are important factors in the selective action. The organisms that are positive fix the dye because they possess compounds in their structure capable of reacting with the dye to form new complexes which limit or destroy the cell activity of the organism. The concentration of the dye is an important factor in determining its power to kill the organism, or in other words, the survival of the organism depends upon the degree to which the destructive reaction between its components and the dye has taken place and this in turn is dependent on the amount of dye which the cell has absorbed.

4. The effectiveness of the dyes used was the same in dilutions of 1 : 100,000 but different in greater dilutions.

5. No one of the dyes was effective for *B. subtilis* in dilutions greater than 1 : 100,000. *B. mycoides* was killed, however, by malachite green in dilution of 1 : 100,000, by rosaniline in dilution of 1 : 200,000, and by gentian violet, pentamethyl- and hexamethyl-*p*-rosaniline hydrochloride in a dilution of 1 : 300,000.

6. The basic nitrogen groups appear to be the reactive groups and their action is intensified by substitution of methyl for amino hydrogen.

I am greatly indebted to Mr. John Burisch, formerly a student at Wesleyan University, for assistance in the bacteriological part of this investigation, and hereby express my deep appreciation of his valuable work.

BOUND BROOK, N. J.

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

SYNTHESES IN THE CINCHONA SERIES. II. QUATERNARY SALTS.

BY WALTER A. JACOBS AND MICHAEL HEIDELBERGER.

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In a recent communication a plan was outlined for the synthesis of aromatic arsenic compounds for biological study.[1] The present paper and that following it represent an attempt to apply a similar method of treatment to the field of the cinchona alkaloids, whose possibilities as material for chemotherapeutic study in one direction have been shown by the remarkable specificity for the pneumococcus displayed by ethylhydrocupreine.[2]

Without entering into any extended discussion it may be stated that previous synthetic studies in the cinchona group have consisted mainly in the preparation of ethers of the phenolic hydroxyl group at (1) in the formula (ethylhydrocupreine being the ethyl ether), and in the formation

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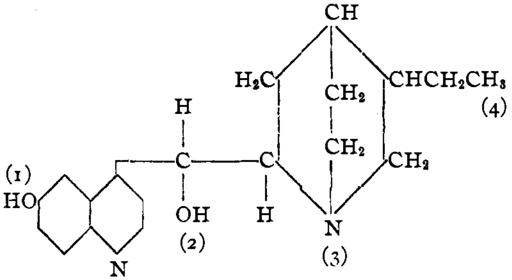
[1] THIS JOURNAL, 41, 1581 (1919).

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

of a large variety of esters, making use of the alcoholic hydroxyl group (2), many of the latter substances having been produced in the search for a tasteless quinine derivative.



Several years ago the writers made an extended study of the quaternary salts of hexamethylene-tetramine, many of which proved to possess considerable bactericidal power.[1] Since the cinchona alkaloids also contain a reactive tertiary amine group at (3) it was thought possible that from these also bactericidal or, more specifically, pneumococcidal substances might be synthesized using this as a basis. The present paper gives the chemical part of the work, and the bacteriological and biological findings will be reported in the appropriate place by Dr. Martha Wollstein, who has had charge of this phase of the work.

The methochlorides are, of course, the simplest quaternary salts possible, and a number of these were prepared as a basis for comparison. Next in complexity come the benzyl chlorides, several of which were obtained crystalline for the first time. Another larger, new group consisted of the salts formed with the chloroacetyl derivatives of ammonia, the lower aliphatic amines, and of benzylamine. Up to this point the salts were in general fairly readily soluble in water and in dilute solution did not give precipitates with alkali. In the case of the chloroacetyl derivatives of the aromatic amines the new series of salts with the alkaloids were only sparingly soluble in cold water, and were, therefore, converted into their water-soluble hydrochlorides in order to render them suitable for biological testing. The aqueous solutions so obtained gave precipitates of the quaternary bases on making alkaline with sodium hydroxide, but in only one case was a crystalline base obtained. The quaternary salts with the aromatic chloroacetyl derivatives also dissolved in dil. nitric acid, most of them soon depositing beautifully crystalline, sparingly soluble dinitrates or chloride nitrates, a representative of each group being described and analyzed. Most of the salts prepared crystallized with water of crystallization, or in cases in which anhydrous solvents were used, came to final equilibrium in the air with water of crystallization. Solutions of all of

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[1] *J. Biol. Chem.*, **20**, 659, 685 (1915); **21**, 103, *et seq.* (1915); *J. Exp. Med.*, **23**, 563, *et seq.* (1916).

the salts, aliphatic as well as aromatic, yielded immediate precipitates with solutions of picric acid or potassium dichromate. The salts of alkaloids in which the side-chain at (4) had been hydrogenated and with halides containing no readily oxidizable group, also gave purple precipitates with potassium permanganate.

Experimental.

The quaternary salts of the alkaloids with the chloroacetyl derivatives of the aliphatic and aromatic amines were prepared by boiling equimolecular amounts of the components in dry acetone for 5 to 7 hours, and this method is to be assumed below unless another is given. Unfortunately, no general method can be given for the isolation and purification of the salts, for although many either crystallized directly from the reaction mixture or remained as a crystalline residue when this was evaporated, most of the salts required different treatment in each case. Water of crystallization was determined in all cases after allowing the salt to come to equilibrium in the air; the water was then driven off *in vacuo* over sulfuric acid at room temperature, 80°, or 100°, depending on the properties of the salt. In the case of the hydrochlorides of the quaternary salts, most of those which were recrystallized from an aqueous solvent were first air-dried; all were dried for analysis to constant weight *in vacuo* at room temperature over sulfuric acid and crushed alkali. Nitrogen was usually determined by the Dumas method, although accurate values were also obtained by proper use of the Kjeldahl method. Halogen was determined in the majority of cases by the Volhard method, and it was sometimes necessary, owing to the formation of difficultly soluble nitrates which occasionally separated as gums before crystallizing, to add a definite excess of the silver nitrate solution and heat on the water bath before proceeding with the analysis. Optical rotations were calculated by means of the formula: $[\alpha] = \alpha \times 100/l \times c$, taking c as g. of substance per 100 cc. solvent, a close approximation for low concentrations. Melting points above 140° were corrected to the short-stem thermometer basis.

(A) Quaternary Salts of Cinchonine.

Cinchonine Methochloride.—Although this salt is mentioned in the literature[1] it does not seem to have been described. 16.8 g. of cinchonine methiodide were suspended in water and shaken for two hours with freshly precipitated silver chloride. The mixture was warmed on the water bath, filtered hot, and the filtrate treated with sodium chloride, causing the gradual deposition of the salt, which was recrystallized from water, forming rhombic crystals containing one molecule of water of crystallization. The yield was 9 g. When rapidly heated to 265°, then slowly, the air-dry or anhydrous chloride decomposes at 270°, with preliminary darkening. It dissolves readily in methyl or ethyl alcohol, less easily in water, and is

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[1] Stahlschmidt, *Ann.*, 90, 219 (1854); Rosenstein, *Compt. rend.*, **130,** 753 (1900).

almost insoluble in acetone. In water $[\alpha]_D^{20.5}$ is +225.1°, $c = 1.482$. The taste is weakly bitter.

Subs. (air-dry), 0.6863: loss, 0.0344 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{20}H_{25}ON_2Cl.H_2O$: H_2O, 4.97. Found: 5.01.
Subs. (anhydrous), 0.2432. AgCl, 0.1012.
Calc. for $C_{20}H_{25}ON_2Cl$: Cl, 10.28. Found: 10.29.

Cinchonine Benzyl Chloride.—Equimolecular amounts of cinchonine and benzyl chloride were boiled daily on the water bath with acetone for about two weeks. Although considerable cinchonine remained unattacked this method avoided the partial decomposition occurring when alcohol is used.[1] The mixture was finally chilled, filtered, and the precipitate boiled with water, filtering hot. The chloride crystallized on cooling as minute rods containing no water of crystallization and melting and decomposing to a purple mass at about 280°, with preliminary darkening. Claus and Treupel give the decomposition point as 248°. The salt dissolves in hot water or alcohol, sparingly in hot acetone or chloroform, or in the cold in water or alcohol. $[\alpha]_D^{22}$ in water = +164.8°, $c = 0.716$.

Subs., 0.2563: AgCl, 0.0870.
Calc. for $C_{26}H_{29}ON_2Cl$: Cl, 8.43. Found: 8.40.

Cinchonine Iodoacetamide, $C_{19}H_{22}ON_2.ICH_2CONH_2$.—15 g. of cinchonine were dissolved in boiling alcohol and treated with 9.3 g. of iodoacetamide. After letting cool the solution was partially concentrated *in vacuo,* let stand overnight, and filtered from the precipitate of unchanged cinchonine. The filtrate, concentrated almost to dryness on the water bath, crystallized on rubbing with water, yielding 16 g. of the crude iodide. Recrystallized from water with the aid of boneblack it forms aggregates of long, thin plates and flat, prismatic needles containing 2 molecules of water of crystallization. The anhydrous salt gradually softens above 145° to a yellow jelly which darkens as the temperature is raised and decomposes slowly at about 190°. It is very easily soluble in methyl or ethyl alcohol and dissolves readily in hot water and sparingly in the cold.

Subs. (air-dry), 0.6344: loss, 0.0414 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{21}H_{28}O_2N_3I.2H_2O$: H_2O, 6.99. Found: 6.53.
Subs. (anhydrous), 0.1403: 10.6 cc. N. (29.0°, 761 mm.). Subs., 0.1641: AgI, 0.0778.
Calc. for $C_{21}H_{28}O_2N_3I$: N, 8.77; I, 26.48. Found: N, 8.56; I, 25.62.

Cinchonine Chloroacetamide.—14.5 g. of cinchonine iodoacetamide were converted into the chloro compound and this isolated exactly as in the case of the methochloride. The product was recrystallized from a small volume of water, separating as rosets of minute, narrow platelets containing two molecules of water of crystallization, and melting with effervescence at 110–20° when rapidly heated. The yield was 9 g. The anhydrous

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[1] Claus and Treupel, *Ber.*, 13, 2294 (1880).

chloride gradually melts to a yellow jelly when heated and liquefies completely at about 195°, with darkening and slow gas evolution. $[\alpha]_D^{25}$ in water is +174.2°, $c = 1.163$. It dissolves readily in water, methyl or ethyl alcohol, or chloroform, and softens under dry acetone, dissolving with difficulty. The air-dry chloride dissolves rather sparingly in cold water, a suspension clearing on adding sodium hydroxide.

Subs. (air-dry), 0.8162: loss, 0.0698 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{21}H_{26}O_2N_3Cl.2H_2O$: H_2O, 8.51. Found: 8.55.
Subs. (anhydrous), 0.1513: 14.3 cc. N (23.0°, 753 mm.).
Subs., 0.1784: 9.01 cc. $AgNO_3$ soln. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{21}H_{26}O_2N_3Cl$: N, 10.84; Cl, 9.15. Found: N, 10.80; Cl, 9.15.

An attempt was made to prepare the substance directly from cinchonine and chloroacetamide in boiling acetone but little ionized halogen was formed.

(B) Quaternary Salts of Cinchonidine.

Cinchonidine Methochloride.—This substance was prepared and isolated in the same way as its cinchonine stereoisomer, except that it was necessary to saturate the solution with salt after removal of the silver iodide. The crude product was sucked as dry as possible, dissolved in absolute alcohol, filtered from sodium chloride, and cautiously precipitated by the addition of dry ether. A repetition of the purification process proved to be necessary. The salt forms minute needles containing between one and 1.5 molecules of water of crystallization. The test for alcohol of crystallization was negative. When rapidly heated to 230°, then slowly, the anhydrous compound melts and decomposes at 232–3° with slight preliminary softening. $[\alpha]_D^{22}$ in water is —142.7°, $c = 1.489$. The air-dry salt begins to melt about 20° lower than the dried portion. Claus and Bock[1] give 158° as the melting point of the anhydrous salt. It dissolves readily in the cold in water, methyl or ethyl alcohol, or chloroform, and only sparingly in dry acetone.

Subs. (air-dry), 0.6458: loss, 0.0394 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{20}H_{25}ON_2Cl.H_2O$: H_2O, 7.27. Found: 6.10.
Subs. (anhydrous), 0.2441: AgCl, 0.1031.
Calc. for $C_{20}H_{25}ON_2Cl$: Cl, 10.28. Found: 10.44.

Cinchonidine Chloroacetamide, $C_{19}H_{22}ON_2.ClCH_2CONH_2$.—15 g. of cinchonidine were dissolved in warm chloroform and treated with 9.5 g. of iodoacetamide, warming until clear. The next day about one-half of the chloroform was evaporated off and the iodide precipitated by means of dry ether. The crude product showed no tendency to crystallize and was accordingly dissolved in hot alcohol, diluted with water until just faintly turbid, and converted into the chloride with freshly precipitated silver chloride. The filtrate was concentrated to dryness *in vacuo*, evaporated down twice with absolute alcohol *in vacuo*, and finally taken up in

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[1] *Ber.*, 13, 2191 (1880).

absolute alcohol and fractionally precipitated with dry ether. The first gummy portions were discarded until finally a white, solid, amorphous product was precipitated. This was filtered off, washed with dry ether, and dried, the yield being 3.5 g. When heated it gradually softens and turns yellow, becoming completely fluid at about 190°. $[\alpha]_D^{22.5}$ in water is —112.5°, c = 1.422. The salt dissolves readily in water, methyl or ethyl alcohol, or chloroform, and forms a gum under dry acetone, dissolving with difficulty.

Subs. 0.1416: 13.3 cc. N (24.5°, 755 mm.).
Subs. 0.1720: 8.59 cc. $AgNO_3$ soln. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{21}H_{26}O_2N_3Cl$: N, 10.84; Cl, 9.15. Found: N, 10.72; Cl, 9.05.

(C) Quaternary Salts of Quinine.

Quinine Methochloride.—20.5 g. of quinine methiodide were converted into the chloride in the usual manner, salting out the compound by means of sodium chloride solution. After recrystallization from absolute alcohol, 11.6 g. of the methochloride were obtained as delicate needles containing two molecules of water of crystallization. A test for alcohol of crystallization was negative. The anhydrous salt melts partially at 170–5°, liquefying completely at 196–8° to an orange fluid filled with bubbles. $[\alpha]_D^{20}$ = —211.7° in water, c = 0.655. The salt is sparingly soluble in cold water, readily on heating, and dissolves freely in alcohol and very easily in methyl alcohol. Claus and Mallmann[1] describe the methochloride as needles containing one molecule of water of crystallization, melting at 181–2° when dry, and dissolving readily in water.

Subs. (air-dry), 0.7396: loss, 0.0642 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{21}H_{27}O_2N_2Cl.2H_2O$: H_2O, 8.77. Found: 8.68.
Subs. (anhydrous), 0.2578: AgCl, 0.0986.
Calc. for $C_{21}H_{27}O_2N_2Cl$: Cl, 9.46. Found: 9.46.

Quinine Benzyl Chloride.—17 g. of quinine were dissolved in warm acetone and allowed to stand in a warm place with 6.3 g. of benzyl chloride, adding acetone from time to time as it evaporated. After about a week a test portion cleared completely on dilution with water and addition of acid. Most of the acetone was then boiled off and absolute alcohol added. On warming and adding several volumes of dry ether crystallization of the salt commenced. The yield was 19.1 g. Recrystallized from absolute alcohol the chloride forms faintly yellow, rhombic prisms containing one molecule of water of crystallization. A test for alcohol of crystallization was negative. When rapidly heated to 180°, then slowly, the air-dry or anhydrous salt melts and darkens at 183–8°. $[\alpha]_D^{22}$ of the anhydrous compound in water is —230.5°, c = 1.479. The chloride has a bitter taste and dissolves freely in cold water, methyl or ethyl alcohol, or acetone; less easily in ethyl acetate, and sparingly in chloroform. Mazzara and

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[1] *Ber.*, 14, 76 (1881).

Possetto,[1] who prepared the salt in alcoholic solution, describe it as amorphous.

Subs. (air-dry), 0.8335: loss, 0.0295 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{27}H_{31}O_2N_2Cl.H_2O$: H_2O, 3.84. Found: 3.54.

Subs. (anhydrous), 0.1311: 7.4 cc. N (23.5°, 749 mm.). Subs., 0.2668: AgCl, 0.0844.

Calc. for $C_{27}H_{31}O_2N_2Cl$: N, 6.22; Cl, 7.87. Found: N, 6.40; Cl, 7.83.

Quinine Iodoacetamide.—After about 1.5 hours an acetone solution of 16.2 g. of quinine and 9.3 g. of iodoacetamide at room temperature began to deposit the quaternary salt as rhombic crystals, 22.8 g. being obtained. Recrystallized from water it first softens to a paste, and separates as prisms containing 1.5 molecules of water of crystallization. In this form the iodide dissolves readily in methyl or ethyl alcohol or acetone, and is sparingly soluble in cold water, readily in hot. The anhydrous salt gradually darkens and forms a jelly when heated, finally melting completely at 175–80°. It dissolves readily in chloroform and shows $[\alpha]_D^{23} = -152.2°$ in water, $c = 1.009$.

Subs. (air-dry), 0.4789: loss, 0.0257 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{22}H_{28}O_3N_3I.1.5H_2O$: H_2O, 5.04. Found: 5.37.

Subs. (anhydrous), 0.1962: AgI, 0.0898.

Calc. for $C_{22}H_{28}O_3N_3I$: I, 24.93. Found: 24.73.

Quinine Chloroacetamide.—20 g. of the iodide were shaken in water for two hours with excess silver chloride, warmed, and filtered. The filtrate was concentrated to dryness *in vacuo*, taken up twice in absolute alcohol and concentrated as before, and finally dissolved in absolute alcohol and cautiously precipitated by the addition of dry ether. The solid, amorphous precipitate was collected, ground up under dry ether, filtered again, and dried, the yield being 11.8 g. The chloride gradually softens above 160° and appears completely fluid at 190°, with gas evolution. $[\alpha]_D^{25}$ in water is $-159.6°$, $c = 1.473$. The salt dissolves readily in water, methyl or ethyl alcohol or chloroform, and only sparingly in acetone. On boiling an aqueous solution with sodium hydroxide ammonia is evolved.

Subs. 0.1387: 12.45 cc. N (24.5°, 768 mm.). Subs. 0.2321: AgCl, 0.0787.

Calc. for $C_{22}H_{28}O_3N_3Cl$: N, 10.06; Cl, 8.49. Found: N, 10.41; Cl, 8.39.

Quinine Chloroacetanilide (Quinine Acetanilide Chloride), $C_{20}H_{24}O_2N_2.ClCH_2CONHC_6H_5$.—The method given at the beginning of the "Experimental Part" was used, with 8.5 g. of chloroacetanilide.[2] After boiling off the acetone dry chloroform was added to the already partially crystalline residue. After letting stand 19 g. of silky needles of the quaternary salt were obtained. It was purified by dissolving in absolute alcohol, filtering with the aid of boneblack, and adding several volumes of dry ether, separating after rubbing or seeding as rosets of delicate needles,

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[1] *Gazz. chim. ital.*, 13, 530 (1884).

[2] THIS JOURNAL, 39, 1441 (1917).

which are quite hygroscopic until dried. When rapidly heated to 220°, then slowly, the salt darkens slightly above 190° and melts with decomposition at 224–5°. $[\alpha]_D^{23.5}$ in absolute alcohol is —131.5°, c = 1.046. It dissolves readily in methyl or ethyl alcohol, sparingly in dry acetone. It dissolves in dry chloroform, quickly separating again apparently with chloroform of crystallization. It gelatinizes under cold water and dissolves on heating, separating again on cooling as a vaseline-like mass. It dissolves with effervescence in conc. sulfuric acid, giving a pale yellow-green, fluorescent solution. The compound also gives the thalleoquinine test.

Subs., 0.1916: 14.35 cc. N (19.0°, 760 mm.).
Subs., 0.1731: 6.92 cc. $AgNO_3$ soln. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{28}H_{32}O_3N_3Cl$: N, 8.51; Cl, 7.18. Found: N, 8.57; Cl, 7.24.

The Hydrochloride.—Quinine chloroacetanilide in absolute alcohol was treated with alcoholic hydrochloric acid, the hydrochloride separating quickly as aggregates of minute, flat needles, and was filtered off after adding an equal volume of dry ether. The crude salt was dissolved in hot absolute alcohol, crystallized by the cautious addition of dry ether, and dried *in vacuo* at room temperature over sulfuric acid and crushed alkali. When rapidly heated to 200°, then slowly, it darkens and melts with decomposition at 204–6° to a deep red mass.

It has a sharp, bitter taste and dissolves readily in water, yielding a solution acid to litmus but not to congo red. It dissolves very readily in methyl alcohol, less easily in absolute alcohol or dry chloroform, and is very difficultly soluble in dry acetone. An aqueous solution gives an amorphous precipitate with excess alkali.

Subs., 0.1881: 13.1 cc. N (24.5°, 758 mm.).
Subs., 0.1258: 9.05 cc. $AgNO_3$ soln. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{28}H_{32}O_3N_3Cl.HCl$: N, 7.93; Cl, 13.37. Found: N, 7.97; Cl, 13.04.

Quinine Chloroacetanilide Nitrate, $C_{20}H_{24}O_2N_2.ClCH_2CONHC_6H_5.HNO_3$.—By analogy with the corresponding derivative of hydroquinine (see below) this salt was originally believed to be quinine acetanilide dinitrate, but as it persistently retained several per cent. of chlorine in spite of attempts to substitute the nitrate ion the preparation was modified as follows: 2 g. of the chloride hydrochloride were dissolved in water with the aid of a drop of dil. nitric acid to drive back dissociation.

A few drops of saturated salt solution were added and then 10% nitric acid until the initial turbidity barely redissolved and crystals began to form. The salt separated rapidly on rubbing and after letting stand in the cold it was filtered off and dissolved in hot water. The solution was then cooled to initial turbidity, cleared with a drop of dil. nitric acid and treated with a few drops of saturated sodium chloride solution, then with 10% nitric acid until crystals began to separate. After finally letting stand in the ice box the deposit of thin, nacreous platelets was filtered off and washed with a little ice water. The yield was 1.4 g. When rapidly heated to 100°, then slowly, the salt decomposes at 201–3° with preliminary browning and softening. It is appreciably soluble in water at room temperature, but is almost insoluble in the presence of nitric acid. It is readily soluble in boiling water, less easily in boiling methyl or ethyl alcohol, and difficultly in boiling acetone or chloroform. The air-dry salt contains no water of crystallization.

Subs. 0.1163: 10.9 cc. N (28.5°, 763 mm.).

Subs. 0.1352: 4.54 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{28}H_{32}O_3N_3Cl.HNO_3$: N, 10.06; Cl, 6.37. Found: N, 10.65; Cl, 6.03.

Quinine *p*-Chloroacetylamino-phenol, $C_{20}H_{24}O_2N_2.ClCH_2CONHC_6H_4$-$OH$(*p*-).—4.7 g. of *p*-chloroacetylamino-phenol[1] were used. Toward the end a dark tar separated, and on standing overnight a portion of this crystallized. The acetone was poured off and the crude material dissolved in a little warm absolute alcohol and treated with several volumes of dry acetone. Dry, alcohol-free ether was then cautiously added until a slight permanent turbidity had formed, and after treating with boneblack, the filtrate was seeded. On rubbing and stirring and occasionally adding additional small amounts of dry ether, 5.1 g. of the chloride separated as rosets of minute, faintly pinkish needles. The salt was washed with dry acetone, dried *in vacuo* over sulfuric acid to remove adhering solvent, and then air-dried, coming to equilibrium with approximately 1.5 molecules of water of crystallization. It then dissolves with difficulty in cold water, freely on heating, separating on cooling as a jelly. An aqueous solution gives a precipitate with sodium hydroxide. The anhydrous salt softens at about 180–90° to an orange red jelly which is completely fluid at about 205° and slowly evolves gas. It dissolves readily in methyl or ethiyl alcohol, forms a gum under dry chloroform, and is sparingly soluble n cold, dry acetone, more easily on warming.

Subs. (air-dry), 0.4644: loss, 0.0258 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{28}H_{32}O_4N_3Cl.1.5H_2O$: H_2O, 5.03. Found: 5.56.

Subs. (anhydrous), 0.1213: 8.6 cc. N (24.0°, 759 mm.). Subs., 0.1998: AgCl, 0.0533.

Calc. for $C_{28}H_{32}O_4N_3Cl$: N, 8.24; Cl, 6.96. Found: N, 8.11; Cl, 6.60.

Quinine *o*-Chloroacetylamino-benzamide, $C_{20}H_{24}O_2N_2.ClCH_2CONH$-$C_6H_4CONH_2$(*o*-).—4.25 g. of *o*-chloroacetylamino-benzamide[1] were used, with alcohol as the solvent. This was then boiled off and the gummy residue taken up in dry acetone, the chloride soon crystallizing from the dark brown, fluorescent solution. The yield was 4.7 g. The crude salt was purified by dissolving in hot, dry chloroform, treating with boneblack, filtering, and adding several volumes of dry acetone, then by recrystal-

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[1] This Journal, 39, 1442 (1917).

lization from absolute alcohol, in which it is sparingly soluble in the cold, quite easily on boiling. It forms pale tan rhombs containing 3.5 molecules of water of crystallization or 1.5 molecules of alcohol. When rapidly heated to 175°, then slowly, the anhydrous salt melts at 178–9° with gas evolution to a red-brown liquid. $[\alpha]_D^{28}$ = —164.4° in absolute alcohol, $c = 0.979$. It is soluble in dry chloroform, difficultly so in cold absolute alcohol, readily on boiling with a yellow color, and is almost insoluble in boiling benzene. A solution in dilute acid gives a gummy precipitate with excess sodium hydroxide and if this is washed well with water and rubbed, it gives the microcrystalline, difficultly soluble quaternary base.

Subs. (air-dry), 0.7616: loss, very slow, 0.0789 *in vacvo* at 100° over H_2SO_4.

Calc. for $C_{29}H_{33}O_4N_4Cl.3.5H_2O$: H_2O, 10.52. For $1.5C_2H_5OH$: 11.40. Found: 10.36.

Subs. (anhydrous), 0.1325: 11.9 cc. N (18.0°, 749 mm.). Subs., 0.2289: AgCl, 0.0588.

Calc. for $C_{29}H_{33}O_4N_4Cl$: N, 10.44; Cl, 6.61. Found: N, 10.39; Cl, 6.36.

(D) Quaternary Salts of Quinidine.

Quinidine Methochloride.—19.9 g. of quinidine methiodide were converted into the methochloride as usual, salting out the product cautiously with sodium chloride solution. Treated in absolute alcoholic solution after filtering from sodium chloride, with several volumes of dry ether the salt crystallizes on rubbing as aggregates of prisms containing solvent equivalent to one molecule of water of crystallization when air dry. The yield was 8.5 g. The anhydrous salt melts with decomposition at 250–1° and gives $[\alpha]_D^{21}$ = +253.1° in water, $c = 1.505$. It dissolves readily in water, methyl or ethyl alcohol, or chloroform and is almost insoluble in dry acetone or benzene.

Subs. (air-dry), 0.5200: loss, 0.0245 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{21}H_{27}O_2N_2Cl.H_2O$: H_2O, 4.59. Found: 4.71.

Subs. (anhydrous), 0.2216: AgCl, 0.0837.

Calc. for $C_{21}H_{27}O_2N_2Cl$: Cl, 9.46. Found: 9.35.

Quinidine Benzyl Chloride.—The components were allowed to stand in a warm place in acetone solution for 15–20 days. After boiling off the acetone the residue soon began to crystallize and the process was hastened by adding dry acetone. The collected salt was ground up with dry acetone, heated to boiling, cooled, filtered again and washed with dry acetone. The yield was 85% of the quinidine used. The chloride forms pale yellow, hair-like needles, containing approximately 2 molecules of water of crystallization when air-dry. The anhydrous salt gradually melts and decomposes up to 180° when heated and gives $[\alpha]_D^{21.5}$ = +219.9° in water, $c = 0.632$. It softens under dry methyl or ethyl alcohol or dry chloroform, dissolving readily, and is more sparingly soluble in dry acetone. The chloride also dissolves readily in water.

Subs. (air-dry), 0.7596: loss, 0.0609 *in vacuo* at 80°, then 100° over H_2SO_4.
Calc. for $C_{27}H_{31}O_2N_2Cl.2H_2O$: H_2O, 7.40. Found: 8.02.
Subs. (anhydrous), 0.1350: 7.5 cc. N (24.0°, 749 mm.).
Subs., 0.1557: 6.70 cc. $AgNO_3$ soln. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{27}H_{31}O_2N_2Cl$: N, 6.22; Cl, 7.87. Found: N, 6.29; Cl, 7.80.

Quinidine Iodoacetamide.—The quaternary salt crystallized in practically quantitative yield on suspending quinidine in hot acetone, adding one equivalent of iodoacetamide, shaking until clear, and letting stand overnight. As so obtained the salt forms a paste under water, crystallizing on rubbing. Recrystallized from water it forms rosets of long, narrow plates containing 1.5 molecules of water of crystallization. The anhydrous iodide melts to a yellow jelly at 165–70°, gradually liquefying and darkening until entirely fluid and filled with bubbles at about 190°. $[\alpha]_D^{22.5} = +166.2°$ in absolute alcohol, $c = 1.008$. It becomes pasty under methyl or ethyl alcohol, dissolving readily, and also dissolves in chloroform. The hydrate is easily soluble in hot water, sparingly in the cold, and dissolves readily in acetone, separating immediately on rubbing, presumably as a less hydrated form.

Subs. (air-dry), 0.6898: loss, 0.0330 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{22}H_{28}O_3N_3I.1.5H_2O$: H_2O, 5.04. Found: 4.78.
Subs. (anhydrous), 0.2585: AgI, 0.1180.
Calc. for $C_{22}H_{28}O_3N_3I$: I, 24.93. Found: 24.67.

Quinidine Chloroacetamide.—After recrystallization from water this salt formed rosets of prismatic needles containing one molecule of water of crystallization, the yield being about 50% of the quaternary iodide used. The anhydrous salt melts at 187–91° to a yellow jelly, gradually darkening and finally liquefying with decomposition at about 205°. $[\alpha]_D^{22} = +207.2°$ in water, $c = 1.031$. The chloride is soluble in cold water or alcohol, more readily in methyl alcohol, and very sparingly in chloroform or acetone.

Subs. (air-dry), 0.6128: loss, 0.0280 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{22}H_{28}O_3N_3Cl.H_2O$: H_2O, 4.14. Found: 4.57.
Subs. (anhydrous), 0.1300: 11.2 cc. N (21.5°, 759 mm.).
Subs., 0.2566: AgCl, 0.0861.
Calc. for $C_{22}H_{28}O_3N_3Cl$: N, 10.06; Cl, 8.49. Found: N, 9.98; Cl, 8.30.

Quinidine Iodoacetylurea.—Equimolecular amounts of quinidine and iodoacetylurea[1] were boiled in acetone until clear. The next day most of the solvent was boiled off and the residue taken up in hot water, treated

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[1] **Iodoacetylurea,** $ICH_2CONHCONH_2$.—13.6 g. of finely powdered chloroacetylurea were added to a solution of 15 g. of dry sodium iodide in 100 cc. of dry acetone, shaken for 2.5 hours, and let stand overnight (cf. L. Finkelstein, *Ber.*, **43**, 1528 (1910)). The mixture, now a paste of minute crystals of the iodo compound, was diluted with water and filtered. The crude iodoacetylurea was recrystallized from 50% alcohol, in which it is quite sparingly soluble, even at the boiling point. 15.4 g. separated as flat prisms which melt and decompose at 182–4° with preliminary darkening and partial de-

with boneblack, filtered, and allowed to cool. The iodide separates in almost quantitative yield on rubbing. Recrystallized again from water it forms rosets of minute plates containing 3 molecules of water of crystallization. When rapidly heated to 165°, then slowly, the anhydrous salt melts at 170–5° to an orange mass which slowly evolves gas and blackens. It is difficultly soluble in cold water, readily in hot, and dissolves easily at room temperature in methyl or ethyl alcohol or acetone. It dissolves slowly in dry chloroform and only sparingly in benzene.

Subs. (air-dry), 0.6290: loss, 0.0532 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{23}H_{29}O_4N_4I.3H_2O$: H_2O, 8.91. Found: 8.46.

Subs. (anhydrous), 0.1360: 12.6 cc. N (30.0°, 755 mm.). Subs., 0.1658: AgI, 0.0681.

Calc. for $C_{23}H_{29}O_4N_4I$: N, 10.14; I, 22.98. Found: N, 10.37; I, 22.20.

Quinidine Chloroacetylurea.—The chloride, prepared from the iodide with silver chloride, was recrystallized from a small volume of water, forming rosets of spears containing 3.5 molecules of water of crystallization. The anhydrous salt melts and swells at 176–8°, with darkening, and gives $[\alpha]_D^{26.5} = +170.9°$ in water, $c = 1.325$. It dissolves readily in water or methyl or ethyl alcohol, less easily in dry acetone or chloroform, and difficultly in benzene. The hydrate dissolves rather sparingly in cold water, readily on heating and yields a highly supersaturated solution on cooling. Such a solution gives an oily precipitate on adding excess sodium hydroxide and evolves ammonia on boiling.

Subs. (air dry), 0.8849: loss, 0.1041 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{23}H_{29}O_4N_4Cl.3.5H_2O$: H_2O, 12.03. Found: 11.77.

Subs. (anhydrous), 0.1418: 15.3 cc. N (28.0°, 762 mm.). Subs., 0.1457: 6.07 cc. $AgNO_3$ soln. (1 cc. = 0.001812 g. Cl).

Calc. for $C_{23}H_{29}O_4N_4Cl$: N, 12.17; Cl, 7.70. Found: N, 12.27; Cl, 7.55.

(E) Quaternary Salts of Hydroquinine.

Hydroquinine Methiodide.—Equimolecular quantities of the base[1] and methyl iodide in chloroform gave the salt in a yield of 78% of the theoretical amount, separation being completed with about two volumes of acetone. Recrystallized from absolute alcohol the methiodide forms faintly yellow prisms which are anhydrous when air-dry. It melts partially at about 170° and liquefies completely, with decomposition at 233–5°. $[\alpha]_D^{20.5}$ is —107.6° in absolute alcohol, $c = 0.855$. The salt is somewhat soluble in cold water, more easily in alcohol, and

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composition. The iodo compound dissolves rather difficultly in boiling water or boiling acetone and very sparingly in chloroform. It is quite soluble in cold methyl alcohol, less readily in the cold in ethyl alcohol, but more freely on boiling. It dissolves in dilute alkali and does not seem to be as active an irritant as chloroacetylurea.

Subs., 0.1510: (Kjeldahl) 18.6 cc. 0.0714 *N* HCl.

Calc. for $C_3H_5O_2N_2I$: N, 12.29. Found: 12.32.

[1] Ger. pat. 252136; This Journal, 41, 819 (1919).

readily in methyl alcohol or chloroform. Hesse[1] states that the methiodide crystallizes with one molecule of alcohol of crystallization and melts at 218° when dried.

Subs., 0.2086: AgI, 0.1048.
Calc. for $C_{21}H_{29}O_2N_2I$: I, 27.10. Found: 27.15.

Hydroquinine Methochloride.—The salt crystallizes from water as balls of hair-like needles containing 2 molecules of water of crystallization, as stated by Hesse. When rapidly heated to 155°, then slowly, the anhydrous methochloride forms a paste at 157–9°, and on further heating finally becomes a yellow liquid filled with bubbles at 172–3°. Hesse gives the melting point as 168°. $[\alpha]_D^{21.5}$ in water is —162.9°, c = 1.470. The anhydrous salt also dissolves very easily in methyl or ethyl alcohol, less readily in dry acetone.

Subs. (anhydrous), 0.2760: AgCl, 0.1052.
Calc. for $C_{21}H_{29}O_2N_2Cl$: Cl, 9.41. Found: 9.43.

Hydroquinine Benzyl Chloride.—The components were boiled for about 15 hours in dry acetone. After long standing the acetone was boiled off and the dark residue taken up in dry methyl alcohol. The chloride crystallized rapidly on adding several volumes of dry ether and was recrystallized from water, separating slowly on seeding at room temperature as a crust of rhombs and prisms containing one molecule of water of crystallization. An additional quantity of equal purity was obtained by adding saturated sodium chloride solution to the aqueous mother liquor, letting stand, and washing the crystals with cold water. The total yield was 3 g., starting with 3.6 g. of the base. When rapidly heated to 200°, then slowly, the anhydrous chloride melts at 202–3.5° to a dark red, viscous liquid which soon decomposes. $[\alpha]_D^{23}$ in water is —196.9°, c = 0.787. It dissolves readily in methyl or ethyl alcohol or chloroform, less easily in dry acetone, and melts under hot benzene, dissolving with difficulty. The air-dry salt dissolves rather sparingly in cold water, quite readily on boiling, the solution having a weak, bitter taste. A not too dilute aqueous solution gives immediate precipitates of the nitrate and permanganate with the appropriate salts. Solutions in dil. sulfuric or nitric acid have a marked blue fluorescence, while the solution in dil. hydrochloric acid is pale yellow and does not fluoresce.

Subs. (air-dry), 0.7928: loss, 0.0281 *in vacuo* at 100° over H_2SO_4. Subs., 0.1238: 7.10 cc. N (25.5°, 755 mm.). Subs., 0.1520: (Kjeldahl, with H_2SO_4, K_2SO_4, and crystal of $CuSO_4$) 8.8 cc. 0.0714 *N* HCl. Subs., 0.1203: 5.1 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{27}H_{33}O_2N_2Cl.H_2O$: H_2O, 3.83; N, 5.95; Cl, 7.53. Found: H_2O, 3.54; N, 6.51, 5.79; Cl, 7.61.

Hydroquinine Iodoacetamide.—Acetone was used as solvent and after several hours it was boiled off and hot water added, the iodide crys-

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[1] *Ann.*, 241, 275 (1887).

tallizing on cooling and rubbing as prismatic plates. The yield was almost quantitative. Recrystallized from water the salt forms prismatic needles containing between 2.5 and 3 molecules of water of crystallization. The anhydrous salt gradually softens to a yellow jelly above 145°, deepening in color as the temperature is raised, and becoming entirely fluid at about 185°. $[\alpha]_D^{23.5}$ in absolute alcohol is $-121.5°$, $c = 0.976$. The dried salt also softens and dissolves readily in dry methyl or ethyl alcohol, dry acetone, or dry chloroform.

Subs. (air-dry), 0.6120: loss, 0.0534 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{22}H_{30}O_3N_3I.2.5H_2O$: H_2O, 8.10. Found: 8.72.
Subs. (anhydrous), 0.2039: AgI, 0.0933.
Calc. for $C_{22}H_{30}O_3N_3I$: I, 24.83. Found: 24.72.

Hydroquinine Chloroacetamide.—Instead of adding sodium chloride to the filtrate from the silver iodide precipitate the solution was allowed to stand overnight, filtered from a small amount of a substance crystallizing in silky needles, and the filtrate concentrated to dryness *in vacuo*. The residue was taken up in absolute alcohol, concentrated to dryness *in vacuo*, again taken up in absolute alcohol, filtered from a slight turbidity with the aid of boneblack, and concentrated as before, giving a friable, white, amorphous residue which could easily be removed from the flask. The dried salt turns yellow and softens at about 160–75° to a jelly which gradually darkens and liquefies completely with gas evolution at about 195°. $[\alpha]_D^{23} = -129.1°$ in water, $c = 0.852$. The product is very easily soluble in acetone or chloroform and also dissolves readily in cold water.

Subs. (anhydrous), 0.1356: 12.2 cc. N (27.5°, 758 mm.).
Subs., 0.1451: 6.92 cc. $AgNO_3$ soln. (1 cc. = 0.001812 g. Cl).
Calc. for $C_{22}H_{30}O_3N_3Cl$: N, 10.02; Cl, 8.45. Found: N, 10.19; Cl, 8.64.

Hydroquinine Chloroacet-methylamide, $C_{20}H_{26}O_2N_2.ClCH_2CONHCH_3$.—This salt was obtained directly from chloroacet-methylamide[1] in boiling dry acetone. As the product could neither be crystallized nor converted into a crystalline bromide or hydrochloride it was precipitated with dry ether, dried *in vacuo* at room temperature over sulfuric acid, and pulverized. The salt intumesces at 110–20°, gradually melting above this to a glassy mass by the time 160° is reached, and forming a dark brown liquid at about 200°. It dissolves readily in methyl or ethyl alcohol, acetone, chloroform, benzene, or water.

Subs., 0.1340: 10.4 cc. N (18.0°, 764 mm.).
Subs., 0.1165: 5.09 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).
Calc. for $C_{23}H_{32}O_3N_3Cl$: N, 9.69; Cl, 8.17. Found: N, 9.16; Cl, 7.84.

Hydroquinine Chloroacet-ethylamide.—This salt was prepared in the same way, using chloroacet-ethylamide.[2] On adding dry ether the gummy material crystallized partially, but as the crystals softened to a

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[1] This Journal, **41**, 472 (1919).

[2] *J. Biol. Chem.*, **21**, 149 (1915).

gum on desiccation or air-drying, and as an attempt at recrystallization by dissolving in dry acetone and precipitating with dry ether proved no better, the substance was left in the crude state and dried *in vacuo* over sulfuric acid. It melted to a yellowish jelly at 110–35°, becoming completely fluid at about 160°. In solubility it resembles the methyl compound.

Subs., 0.1680: 13.7 cc. N (23.0°, 751 mm.). Subs., 0.1561: AgCl, 0.0479.

Calc. for $C_{24}H_{34}O_3N_3Cl$: N, 9.39; Cl, 7.92. Found: N, 9.30; C, 7.59.

Hydroquinine Chloroacet-dimethylamide, $C_{20}H_{26}O_2N_2.ClCH_2CON(CH_3)_2$.—An amorphous salt was obtained from chloroacet-dimethylamide,[1] melting partially and intumescing at 130–40°, becoming transparent at about 180°, and liquefying completely at about 200°. It resembles the monomethyl and -ethyl derivatives in its solubility relationships.

Subs., 0.1362: 10.4 cc. N (19.5°, 765 mm.).

Subs., 0.1797: 7.68 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{24}H_{34}O_3N_3Cl$: N, 9.39; Cl, 7.92. Found: N, 8.97; Cl, 7.67.

Hydroquinine Chloroacet-diethylamide, $C_{20}H_{26}O_2N_2.ClCH_2CON(C_2H_5)_2$.—1.6 g. of chloroacet-diethylamide[2] were used. On adding ligroin until the initial turbidity just redissolved the chloride crystallized on standing as rosets of prismatic needles, precipitation being completed by the addition of more ligroin and letting stand. The yield was 3.5 g. On dissolving in not too little dry chloroform and treating cautiously with ligroin, seeding, and adding more ligroïn from time to time the salt forms minute prisms containing solvent approximately equivalent to one molecule of water of crystallization. The anhydrous salt darkens somewhat above 205° and melts and decomposes at 209–10°. $[\alpha]_D^{27.5} = -84.8^\circ$ in water, $c = 0.854$. It dissolves readily at room temperature in water, methyl or ethyl alcohol, or chloroform, sparingly in cold acetone, more easily on heating, and is almost insoluble in benzene. It has a sharp, bitter taste.

Subs. (air-dry), 0.6028: loss, 0.0182 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{26}H_{38}O_3N_3Cl.H_2O$: H_2O, 3.65. Found: 3.02.

Subs. (anhydrous), 0.1226: 10.0 cc. N (30.0°, 757 mm.). Subs., 0.1247: 5.15 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{26}H_{38}O_3N_3Cl$: N, 8.84; Cl, 7.45. Found: N, 9.16; Cl, 7.48.

Hydroquinine Chloroacetyl-benzylamine, $C_{20}H_{26}O_2N_2.ClCH_2CONHCH_2C_6H_5$.—Starting with chloroacetyl-benzylamine[3] in dry acetone the salt crystallized from the reaction mixture. Recrystallized from butyl alcohol[4] the chloride separates as delicate, glistening needles. The an-

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[1] *J. Biol. Chem.*, 21, 148 (1915).

[2] *Ibid.*, 21, 149 (1915).

[3] *Ibid.*, 20, 686 (1915).

[4] We have found commercial butyl alcohol to be a very useful solvent.

hydrous salt melts at 197–8° to an orange liquid containing bubbles. $[\alpha]_D^{23}$ in water is —42.5°, c = 0.670. The compound dissolves fairly readily in water, easily in methyl or ethyl alcohol, or chloroform. A dilute aqueous solution gives a precipitate with sodium hydroxide.

Subs., 0.1409: 10.2 cc. N (23.0°, 744 mm.). Subs., 0.1697: 6.45 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{29}H_{34}O_3N_3Cl$: N, 8.29; Cl 6.99. Found: N, 8.18; Cl, 6.88.

Hydroquinine Chloroacetanilide.—On adding hot water to the residue after boiling off the acetone the crude product separated at first oily on cooling but soon crystallized in almost quantitative yield. Recrystallized from 50% alcohol the chloride forms rosets of delicate needles containing 3 molecules of water of crystallization. When anhydrous it softens to an orange jelly at 160–70°, liquefying completely at about 210° with darkening and slow gas evolution. $[\alpha]_D^{24}$ = —95.9° in absolute alcohol, c = 0.824. It dissolves readily in methyl or ethyl alcohol, acetone, chloroform, or benzene, and only sparingly in dry ether. The hydrate is difficultly soluble in cold water, more readily on heating, and is rather sparingly soluble in cold 50% alcohol. It dissolves in 10% aqueous hydrochloric acid, the *hydrochloride* soon separating as sheaves of minute needles.

Subs. (air-dry), 0.5450: loss, 0.0534 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{28}H_{34}O_3N_3Cl.3H_2O$: H_2O, 9.83. Found: 9.80.

Subs. (anhydrous), 0.1469: 11.0 cc. N (26.0°, 762 mm.). Subs., 0.1556: AgCl, 0.0443.

Calc. for $C_{28}H_{34}O_3N_3Cl$: N, 8.48; Cl, 7.15. Found: N, 8.58; Cl, 7.05.

Hydroquinine Acetanilide Dinitrate, $C_{20}H_{25}O_2N_2.O_3NCH_2CONHC_6H_5.HNO_3$.—One g. of hydroquinine chloroacetanilide was dissolved in about 100 cc. of boiling water, and a few drops of dil. nitric acid added on cooling. The solution was chilled, acidified strongly with dil. nitric acid and rubbed, 0.6 g. of the dinitrate separating as long, delicate needles. The salt was washed with a little ice-cold water and air-dried, containing then approximately 2 molecules of water of crystallization. When heated the anhydrous salt melts to a jelly at about 145–50° with slight preliminary softening, then darkens and intumesces. It softens under the usual anhydrous solvents, dissolving readily in dry methyl or ethyl alcohol or dry acetone, sparingly in dry chloroform, even on boiling, and is practically insoluble in boiling benzene. The hydrate dissolves very sparingly in cold water, fairly readily on boiling, with a faint greenish yellow color.

Subs. (air-dry), 0.5877: loss, 0.0317 *in vacuo* at room temp. over H_2SO_4 + NaOH.

Calc. for $C_{28}H_{34}O_3N_3.NO_3.HNO_3.2H_2O$: H_2O, 5.80. Found: 5.39.

Subs. (anhydrous), 0.1265: 13.4 cc. N (23.0°, 755 mm.).

Calc. for $C_{28}H_{34}O_3N_3.NO_3.HNO_3$: N, 11.97. Found: 12.14.

Hydroquinine *m*-Nitro-chloroacetanilide.—The gelatinous reaction mixture was disintegrated with hot water and let stand. The resulting precipitate, recrystallized first from 25%, then from 50% alcohol, separated as pale drab-colored, minute needles which contained approximately 2 molecules of water of crystallization. When slowly heated, the anhydrous salt begins to soften at 150°, gradually melting to a brownish jelly up to 160°, and liquefying completely and decomposing at 195–200°. It softens under and dissolves readily with a pale yellow color in dry methyl or ethyl alcohol, dry acetone, dry chloroform, or ethyl acetate, dissolving sparingly in cold benzene and readily on boiling. The hydrate is quite difficultly soluble in cold water, more easily on boiling. An aqueous suspension turns bright yellow and flocculates with a few drops of aqueous sodium hydroxide.

Subs. (air-dry), 0.5443: loss, 0.0374 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{28}H_{33}O_5N_4Cl.2H_2O$: H_2O, 6.25. Found: 6.87.

Subs. (anhydrous), 0.1279: 12.0 cc. N (24.0°, 759 mm.). Subs., 0.1175: 4.05 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{28}H_{33}O_5N_4Cl$: N, 10.36; Cl, 6.56. Found: N, 10.77; Cl, 6.19.

Hydroquinine *m*-Chloroacetylamino-acetanilide, $C_{20}H_{26}O_2N_2.ClCH_2CONHC_6H_4NHCOCH_3$(*m*-).—Starting with *m*-chloroacetylamino-acetanilide,[1] a gummy quaternary salt separated, from which the acetone was eventually poured off and the residue boiled with dry methyl ethyl ketone. The gum which separated on cooling was filtered off and on letting stand and rubbing the chloride separated from the filtrate as practically colorless, radiating masses of minute crystals. A further quantity was obtained by again extracting the crude gummy material with the filtrate. The air-dry salt contained solvent of crystallization corresponding to 3 to 3.5 molecules of water. When heated the anhydrous salt gradually melts to an orange mass above 150°, with slow gas evolution, becoming completely fluid at about 205–10°. It first softens under, and then dissolves freely in dry methyl or ethyl alcohol, also dissolves readily in chloroform, and is very difficultly soluble in boiling dry acetone, benzene, or ethyl acetate.

Subs. (air-dry), 0.4457: loss, 0.0432 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{30}H_{37}O_4N_4Cl.3H_2O$: H_2O, 8.91. Found: 9.69.

Subs. (anhydrous), 0.1309: 11.25 cc. N (21.5°, 755 mm.). Subs., 0.1412: 4.92 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{30}H_{37}O_4N_4Cl$: N, 10.13; Cl, 6.41. Found: N, 9.90; Cl, 6.25.

Hydroquinine *p*-Chloroacetylamino-acetanilide.—In the case of the sparingly soluble *p*-chloroacetylamino-acetanilide[2] absolute alcohol was used as solvent. After letting stand in the cold the insoluble material was filtered off, and the filtrate concentrated to small bulk. The residue was taken up in boiling water, treated with boneblack and the filtrate cooled, diluting so that it became only faintly turbid at room temperature. After filtering again the solution was seeded with crystals obtained by adding sodium chloride to a test portion. The crude quaternary salt

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[1] THIS JOURNAL, 39, 1448 (1917).

[2] *Ibid.*, 39, 1455 (1917).

was recrystallized from water, separating as rosets and sheaves of delicate, silky needles. Additional amounts were obtained by adding sodium chloride to the mother liquors. The air-dry salt contains 3 molecules of water of crystallization and dissolves sparingly in cold water, more easily on heating. The anhydrous chloride begins to soften at about 160° and darkens and becomes completely fluid, with slow gas evolution, at about 205°. It dissolves readily in methyl or ethyl alcohol, acetone, or chloroform, and only sparingly in boiling benzene or ethyl acetate. Analysis indicated that the substance was not entirely pure.

Subs. (air-dry), 0.5336: loss, 0.0477 *in vacuo* at room temp. over H_2SO_4.

Calc. for $C_{30}H_{37}O_4N_4Cl.3H_2O$: H_2O, 8.91. Found: 8.94.

Subs. (anhydrous), 0.1403: 12.0 cc. N (22.0°, 751 mm.). Subs., 0.1260: 4.0 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{30}H_{37}O_4N_4Cl$: N, 10.13; Cl, 6.41. Found: N, 9.79; Cl, 5.70.

Hydroquinine *p*-Chloroacetylamino-dimethylaniline, $C_{20}H_{26}O_2N_2.ClCH_2CONHC_6H_4N(CH_3)_2(p\text{-})$.—After boiling off the acetone the residue, using 3.5 g. of base, was taken up in about 500 cc. of boiling water and treated with boneblack, yielding 4.3 g. of the crystalline salt on cooling. Recrystallized from 50% alcohol it separates as aggregates of minute, cream-colored needles containing 2.5 molecules of water of crystallization and dissolving very difficultly in cold water, quite easily on boiling. An aqueous suspension gives a brownish rose color with ferric chloride. The anhydrous salt gradually melts to a jelly at about 165°, becoming completely fluid, with partial decomposition at about 200°. $[\alpha]_D^{18.5} = -82.9°$ in absolute alcohol, $c = 1.037$. It softens under and dissolves freely in dry methyl or ethyl alcohol, dry acetone, or dry chloroform.

Subs. (air-dry), 0.5172: loss, 0.0407 *in vacuo* first at room temp., then 80° over H_2SO_4.

Calc. for $C_{30}H_{39}O_3N_4Cl.25H_2O$: H_2O, 7.72. Found: 7.87.

Subs. (anhydrous), 0.1185: 10.4 cc. N (20.5°, 763 mm.). Subs., 0.1196: 4.2 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{80}H_{39}O_3N_4Cl$: N, 10.39; Cl, 6.58. Found: N, 10.25; Cl, 6.30.

Hydroquinine *p*-Chloroacetylamino-diethylaniline.—In the case of *p*-chloroacetylamino-diethylaniline[1] the reaction mixture was diluted with dry acetone and the salt precipitated as amorphous flocks with the aid of dry ether. The product was filtered off, washed with a little dry ether, dried, and then dissolved in hot ethyl acetate and seeded while still warm with a few of the crystals left in the reaction flask on evaporation of the solvent. On letting stand in a warm place the salt separated slowly as sheaves of delicate needles. The air dry product still possessed the odor of ethyl acetate. The anhydrous salt begins to soften at about 150°, and when slowly heated above this point forms a transparent jelly at 165–70°, and a red fluid at 190–5°, with slight gas evolution. $[\alpha]_D^{20} =$

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[1] *J. Biol. Chem.*, 21, 115 (1915).

—80.5° in absolute alcohol, $c = 1.118$. It dissolves readily in methyl or ethyl alcohol, acetone, chloroform, or benzene, and also in boiling ethyl acetate, although sparingly in the cold. It is very difficultly soluble in cold water, more easily on boiling. An aqueous suspension gives a slowly-developing salmon color with ferric chloride.

Subs. (anhydrous), 0.1277: 11.0 cc. N (20.5°, 757 mm.). Subs., 0.1034: 3.64 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{32}H_{43}O_3N_4Cl$: N, 9.89; Cl, 6.26. Found: N, 9.99; Cl, 6.32.

Hydroquinine *o*-Chloroacetylamino-phenol.—To the reaction mixture from *o*-chloroacetylamino-phenol,[1] a few cc. of absolute alcohol were added and then dry ether and ligroin to incipient turbidity. The quaternary salt crystallized on rubbing and letting stand. Recrystallized by dissolving in hot absolute alcohol and adding dry ether until just turbid, it separated on seeding as rosets of long, flat platelets containing solvent equivalent to 1.5 molecules of water of crystallization. It dissolves sparingly in cold water, more freely on heating, separating as a jelly on cooling. The anhydrous salt gradually melts to a jelly above 155°, finally reddens, and becomes completely fluid and evolves gas at 185°. It dissolves very easily in dry methyl alcohol and less readily in absolute alcohol or dry acetone. An alkaline suspension couples with diazotized sulfanilic acid.

Subs. (air-dry), 0.5750: loss, 0.0308 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{28}H_{34}O_4N_3Cl.1.5H_2O$: H_2O, 5.01. Found: 5.36.

Subs. (anhydrous), 0.1449: 10.35 cc. N (20.5°, 758 mm.). Subs., 0.1539: AgCl, 0.0469.

Calc. for $C_{28}H_{34}O_4N_3Cl$: N, 8.21; Cl, 6.93. Found: N, 8.29; Cl, 7.54.

Hydroquinine *m*-Chloroacetylamino-phenol.—Starting with 1.9 g. of *m*-chloroacetylamino-phenol[2] 4.5 g. of the salt crystallized from the reaction mixture as hard nodules. Recrystallized from not too little 50% alcohol, seeding and rubbing while still warm, the chloride separates as cream-colored aggregates of microscopic leaflets containing 3 molecules of water of crystallization. If care is not taken the solution gelatinizes. The anhydrous salt softens and sinters above 160°, melts to a reddish jelly at about 180–5°, and is completely fluid, with slow gas evolution, at about 205°. $[\alpha]_D^{21} = -115.7°$ in absolute alcohol, $c = 0.800$. It first softens under, then resolidifies, dissolving freely, in absolute alcohol or dry methyl alcohol, also softening under boiling dry acetone and dissolving with difficulty. The salt is very difficultly soluble in cold water, more easily on boiling, and is readily soluble in hot 50% alcohol, quite sparingly in the cold.

Subs. (air-dry), 0.5070: loss, 0.0489 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{28}H_{34}O_4N_3Cl.3H_2O$: H_2O, 9.56. Found: 9.64.

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[1] THIS JOURNAL, 41, 458 (1919).

[2] *Ibid.*, 39, 1442 (1917).

Subs. (anhydrous), 0.1262: 9.55 cc. N (26.0°, 754 mm.). Subs., 0.1535: AgCl, 0.0409.

Calc. for $C_{28}H_{34}O_4N_3Cl$: N, 8.21; Cl, 6.93. Found: N, 8.57; Cl, 6.59.

The Hydrochloride.—The purified salt was rubbed in a mortar with 1 : 1 hydrochloric acid, yielding a pasty mass which eventually crystallized. Recrystallized from hot water containing a little hydrochloric acid it separates on cooling and seeding as cream-colored prismatic needles and short rods, separation being completed by further small additions of 10 % hydrochloric acid. The hydrochloride contains 4.5 molecules of water of crystallization and dissolves fairly readily in water. The anhydrous salt is a pale sulfur-yellow and forms an orange jelly at 195–7°, melting and evolving gas at about 200°. It dissolves readily in methyl or ethyl alcohol and is practically insoluble in dry acetone. It does not dissolve in excess dil. alkali, the suspension coupling with diazotized sulfanilic acid.

Subs. (air-dry), 0.5030: loss, 0.0650.
Calc. for $C_{28}H_{34}O_4N_3Cl.HCl.4.5H_2O$: H_2O, 12.88. Found: 12.92.
Subs. (anhydrous), 0.1654: AgCl, 0.0860.
Calc. for $C_{28}H_{34}O_4N_3Cl.HCl$: Cl, 12.93. Found: 12.86.

Hydroquinine *p*-Chloroacetylamino-phenol Hydrochloride.—In the case of *p*-chloroacetylamino-phenol[1] a portion of the quaternary addition product separated as a gum, followed on standing by radiating masses of fibrous needles and the ultimate crystallization of the gum. As the salt could not be recrystallized it was converted into the hydrochloride by dissolving in a slight excess of very dilute hydrochloric acid, adding the conc. acid, with cooling, until slightly turbid, treating with boneblack, and again adding conc. hydrochloric acid to the filtrate until the initial turbidity just redissolved. The hydrochloride separated on seeding with crystals obtained from a test portion, precipitation being completed by the further careful addition of conc. hydrochloric acid. Recrystallized from warm water, adding conc. hydrochloric acid to the cooled solution until just turbid, the hydrochloride crystallized as cream-colored rosets of prismatic needles containing 4.5 molecules of water of crystallization, completing the separation as before. The yield was 7.2 g. The salt dissolves fairly readily in water at room temperature and is readily salted out by the addition of hydrochloric acid. An aqueous solution gives a dull, grayish color with ferric chloride. The anhydrous salt is darker than the hydrate and when rapidly heated to 195° then slowly, melts at 196–7° to a red-brown jelly which soon evolves gas. It turns gummy under dry methyl or ethyl alcohol, dissolving readily, and also softens under dry chloroform but remains insoluble. It is also practically insoluble in dry acetone.

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[1] *Loc. cit.*

Subs. (air-dry), 0.4937: loss, 0.0632.

Calc. for $C_{28}H_{34}O_4N_3Cl.HCl.4.5H_2O$: H_2O, 12.88. Found: 12.80.

Subs. (anhydrous), 0.1414: 9.4 cc. N (24.5°, 759 mm.). Subs., 0.1744: AgCl, 0.0907.

Calc. for $C_{28}H_{34}O_4N_3Cl.HCl$: N, 7.67; Cl, 12.93. Found: N, 7.62; Cl, 12.86.

Hydroquinine 4-Chloroacetylamino-pyrocatechol Hydrochloride, $C_{20}H_{26}O_2N_2.ClCH_2CONHC_6H_3(OH)_2.HCl(3,4-)$.—After pouring off the acetone from the gummy precipitate in the case of 4-chloroacetylamino-pyrocatechol[1] 10% aqueous hydrochloric acid was added, as well as a little alcohol to facilitate solution. On cautiously adding further portions of hydrochloric acid and treating with boneblack to remove the first gummy precipitates a clear, red-brown solution was finally obtained. This was seeded with crystals obtained by rubbing a portion of the crude gummy salt with 1 : 1 hydrochloric acid and letting stand. The hydrochloride separated in poor yield as pale yellow needles containing 4.5 molecules of water of crystallization, precipitation being completed by finally adding more acid. The salt dissolves in water, the solution giving an olive-green color with ferric chloride, changing rapidly to yellow-brown. An aqueous solution gave a precipitate with sodium hydroxide, insoluble in excess. When rapidly heated to 195°, then slowly, the anhydrous hydrochloride melts to a jelly at 196–8°, gradually decomposing as the temperature is further raised. It dissolves readily in methyl alcohol, more slowly in absolute alcohol, and is practically insoluble in dry acetone or dry chloroform.

Subs. (air-dry), 0.4249: loss, 0.0530.

Calc. for $C_{28}H_{34}O_5N_3Cl.HCl.4.5H_2O$: H_2O, 12.57. Found: 12.48.

Subs. (anhydrous), 0.1176: 7.4 cc. N (21.5°, 767 mm.). Subs., 0.1758: AgCl, 0.0877.

Calc. for $C_{28}H_{34}O_5N_3Cl.HCl$: N, 7.45; Cl, 12.57. Found: N, 7.36; Cl, 12.34.

Hydroquinine Chloroacetyl-*o*-anisidine.—Starting with 4 g. of chloroacetyl-*o*-anisidine,[2] 7 g. of the crude quaternary salt were finally deposited from the ice-cold solution on seeding with crystals obtained by spontaneous evaporation. The substance was recrystallized from butyl alcohol, letting stand in the ice box, and seeding, 6.4 g. separating as radiating, hair-like needles. The anhydrous compound gradually sinters and softens to a jelly above 110°, turns yellow above 150°, and is completely fluid at about 185°. $[\alpha]_D^{32} = -72.5°$ in absolute alcohol, $c = 0.904$. It softens under and dissolves readily in dry methyl or ethyl alcohol, dry chloroform, or dry acetone, dissolves less readily in benzene, and gives a pale yellow color in conc. sulfuric acid. The air-dry salt dissolves slowly but freely in water.

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[1] THIS JOURNAL, 41, 468 (1919).

[2] *Ibid.*, 41, 1451 (1919).

Subs. (anhydrous), 0.1268: 9.2 cc. N (29.5°, 755 mm.). Subs., 0.1337: 5.07 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl$: N, 7.99; Cl, 6.75. Found: N, 8.14; Cl, 6.87.

Hydroquinine Chloroacetyl-*m*-anisidine.—(From 2 g. of chloroacetyl-*m*-anisidine.[1]) The solvent was boiled off and the residue taken up in 50% alcohol and cautiously diluted with hot water, filtering off the slight turbidity which first formed. On seeding the solution with crystals obtained by several days' standing of a dilute solution of the crude material in hot water, the salt gradually crystallized, especially on the further addition of small quantities of water and occasional warming. Recrystallized by dissolving in alcohol, diluting with ether, and seeding, the quaternary salt separates as radiating aggregates of delicate needles containing solvent equivalent to 3 molecules of water of crystallization when air-dry. The anhydrous salt gradually sinters and softens above 140° and forms an orange fluid at about 190°. $[\alpha]_D^{23} = -102.9°$ in absolute alcohol, $c = 1.292$. It melts under and dissolves readily in the following dry solvents: methyl or ethyl alcohol, chloroform, acetone, or benzene; and dissolves partly in cold water, the solution foaming readily and soon setting to a jelly. It is readily soluble in boiling water.

Subs. (air-dry), 0.7289: loss, 0.0715 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{29}H_{36}O_4N_3Cl.3H_2O$: H_2O, 9.32. Found: 9.81.

Subs. (anhydrous), 0.1489: 10.5 cc. N (25.5°, 760 mm.). Subs., 0.1085: 3.9 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl$: N, 7.99; Cl, 6.75. Found: N, 8.07; Cl, 6.45.

The Hydrochloride.—3.5 g. of the quaternary salt were dissolved in absolute alcohol containing an excess of dry hydrochloric acid and treated with dry ether until a faint turbidity persisted. On rubbing and letting stand 3.2 g. of the hydrochloride separated slowly as pale yellow, radiating aggregates of rhombic crystals. When rapidly heated to 165°, then slowly, the salt begins to soften, and melts at 170–1° with gas evolution. It dissolves readily in methyl alcohol or chloroform, less easily in absolute alcohol, and only sparingly in hot, dry acetone, the insoluble portion changing to a gummy mass. As obtained above the hydrochloride apparently retains 2 molecules of water of crystallization. An attempt to drive this off at 80° *in vacuo*, resulted in the loss of hydrochloric acid.

Subs., 0.1487: 9.0 cc. N (22.5°, 765 mm.). Subs., 0.1201: 7.92 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl.HCl.2H_2O$: N, 7.03; Cl, 11.85. Found: N, 7.05; Cl, 11.83.

Hydroquinine Chloroacetyl-*p*-anisidine.—After boiling off the acetone the residue was taken up in hot commercial butyl alcohol. The filtrate deposited radiating masses of delicate needles and the separation was completed by the cautious additon of dry ether. The salt was recrystal-

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[1] THIS JOURNAL, 41, 1452 (1919).

lized by dissolving in dry acetone, adding ligroin until the initial turbidity just dissolved, and seeding. When air-dry it retained an amount of solvent equivalent to between 1 and 1.5 molecules of water of crystallization. The anhydrous salt gradually softens to a jelly above 150° and is completely fluid at about 190°. $[\alpha]_D^{20} = -93.9°$ in absolute alcohol, $c = 1.128$. The salt dissolves very readily in methyl or ethyl alcohol or chloroform, somewhat less easily in dry acetone, and very sparingly in dry ether. It is difficultly soluble in cold water or benzene, readily on boiling, and separates from the former as a jelly on cooling. It dissolves in conc. sulfuric acid with a dull yellow color.

Subs. (anhydrous), 0.1424: 10.0 cc. N (18.5°, 745 mm.). Subs., 0.1461: 5.20 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl$: N, 7.99; Cl, 6.75. Found: N, 8.06; Cl, 6.45.

The Hydrochloride.—The quaternary salt was dissolved in a small volume of absolute alcohol, treated with absolute alcoholic hydrochloric acid, and seeded with crystals obtained by manipulating a test portion with dry ether. The hydrochloride separated rapidly on rubbing as thick, yellow, hexagonal, microscopic plates. When rapidly heated to 180°, then slowly, the substance melts at 180–4° to an orange mass containing bubbles and becomes completely fluid and decomposes at about 190°. It is rather sparingly soluble in the cold in absolute alcohol, easily on warming, and dissolves readily in dry methyl alcohol. The aqueous solution foams readily.

Subs., 0.1051: 7.40 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl.HCl$: Cl, 12.61. Found: 12.64.

Hydroquinine Chloroacetyl-*o*-phenetidine, $C_{20}H_{26}O_2N_2.ClCH_2CONH$-$C_6H_4OC_2H_5$(*o*-).—In the case of chloroacetyl-*o*-phenetidine[1] the acetone was boiled off and the residue taken up in boiling water and treated with boneblack. As the salt separated from the filtrate as an oil on rapid chilling it was necessary to cool slowly and seed with crystals obtained by adding sodium chloride to a diluted test portion. Recrystallized from water it separates very slowly on seeding as rosets and sheaves of delicate needles containing 2.5 molecules of water of crystallization. Additional quantities were recovered by treating the mother liquors carefully with saturated salt solution. The anhydrous salt softens above 125°, forms a transparent jelly at about 140° and a yellow fluid at 170–2°. It dissolves readily in methyl or ethyl alcohol, chloroform, or acetone, and only very sparingly in dry ether.

Subs. (air-dry), 0.7096: loss, 0.0573 *in vacuo* at room temp. over H_2SO_4.

Calc. for $C_{30}H_{38}O_4N_3Cl.2.5H_2O$: H_2O, 7.70. Found: 8.08.

Subs. (anhydrous), 0.1531: 11.0 cc. N (23.5°, 744 mm.). Subs., 0.1317: 4.45 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{30}H_{38}O_4N_3Cl$: N, 7.79; Cl, 6.57. Found: N, 8.10; Cl, 6.07.

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[1] THIS JOURNAL, 41, 1452 (1919).

Hydroquinine Chloroacetyl-*m*-phenetidine Hydrochloride.—(From 2.2 g. of chloroacetyl-*m*-phenetidine.[1]) As the quaternary salt itself could not be obtained crystalline the acetone was boiled off and the residue taken up in absolute alcohol and treated with an excess of absolute alcoholic hydrochloric acid. The salt crystallized after adding dry ether to incipient turbidity and rubbing. The supernatant solution was then decanted off and the precipitate washed twice by decantation with dry alcohol-ether mixture containing a little hydrochloric acid. After dissolving the residue in boiling absolute alcohol, filtering hot from traces of impurities. and adding a little absolute alcoholic hydrochloric acid, the salt separated when seeded as lemon-yellow, rhombic crystals, which are hygroscopic when moist. 4.2 g. were obtained, melting at 173–4° with preliminary sintering and softening. As so obtained the hydrochloride apparently retained 2 molecules of water of crystallization or one molecule of alcohol. It dissolves readily in water, a concentrated solution soon setting to a jelly. It also dissolves readily in chloroform and lightens in color and turns pasty under boiling dry acetone, possibly owing to dehydration. It dissolves sparingly in cold absolute alcohol, more easily on warming.

Subs., 0.1428: 8.3 cc. N (22.0°, 773 mm.). Subs., 0.1261: 8.15 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).

Calc. for $C_{30}H_{38}O_4N_3Cl.HCl.2H_2O$: N, 6.87; Cl, 11.58. Found: N, 6.85; Cl, 11.60.

Hydroquinine Chloroacetyl-*p*-phenetidine.—After removing the acetone the residue was taken up in boiling water, treated with boneblack, and the filtrate seeded with crystals obtained by slow, spontaneous evaporation of a test portion of the original solution. The salt was recrystallized from water, forming sheaves of delicate needles containing 2.5 molecules of water of crystallization, dissolving with difficulty in water, and giving $[\alpha]_D^{27.5} = -89.1°$ in 95% alcohol, $c = 1.033$. The anhydrous salt softens slightly above 110°, sinters to a jelly at 150–60°, turns yellow, slowly evolve gas, and becomes more fluid as the temperature is further raised, and is completely molten at 210°. It is very easily soluble in absolute alcohol, acetone, chloroform, or benzene, and only difficultly in dry ether. It gives a straw-yellow solution in conc. sulfuric acid.

Subs. (air-dry), 0.4068: loss, 0.0297 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{30}H_{38}O_4N_3Cl.2.5H_2O$: H_2O, 7.70. Found: 7.30.

Subs. (anhydrous), 0.1229: 8.85 cc. N (29.5°, 759 mm.). Subs., 0.1507: 5.62 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{30}H_{38}O_4N_3Cl$: N, 7.79; Cl, 6.57. Found: N, 8.11; Cl, 6.75.

Hydroquinine 4-Chloroacetylamino-guaiacol, $C_{20}H_{26}O_2N_2.4,5\text{-}HO(CH_3O)C_6H_3NHCOCH_2Cl$.—In the case of 4-chloroacetylamino-guaiacol[2] the acetone was poured off from the gummy product and this taken up

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[1] THIS JOURNAL, 41, 1452 (1919).

[2] *Ibid.*, 41, 1457 (1919).

in a relatively large volume of boiling water and treated with bone black. The practically colorless filtrate gradually darkened on standing, depositing the salt at the same time from the still warm solution as delicate, felted, almost colorless needles containing 2 molecules of water of crystallization. It is very difficultly soluble in cold water, fairly readily on boiling, and, judging by the low halogen figure obtained on analysis, appears to be somewhat hydrolyzed by this method of crystallization. An aqueous suspension gives a slowly developing orange color with ferric chloride. The anhydrous salt forms a brown jelly above 160°, becomes semifluid at about 190°, and is completely fluid and partially decomposed at 215°. It dissolves readily in methyl or ethyl alcohol or chloroform, and is difficultly soluble in boiling dry acetone, almost insoluble in boiling benzene. It dissolves in conc. sulfuric acid with a pale greenish yellow color.

Subs. (air-dry), 0.6924: loss, 0.0444 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{29}H_{36}O_5N_3Cl.2H_2O$: H_2O, 6.24. Found: 6.43.

Subs. (anhydrous), 0.1269: 8.6 cc. N (22.0°, 757 mm.). Subs., 0.1832: AgCl, 0.0415.

Calc. for $C_{29}H_{36}O_5N_3Cl$: N, 7.76; Cl, 6.55. Found: N, 7.81; Cl, 5.61.

Hydroquinine 3,4-Methylenedioxy-chloroacetanilide, $C_{20}H_{26}O_2N_2$.-3,4-$CH_2O_2C_6H_3NHCOCH_2Cl$.—Starting with 2.2 g. of 3,4-methylenedioxy-chloroacetanilide[1] the reaction mixture deposited the crystalline salt on standing. Recrystallized from dry methyl ethyl ketone it separated as sheaves of long, delicate needles. These were warmed slightly and evacuated to remove adhering solvent and allowed to come to equilibrium in the air, retaining one molecule of water of crystallization or its equivalent. The yield was 1.5 g. The salt dissolves appreciably in cold water, quite readily on boiling, the solution forming a jelly on cooling and depositing a portion of the substance on standing as rosets of delicate needles. The anhydrous salt gradually melts, with slight preliminary softening, above 155–60°, turning orange and slowly evolving gas, and becoming completely fluid at 185°. It dissolves readily in methyl or ethyl alcohol, or chloroform, less easily in dry acetone. It gives a lemon-yellow color with conc. sulfuric acid.

Subs. (air-dry), 0.5956: loss, 0.0196 *in vacuo* at 80° over H_2SO_4.

Calc. for $C_{29}H_{34}O_5N_3Cl.H_2O$: H_2O, 3.23. Found: 3.29.

Subs. (anhydrous), 0.1275: 8.6 cc. N (20.0°, 757 mm.). Subs., 0.1527: AgCl, 0.0398.

Calc. for $C_{29}H_{34}O_5N_3Cl$: N, 7.79; Cl, 6.57. Found: N, 7.83; Cl, 6.45.

Hydroquinine 3,4-Dimethoxy-chloroacetanilide.—(From 2.3 g. of 3,4-dimethoxy-chloroacetanilide.[2]) The salt crystallized on standing and was dissolved in hot, dry acetone, filtered with the aid of boneblack, and the filtrate cautiously treated with ligroin, shaking to redissolve

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[1] THIS JOURNAL, 41, 1457 (1919).

[2] *Ibid.*, 41, 1461 (1919).

the gelatinous precipitate first formed. On seeding and letting stand overnight the salt separated as masses of hair-like needles and diamond-shaped plates containing solvent of crystallization. The yield was 3.1 g., an additional quantity, though less pure, separating from the mother liquors on standing. The anhydrous salt gradually softens and melts above 130° with gas evolution, becoming transparent at about 175° and completely fluid with decomposition at 205–10°. It softens under and dissolves readily in dry methyl or ethyl alcohol, dry chloroform, less readily, but freely in dry acetone. It is difficultly soluble in cold water, readily on heating, the solution gelatinizing on cooling. It dissolves with a yellow color in dil. hydrochloric or conc. sulfuric acid.

Subs. (anhydrous), 0.1347: 9.4 cc. N (21.0°, 765 mm.). Subs., 0.1237: 4.25 cc. $AgNO_3$ (1 cc. = 0.001794 g. Cl).

Calc. for $C_{30}H_{38}O_5N_3Cl$: N, 7.57; Cl, 6.38. Found: N, 8.16; Cl, 6.17.

Hydroquinine *m*-Chloroacetylamino-benzenesulfonamide, $C_{20}H_{26}O_2N_2.ClCH_2CONHC_6H_4SO_2NH_2$(*m*-).—Using *m* - chloroacetylamino - benzenesulfonamide[1] the reaction mixture deposited a portion of the quaternary salt as a gum. This was dissolved by adding $^1/_2$ volume of absolute alcohol, after which the salt soon began to separate. Recrystallized from dry methyl alcohol it forms faintly pinkish, glistening, hexagonal platelets which gradually soften to a jelly above 180°, darkening, and finally decomposing slowly at 200–5°. Aqueous suspensions dissolve on boiling or on adding dil. acid or alkali. The salt is difficultly soluble in cold dry methyl or ethyl alcohol, more easily on boiling, and is also somewhat soluble in boiling dry acetone and practically insoluble in boiling dry chloroform.

Subs. (anhydrous), 0.0926: 8.0 cc. N (26.0°, 770 mm.). Subs., 0.1961: AgCl, 0.0468.

Calc. for $C_{28}H_{35}O_5N_4ClS$: N, 9.75; Cl, 6.1.7 Found: N, 9.99; Cl, 5.90.

(F) Quaternary Salts of Hydroquinidine.

Hydroquinidine Chloroacetamide.—Hydroquinidine iodoacetamide was prepared in almost quantitative yield by suspending the finely pulverized base in hot acetone and adding one equivalent of iodoacetamide in small portions, the alkaloid going into solution as the reaction proceeded. After boiling for a few moments the salt began to separate as glistening hexagonal plates and was converted into the chloride as were its previously discussed isomers and analogs. The chloride was salted out from the aqueous solution and recrystallized from a small volume of water, forming aggregates of minute leaflets containing 5 molecules of water of crystallization and dissolving readily in water at room temperature, rather sparingly at 0°. The yield was about $^1/_2$ the amount of quaternary iodide used. The anhydrous salt gradually softens up to 185° to a yellow jelly

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[1] THIS JOURNAL, 39, 2429 (1917).

which becomes completely fluid and decomposes at 210°. $[\alpha]_D^{26} = +179.9°$ in water, $c = 1.078$. It dissolves readily at room temperature in methyl or ethyl alcohol, chloroform or acetone, and less easily in benzene.

Subs. (air-dry), 0.8437: loss, 0.1443 *in vacuo* at room temp., then at 80° over H_2SO_4.

Calc. for $C_{22}H_{30}O_3N_3Cl.5H_2O$: H_2O, 17.67. Found: 17.11.

Subs. (anhydrous), 0.1305: 11.5 cc. N (29.0°, 763 mm.). Subs., 0.1572: 7.16 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{22}H_{30}O_3N_3Cl$: N, 10.02; Cl, 8.45. Found: N, 10.0; Cl, 8.25.

Hydroquinidine *p*-Chloroacetylamino-phenol.—A suspension of the components in dry acetone soon cleared on boiling and after $^1/_2$ hour the salt suddenly crystallized and the mixture was allowed to stand in a warm place for 4 hours. The yield was 83% of the theoretical amount. Recrystallized by dissolving in hot absolute alcohol, adding about 3 volumes of dry ether, and seeding, the salt forms rosets of delicate needles which darken and soften slightly when heated and melt only when kept in the bath at 285° for a few moments. It is very difficultly soluble in boiling water and practically insoluble in dry chloroform or acetone, but dissolves at room temperature in absolute alcohol, more easily in dry methyl alcohol.

Subs. 0.1129: 8.4 cc. N (27.0°, 758 mm.). Subs., 0.1668: AgCl, 0.0460.

Calc. for $C_{28}H_{34}O_4N_3Cl$: N, 8.21; Cl, 6.93. Found: N, 8.45; Cl, 6.82.

The Hydrochloride.—The quaternary salt, rubbed under a small volume of 10% hydrochloric acid, formed a gummy mass which crystallized on standing. A solution of the salt in hot water containing a few drops of dil. hydrochloric acid was cooled and treated with the conc. acid until the initial turbidity barely redissolved on stirring. On seeding and letting stand in the cold the hydrochloride separated as faintly yellow, minute rhombs which deliquesced rapidly in the warm, moist room. The dried salt does not have this objectionable property. It melts and decomposes at 245–50° with preliminary darkening and dissolves rather sparingly in cold water. It dissolves in dry methyl alcohol, sparingly in absolute alcohol, and is almost insoluble in boiling dry chloroform or acetone.

Subs. 0.2039: AgCl, 0.1050.

Calc. for $C_{28}H_{34}O_4N_3Cl.HCl$: Cl, 12.93. Found: 12.74.

Hydroquinidine Chloroacetyl-*p*-anisidine.—This salt was prepared in the same way and in the same yield as hydroquinidine-*p*-chloroacetylamino-phenol. Recrystallized from 25% alcohol it forms rosets of flat, cream-colored prisms which melt and decompose at 260–5°. It dissolves in dry chloroform and appreciably in methyl alcohol. It is sparingly soluble in absolute alcohol, more easily on boiling, and only very difficultly soluble in boiling water or dry acetone. It is optically inactive in dry chloroform, where $c = 1.019$.

Subs., 0.1110: 8.0 cc. N (26.0°, 765 mm.). Subs., 0.1209: 4.5 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl$: N, 7.99; Cl, 6.75. Found: N, 8.28; Cl, 6.74.

The Hydrochloride.—3 g. of the quaternary salt were dissolved in a few cc. of conc. hydrochloric acid and the solution then treated with small amounts of dry acetone, with shaking, until the volume was about 50 cc. On letting stand and rubbing occasionally the salt crystallized as faintly yellow, nacreous, rounded scales, crystallization being facilitated by the addition of more dry acetone and ether. The dried product, when rapidly heated to 195°, then slowly, melts and decomposes at 196–200°. It dissolves readily in water, methyl or ethyl alcohol, less easily in dry chloroform, and very difficulty in dry acetone.

Subs., 0.1148: 7.64 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl.HCl$: Cl, 12.61. Found: 12.05.

(G) Quaternary Salts of Hydrocupreine.

Hydrocupreine Chloroacetanilide Hydrochloride.—As hydrocupreine showed only very little tendency to combine with chloroacetanilide in boiling dry acetone it was found necessary to use iodoacetanilide, combining the substances in hot alcoholic solution. As the iodide showed no tendency to crystallize the solution was diluted until just turbid and shaken with freshly precipitated silver chloride. Most of the alcohol was removed from the filtrate by concentration *in vacuo* and after dilution with hot water and treating with boneblack the clear yellow filtrate was treated with saturated sodium chloride solution, precipitating the chloride as an amorphous, yellow solid. This was collected and rubbed up with conc. hydrochloric acid, changing to a faintly yellow mass of spherules of microscopic needles, which were filtered off after dilution with a little more than an equal volume of water. When rapidly heated to 210°, then slowly, it melts and decomposes at 213–4°. It dissolves readily in dry methyl alcohol, less easily in cold water or absolute alcohol, and is almost insoluble in dry chloroform or acetone.

Subs., 0.1428: 10.0 cc. N (21.5°, 759 mm.). Subs., 0.1566: AgCl, 0.0888.

Calc. for $C_{27}H_{32}O_3N_3Cl.HCl$: N, 8.11; Cl, 13.68. Found: N, 8.11; Cl, 14.03.

Hydrocupreine Chloroacetyl-*p*-anisidine Hydrochloride.—3.3 g. of hydrocupreine, 2 g. of anhydrous sodium iodide, and 2 g. of chloroacetyl-*p*-anisidine were boiled for one hour in dry acetone. The base quickly dissolved and was replaced by a heavy precipitate of sodium chloride. The filtrate and washings were diluted with water and shaken for 45 minutes with freshly precipitated silver chloride. After adding an excess of hydrochloric acid to the filtrate it was concentrated to small bulk *in vacuo*, the last portions of the salt separating as colorless, hair-like needles. After washing with a little 10% hydrochloric acid the residue was dried *in vacuo*, dissolved in boiling absolute alcohol containing a little dry hydrochloric acid, cooled, and seeded with crystals obtained by rubbing a portion of the crude salt with absolute alcohol. The pure salt forms radiating masses of minute, pale yellow needles, which, after drying as usual melt to an orange jelly at 203–5.5° and become completely fluid, with gas evolution and darkening, at about 210°. It dissolves easily in water or methyl alcohol, slowly but freely in dry chloroform, and is appreciably soluble in absolute alcohol at room temperature, readily on warming. An aqueous solution gives a pale brownish color with ferric chloride.

Subs., 0.1205: 8.4 cc. N (24.5°, 750 mm.). Subs., 0.1088: 7.8 cc. $AgNO_3$ soln. (1 cc. = 0.001794 g. Cl).
Calc. for $C_{28}H_{34}O_4N_3Cl.HCl$: N, 7.67; Cl, 12.93. Found: N, 7.89; Cl, 12.86.

(H) Quaternary Salts of Ethylhydrocupreine.

Ethylhydrocupreine Methochloride.—The methiodide[1] in aqueous suspension, was quantitatively converted into the chloride in the usual manner. Recrystallized from water it forms aggregates of silky needles containing 2.5 molecules of water of crystallization and is rather difficultly soluble in cold water. The anhydrous salt softens when heated, melting to a paste at about 160°, then turning yellow and finally melting completely to an orange liquid filled with bubbles at 198–9°. $[\alpha]_D^{22} = -176.7°$ in water, $c = 0.651$. It dissolves readily in dry methyl or ethyl alcohol or dry chloroform, less easily in dry acetone.

Subs. (air-dry), 0.6166: loss, 0.0633 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{22}H_{31}O_2N_2Cl.2.5H_2O$: H_2O, 10.33. Found: 10.27.
Subs. (anhydrous), 0.2442: AgCl, 0.0902.
Calc. for $C_{22}H_{31}O_2N_2Cl$: Cl, 9.07. Found: 9.14.

Ethylhydrocupreine Iodoacetamide.—Ethylhydrocupreine and iodoacetamide reacted quickly in acetone solution. Most of the acetone was evaporated off and the residue dissolved in hot water, the iodide separating in almost quantitative yield on cooling and rubbing. Recrystallized twice from water, using boneblack, it forms rosets of needles and long, narrow plates containing 3 molecules of water of crystallization. The anhydrous substance softens to a jelly at 140–50°, gradually liquefying and darkening, and becoming completely fluid at about 185°. $[\alpha]_D^{26} = -115.4°$ in absolute alcohol, $c = 0.910$. It dissolves readily in methyl or ethyl alcohol, chloroform or acetone.

Subs. (air-dry), 0.5403: loss, 0.0501 *in vacuo* at 100° over H_2SO_4.
Calc. for $C_{23}H_{32}O_3N_3I.3H_2O$: $H_2O = 9.33$. Found: 9.27.
Subs. (anhydrous), 0.1611: AgI, 0.0709.
Calc. for $C_{23}H_{32}O_3N_3I$: I, 24.17. Found: 23.78.

Ethylhydrocupreine Chloroacetamide.—The iodide was converted into the chloride and salted out with sodium chloride. Recrystallized from water it forms faintly yellow aggregates of long, narrow plates containing

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[1] THIS JOURNAL, 41, 825 (1919).

a little over 3 molecules of water of crystallization and dissolving fairly readily in water. The anhydrous salt melts to a jelly at 145–60°, turns yellow, then orange, and becomes completely fluid at about 195°. $[\alpha]_D^{23} = -114.8°$ in water, $c = 1.124$. It dissolves readily in absolute alcohol.

Subs. (air-dry), 0.6813: loss, 0.0815 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{23}H_{32}O_3N_3Cl.3H_2O$: H_2O, 11.08. Found: 11.97.

Subs. (anhydrous), 0.0852: 7.3 cc. N (27.0°, 753 mm.). Subs., 0.1705: 7.68 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{23}H_{32}O_3N_3Cl$: N, 9.69; Cl, 8.17. Found: N, 9.66; Cl, 8.16.

Ethylhydrocupreine *p*-Chloroacetylamino-phenol.—The salt, prepared by the direct method, crystallized in good yield on letting stand. Recrystallized from dry methyl ethyl ketone it formed rosets of delicate needles which came to equilibrium in the air with one molecule of water of crystallization. When rapidly heated to 175°, then slowly, it melted at 178–82° to a jelly. $[\alpha]_D^{22} = -71.8°$ in absolute alcohol, $c = 0.844$. The salt dissolves readily in absolute alcohol and very difficultly in water or dry acetone. It softens under dry chloroform and dissolves to some extent.

Subs. (air-dry), 0.5319: loss, 0.0181 *in vacuo* at 100° over H_2SO_4.

Calc. for $C_{29}H_{36}O_4N_3Cl.H_2O$: H_2O, 3.31. Found: 3.40.

Subs. (anhydrous), 0.1359: 9.4 cc. N (18.0°, 760 mm.).

Calc. for $C_{29}H_{38}O_4N_3Cl$: N, 7.99. Found: 8.12.

The Hydrochloride.—On rubbing with 1:1 hydrochloric acid the quaternary salt changed to a pasty mass which gradually crystallized. Its solution in hot water containing a little hydrochloric acid was cooled, treated with the concentrated acid until the initial turbidity barely redissolved, and seeded. The hydrochloride separated in the refrigerator as almost colorless rosets of delicate needles. The anhydrous salt darkens at about 185°, gradually melting to an orange liquid and evolving gas at 196–7°. It dissolves readily in water, methyl or ethyl alcohol, and is practically insoluble in dry acetone.

Subs., 0.1528: 10.62 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{29}H_{36}O_4N_3Cl.HCl$: Cl, 12.61. Found: 12.58.

Ethylhydrocupreine Chloroacetyl-*p*-anisidine.—The salt was obtained crystalline by evaporation of the acetone solution. After recrystallization from methyl ethyl ketone the yield was 82.5% of the theory. Recrystallized from boiling water, in which it is only difficultly soluble, it separates as delicate, hair-like needles containing 1.5 molecules of water of crystallization. The anhydrous salt softens to a jelly at 145–55°, turning yellow and liquefying completely by the time 200° is reached. $[\alpha]_D^{25} = -69.0°$ in absolute alcohol, $c = 1.574$. It dissolves readily in methyl or ethyl alcohol or chloroform, more slowly in dry acetone. It gives a pale yellow color in conc. sulfuric acid.

Subs. (air-dry), 0.7569: loss, 0.0334 *in vacuo* at 80°, then 100° over H_2SO_4.

Calc. for $C_{30}H_{38}O_4N_3Cl.1.5H_2O$: H_2O, 4.41. Found: 4.77.

Subs. (anhydrous), 0.1533: 10.6 cc. N (25.0°, 767 mm.). Subs., 0.1188: 4.3 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{30}H_{38}O_4N_3Cl$: N, 7.79; Cl, 6.57. Found: N, 7.99; Cl, 6.56.

The Hydrochloride.—A solution of the quaternary salt in an excess of absolute alcoholic hydrochloric acid was concentrated to dryness *in vacuo* and the gummy residue digested in the flask with dry acetone, a portion dissolving. After several days the hydrochloride began to crystallize as prismatic needles and became entirely crystalline on rubbing and letting stand. When rapidly heated to 200°, then slowly, the dried salt darkens and sinters at 201–4° and melts and decomposes at 204–5°. It dissolves readily in methyl or ethyl alcohol and only incompletely in water, owing to hydrolysis.

Subs. 0.1374: 9.46 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{30}H_{38}O_4N_3Cl.HCl$: Cl, 12.30. Found: 12.47.

Ethylhydrocupreine Chloroacetyl-*p*-phenetidine.—Ligroin was added to the reaction mixture and the solution allowed to stand in the ice box with occasional rubbing, the salt crystallizing in a yield of 80% of the theoretical amount. Recrystallized with the aid of boneblack from boiling water, in which it is sparingly soluble it separated on seeding as woolly masses of delicate needles containing 1.5 molecules of water of crystallization. The anhydrous salt softens to a jelly above 130°, gradually liquefying and turning yellow as the temperature is raised, until completely fluid, with slow decomposition at about 210°. $[\alpha]_D^{25.5} = -75.25°$ in 95% alcohol, $c = 0.917$. It dissolves extremely easily in chloroform, very readily in methyl or ethyl alcohol, and easily in dry acetone.

Subs. (air-dry), 0.5089: loss, 0.0232 *in vacuo* at 80°, then 100° over H_2SO_4.

Calc. for $C_{31}H_{40}O_4N_3Cl.1.5H_2O$: H_2O, 4.65. Found: 4.56.

Subs. (anhydrous), 0.1198: 8.25 cc. N (27.0°, 762 mm.). Subs., 0.1276: 4.47 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{31}H_{40}O_4N_3Cl$: N, 7.59; Cl, 6.40. Found: N, 7.86; Cl, 6.35.

The Hydrochloride.—This salt was obtained in exactly the same way as the corresponding anisidine compound, forming aggregates of minute, thick plates with tapering ends. It begins to turn yellow above 150°, darkens at about 200°, then softens and sinters, and melts and decomposes at 208°. It softens under water and dissolves slowly but completely on shaking. It is also readily soluble in absolute alcohol or chloroform and only very sparingly in dry acetone.

Subs., 0.1357: 8.7 cc. N (25.0°, 750 mm.). Subs., 0.1415: 9.42 cc. $AgNO_3$ soln. (1 cc. = 0.00181 g. Cl).

Calc. for $C_{31}H_{40}O_4N_3Cl.HCl$: N, 7.12; Cl, 12.02. Found: N, 7.25; Cl, 12.05.

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