallized from absolute alcohol, with the addition of a little dry ether to the cooled solution. The salt forms woolly, cream-colored needles which show $[\alpha]_D^{25} = +47.7°$ in water, $c = 1.017$. When rapidly heated to 195°, then slowly, it gradually melts and decomposes from 199–206°. It dissolves readily in water with a faint yellow color, and also dissolves easily in dry methyl alcohol, less readily in dry chloroform, and is practically insoluble in dry acetone.

Subs., 0.1278: 8.4 cc. N (29.0°, 752 mm.).
Subs., 0.1216: 6.26 cc. $AgNO_3$ sol. (1 cc. = 0.00181 g. Cl).
Calc. for $C_{20}H_{23}ON_2Cl.HCl$: N, 7.39; Cl^-, 9.35. Found: N, 7.35; Cl^-, 9.33.

Quinidane (Desoxy-quinidine) Hydrochloride.—Quinidane (desoxy-quinidine[2]) was dissolved in a little absolute alcohol, treated with a molecular equivalent of conc. hydrochloric acid, and then with 6–8 volumes of dry ether. The hydrochloride crystallized on rubbing, and was dissolved in warm 95% alcohol, and the solution treated with 6–8 volumes of dry ether and filtered rapidly from the slight precipitate which carried considerable colored impurity with it. The salt separated slowly on seeding as aggregates of minute crystals which retained solvent equivalent to one molecule of water of crystallization on air drying. The anhydrous salt shows $[\alpha]_D^{30} = +81.9°$ in water $c = 1.313°$, and sinters and gradually melts above 125°, forming a yellow liquid at about 145°. It dissolves readily in water, methyl or ethyl alcohol, or chloroform, sparingly in cold, dry acetone, although fairly easily on boiling, and is very difficultly soluble in boiling benzene.

Air dry: Subs., 0.6065: loss, 0.0322 *in vacuo* at 80° over H_2SO_4.
Calc. for $C_{20}H_{24}ON_2.HCl.H_2O$: H_2O, 4.97. Found: 5.31.
Anhydrous: Subs., 0.1575: 11.4 cc. N (25.5°, 759 mm.).
Subs., 0.1196: 6.96 cc. $AgNO_3$ sol. (1 cc. = 0.00181 g. Cl).
Calc. for $C_{20}H_{24}ON_2.HCl$: N, 8.13; Cl, 10.28. Found: N, 8.27; Cl, 10.54.

Quinene Dihydrochloride.—Crude quinene, prepared and isolated according to Comstock and Koenigs,[3] was dissolved in absolute alcohol, treated with an excess of absolute alcoholic hydrochloric acid, and the

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[1] *Ber.*, **18**, 1223 (1885).

[2] Koenigs, *Ber.*, **28**, 3147 (1895); Rabe, *et al.*, *Ann.*, **373**, 107 (1910).

[3] *Ber.*, **17**, 1988 (1884).

dihydrochloride precipitated with dry ether. Recrystallized from absolute alcohol it forms sheaves and rosets of delicate, lemon-yellow needles which retain solvent equivalent to one molecule of water of crystallization when air-dry. The anhydrous salt shows $[\alpha]_D^{24.5} = +18.4°$ in water, $c = 1.060$, and gradually sinters and darkens when heated, melting to a dark red-brown liquid at 180–5°. It dissolves readily in water or methyl alcohol, less easily in absolute alcohol or dry chloroform, and is practically insoluble in dry acetone.

Air dry: Subs., 0.6382: loss, 0.0267 *in vacuo* at room temperature over H_2SO_4.
Calc. for $C_{20}H_{22}ON_2.2HCl.H_2O$: H_2O, 4.54. Found: 4.18.
Anhydrous: Subs., 0.1329: 8.8 cc. N (25.0°, 756 mm.).
Subs., 0.1297: 13.85 cc. $AgNO_3$ sol. (1 cc. = 0.00176 g. Cl).
Calc. for $C_{20}H_{22}ON_2.2HCl$: N, 7.39; Cl, 18.69. Found: N, 7.55; Cl, 18.81.

Summary.

The so-called "desoxy" derivatives of dihydro-quinine and dihydro-quinidine are described, together with certain of their salts, homologs, and the alkaloidal derivatives encountered in their preparation. It is proposed that the substitution of the suffix "ane" for the prefix "desoxy" would simplify the terminology of this group of substances. The series dihydro-quinine ⟶ chlorodihydro-quinine ⟶ dihydro-quinane ⟶ dihydro-cupreane ⟶ ethyl-dihydro-cupreane, resulting in the preparation of an analog of ethyl-dihydro-cupreine (optochin) was prepared and studied.

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DERIVATIVES OF TRIHALOGEN TERTIARY-BUTYL ALCOHOLS. III. THE BENZOIC ACID ESTER OF TRICHLORO-TERTIARY-BUTYL ALCOHOL OR CHLORETONE BENZOIC ACID ESTER.

BY T. B. ALDRICH.

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Under the title, "Benzoyloxyisobuttersäure trichlorid," Willgerodt and Dürr[1] have described an oil which they obtained through the interaction of trichloro-tertiary-butyl alcohol on benzoyl chloride in molecular quantities. They state

> "On heating the mixture there is a rapid evolution of hydrochloric acid gas. The liquid, boiling at 270–290°, obtained by fractionation is then dissolved in ether and shaken with an aqueous solution of sodium carbonate. After drying the ethereal solution, the ether is evaporated, and the yellowish oil remaining is distilled. The principal part of the ester distils between 275–280°, but on standing in the receptacle deposits crystals of benzoic acid which are removed by filtration. The oil thus obtained and further purified has finally a B. P. of 282° and is yellow in color. Chlorine determination: Theoretical 37.8%. Found 37.6%."

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[1] Willgerodt and Dürr, *J. prakt. Chem. N. F.*, 39, 286 (1889).