

SOME ORGANO-MERCURY COMPOUNDS DERIVED FROM QUININE AND CINCHONINE

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QUININE, the most important component of the cinchona bark, is well known as a specific for malaria. It is also generally used as a febrifuge and as a component of tonics. Though it has a reputation as a universal and powerful protoplasm poison which is very destructive to protozoa, its action towards bacteria and cocci is considerably less prominent. For producing any definite effect on these, large concentrations are found necessary. It is claimed that the growth of typhoid bacilli may be stopped by 1:30,000 solution. However, they are not killed even by 1:100 concentration. Similarly high concentrations, as much as 2%, are required to kill putrefactive bacteria. Mercury compounds are among the oldest of the antisyphilitics and still have an important place in the treatment of Syphilis. Soluble mercury salts such as mercuric chloride are employed chiefly as washes for wounds in which infection is present or anticipated. Even in very low dilutions bacteria are killed and their growth is inhibited at still greater dilutions. The use of soluble mercury salts is limited owing to their high toxicity and their corrosive effect on instruments. They have therefore been largely displaced by organic mercurials which do not have these defects and at the same time possess the required antiseptic power. A suitable combination of mercury and quinine may be expected to possess the good features of both quinine and mercury compounds and be devoid of their defects. The combination may have a larger range of utility and at the same time be less toxic.

In the course of the preparation of the mercuric chloride compounds of alkaloids in general, Hinterberger¹ obtained a compound from quinine and another from cinchonine containing the respective alkaloid, hydrogen chloride and mercuric chloride in the molecule. His procedure was to add an alcoholic solution of mercuric chloride to a solution of the alkaloid in alcoholic hydrochloric acid. The compounds were described as sparingly soluble in alcohol, water and other solvents. Though he gave wrong formulæ, his analytical results indicate the general formula $B, 2 HCl, HgCl_2$ for these compounds. In an attempt to prepare sparingly soluble compounds of alkaloids which will be useful for characterising them, iodo-mercurates having the formula $B, 2 HI, HgI_2$ of quinine and cinchonine were prepared by Francois and Blanc² by treatment of the acid solutions of the alkaloids with

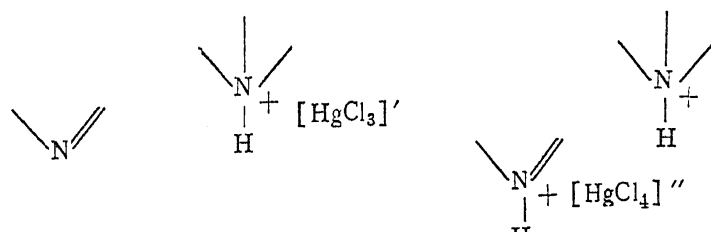
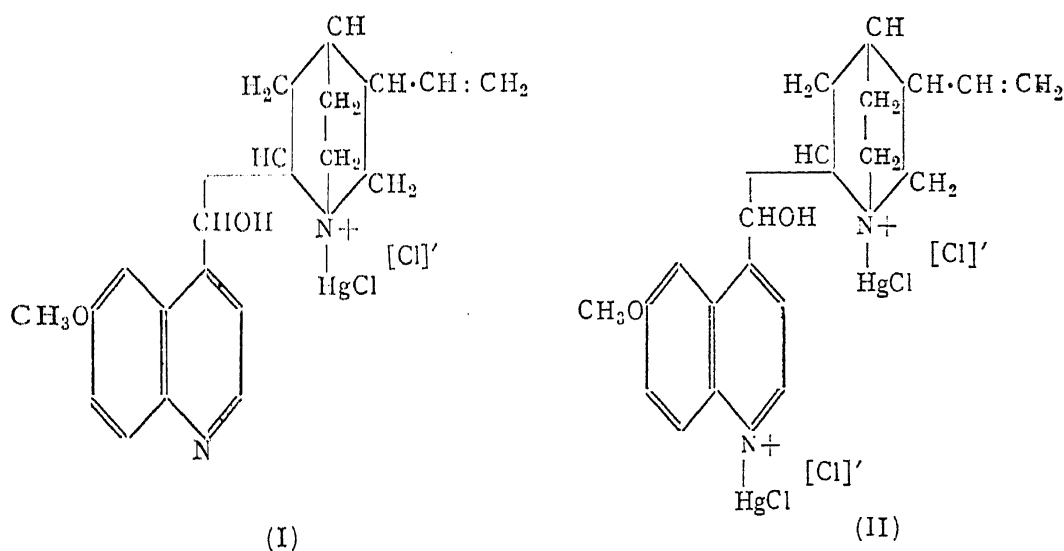
potassium iodo-mercurate. By the action of mercuric acetate on quinine, Thron³ claimed to have prepared a compound having the formula $R\text{CHOH-CH}_2\text{HgOCOCH}_3$ possessing marked properties of disinfection. In the form of its sulphate it is claimed to be highly useful for the treatment of venereal infection. More recently Craig⁴ has taken a patent for the preparation of quinine hydrochloride mercury bichloride which is suitable for therapeutic use. Definite details for the preparation of these compounds and regarding their properties are not available.

There are three important centres of reactivity in the quinine molecule: (1) Tertiary N atoms belonging to the quinuclidine and quinoline halves; the former of these is the more basic of the two since it is present in a saturated ring structure; (2) the vinyl side chain where addition of mercury compounds may be expected; (3) the secondary alcoholic group which may undergo oxidation under suitable conditions. From the existing literature on quinine-mercury compounds adequate details of their preparation and properties are not available. Neither are all the possibilities of compound formation investigated exhaustively. An investigation with the object of obtaining accurate and detailed information relating to useful compounds containing quinine and mercury has therefore been undertaken and the results are presented in this paper. Besides possible therapeutic applications, compounds of cinchonine supply data confirming results obtained relating to the chemistry of the quinine derivatives. Hence parallel series of experiments have been conducted with cinchonine also.

By the action of mercuric chloride on quinine four definite compounds have been prepared: (1) a substance having the formula B, HgCl_2 (I) obtained by mixing cold alcoholic solutions containing one molecule each of quinine and mercuric chloride; (2) a compound having the formula $B, 2\text{HgCl}_2$ (II) by using two or more molecular proportions of mercuric chloride instead of one as above; (3) a compound having the formula $B, \text{HCl}, \text{HgCl}_2$ (III) obtained when the alkaloid is dissolved in water containing just enough hydrochloric acid to produce a clear solution and treated with an aqueous solution of mercuric chloride in the cold; (4) a compound having the formula $B, 2\text{HCl}, \text{HgCl}_2$ (IV), obtained when hot aqueous solutions and excess of hydrochloric acid are used. No change occurs when excess of mercuric chloride is employed in cases (3) and (4).

All the above compounds are quite crystalline, the first two being almost insoluble in alcohol and water. Compound III is sparingly soluble in cold alcohol, soluble to some extent in cold water, and easily soluble in hot water and hot alcohol. Compound IV is fairly easily soluble in cold water and hot alcohol, though it is sparingly soluble in cold alcohol and it is the most stable

of all the compounds. Hence it is the most convenient substance for preparing aqueous solutions suitable for injections. All the other compounds undergo conversion into IV, when boiled with dilute hydrochloric acid. On the addition of 10% aqueous sodium hydroxide to the four compounds in the solid state none of them went into solution. All of them assumed however a yellow appearance. It was easy to recover compound III in a pure form by washing with water and recrystallising from alcohol. On the other hand compound IV was found to have undergone a change yielding compound III obviously due to the removal of a molecule of HCl. Thus it is possible to convert III into IV by treatment with hot hydrochloric acid and the reverse change can be effected by the action of cold alkali on IV in the solid state. When however boiling alkali is employed decomposition takes place with the liberation of mercuric oxide and the base. Cold aqueous solutions of compounds III and IV, behave in a different way. When treated with alkali they yielded precipitates of the nitrogenous base only, mercury being retained in solution. It is obvious therefore that in this alkaline medium mercury is present in the form of stable complex ions as found in $K^+ (HgCl_3)'$ and $K_2^{++}(HgCl_4)''$ and for the separation of mercuric oxide prolonged boiling with alkali is necessary. Ammonium sulphide however precipitates mercury as the sulphide from these compounds. According to the division of organo-mercury compounds in regard to their use in therapy already mentioned by us,⁵ these compounds can be said to belong to the pseudo-complex category. The constitutions of the compounds can be satisfactorily represented as below :

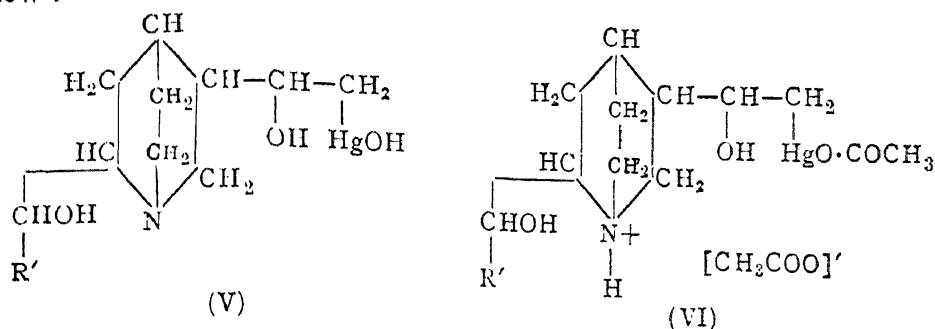


Mercuric chloride does not obviously affect the secondary alcoholic group as there is no reduction of the salt. That the above compounds are not produced by the attack of mercuric chloride on the vinyl side chain is clear from their properties especially their behaviour towards alkali. Such compounds produced by addition at the double bond are usually soluble in sodium hydroxide. On the other hand, simple nitrogenous ring structures like pyridine and quinoline which have no unsaturated side chains produce compounds with mercuric chloride⁶ quite analogous to the above. In the formation of compounds I and III the more strongly basic nitrogen of the quinuclidine half takes part and the nitrogen of the quinoline ring enters into combination only later. Compounds III and IV correspond to the chloro-mercurates of potassium, $K HgCl_3$ and K_2HgCl_4 respectively.

In the case of cinchonine, the position though similar is slightly different. A compound of type II is obtained only when a large excess of mercuric chloride is employed; otherwise a mixture of I and II is obtained. This difference may be attributed to the fact that the quinoline nitrogen in cinchonine is considerably less basic than the one present in the quinine molecule.

When quinine was mixed with mercuric acetate in methyl alcoholic solution and the mixture allowed to stand in the cold, considerable amounts of mercurous acetate separated in the course of an hour. No other sparingly soluble compound came down. On boiling the mixture, the reduction of mercuric acetate was faster and globules of mercury began to appear. It is therefore obvious that these conditions were not suitable for the production of any organo-mercury compound since the alkaloid underwent rapid oxidation. A similar behaviour is exhibited by cinchonine also. That the secondary alcoholic group is concerned in this reaction could be inferred from the results recorded by us⁷ in a recent publication. The same phenomena is noticed even in dilute acetic acid solution. However, by adopting a different procedure the details of which are given in the experimental part a colourless compound having the formula $B, OH \cdot HgOH, 2 H_2O$ (V) has been obtained from quinine. This substance is sparingly soluble in water. It is however easily soluble in very dilute aqueous sodium hydroxide, ammonia or acetic acid. In view of the usage of quinine in therapy in an ammoniacal medium, compound V can also be conveniently administered in slightly ammoniacal solutions. By dissolving the compound in dilute acetic acid just enough for producing a clear solution and evaporating it to dryness, a soluble salt having the formula $B, OH, HgO, CO, CH_3, CH_3, COOH, 2 H_2O$ (VI) is obtained. This can be easily employed in aqueous solution for therapeutic purposes. Cinchonine behaves

in an identical manner and yields compounds quite similar in composition and properties. The constitution of these compounds can be represented as below :



That in their formation addition at the vinyl side chain of the alkaloids has taken place is evident since the base or mercuric oxide is not precipitated on the addition of alkali, a clear solution being produced. The analytical results are quite in conformity with the structures given. Since ammonium sulphide does not liberate mercury from the combination even on heating, these compounds come under the category of fully complex organic compounds. In acid medium, however, mercury is precipitated by H_2S and in such medium it is obviously more easily available.

Experimental

Compounds of Quinine :

Quinine mono-mercuric chloride (I).—To a cold alcoholic solution of quinine (3 g. in 10 c.c.) was added in small quantities at a time an alcoholic solution of mercuric chloride (3 g. in 25 c.c.) and the mixture shaken. A colourless solid began to separate rapidly and the reaction was completed by keeping overnight. The next day the solid was filtered, washed with small quantities of alcohol and air-dried (5.4 g.). (Found : Hg, 34.0 ; Cl, 11.9% ; $C_{20}H_{24}O_2N_2$, $HgCl_2$ requires Hg, 33.7 ; Cl, 11.9%).

Though it appeared to be crystalline under the microscope, the structure was not well defined and it had an indefinite melting point (140–70°). It was sparingly soluble in water, alcohol or any other organic solvent. On recrystallisation from dilute hydrochloric acid it gave a compound melting at 255° with decomposition and resembling in properties and composition the compound IV (see below). It turned yellow on treatment with alkali and a suspension of the compound in aqueous medium gave rise to black mercuric sulphide with ammonium sulphide.

Quinine dimercuric chloride (II).—A boiling solution of quinine (3 g.) in alcohol (10 c.c.) was added to a similar solution of mercuric chloride (6 g. in 15 c.c.). On cooling the mixture under the tap a pale yellow heavy precipitate rapidly settled down. It was filtered, washed with alcohol and

dried in air (7.6 g.). (Found: Hg, 45.8%; $C_{20}H_{24}O_2N_2$, 2 $HgCl_2$ requires Hg, 46.3%).

The substance was in the form of a crystalline powder though the structure was not definite and it melted between 130–60°. This compound was also sparingly soluble in all the solvents and its behaviour towards hydrochloric acid, alkali and ammonium sulphide was exactly similar to that of compound (I).

Quinine mono-hydrochloride monomeric chloride (quinine-trichloro-mercurate III).—Quinine (3 g.) was dissolved in just enough of dilute hydrochloric acid (the solution should be neutral or very slightly acidic to litmus) and to the clear solution was added an aqueous solution of mercuric chloride (2.5 g.). A crystalline solid was immediately precipitated and it settled down rapidly. It was filtered, washed with a little water and recrystallised from alcohol (4.8 g.). (Found: Cl, 16.7; $C_{20}H_{24}O_2N_2$, HCl, $HgCl_2$ requires Cl, 16.9%).

Under the microscope it appeared as colourless plates and on heating melted at 204° with charring. It was sparingly soluble in cold alcohol, soluble to some extent in cold water and easily soluble in hot water and hot alcohol. When dissolved in hot dilute hydrochloric acid it gave rise to compound IV. When treated with 10% aqueous sodium hydroxide, it turned yellow and after stirring very well for 15 minutes the solid was filtered from the alkali and recrystallised from alcohol. The original compound III was recovered still unchanged. But when the substance was boiled with alkali, insoluble mercuric oxide separated. When this reagent was added to a clear cold aqueous solution of the compound, a white precipitate of quinine separated the mercury being retained in the filtrate. Ammonium sulphide precipitated mercury as sulphide from the compound.

When the above preparation was conducted using two molecular proportions of mercuric chloride in order to investigate the possibility of obtaining a compound of the type Q, HCl, 2 $HgCl_2$, it was found that compound III alone resulted. (Found: Hg, 31.8%; $C_{20}H_{24}O_2N_2$, HCl, 2 $HgCl_2$ requires Hg, 44.4%, whereas compound III requires Hg, 31.7%).

Quinine dihydrochloride monomeric chloride (Quinine tetrachloromercurate IV).—Quinine (3.2 g.) was dissolved in excess of dilute hydrochloric acid and to the boiling solution was added a hot aqueous solution of mercuric chloride (2.7 g.) and the mixture allowed to cool. There was a rapid precipitation of a crystalline solid which was allowed to accumulate overnight, filtered and washed with small quantities of alcohol. It was dried in air (4.8 g.) and analysed. (Found: Cl, 21.1%; $C_{20}H_{24}O_2N_2$, 2 HCl, $HgCl_2$ requires Cl, 21.2%).

The compound was very easily soluble in hot water, fairly easily in cold water and hot alcohol, though sparingly soluble in cold alcohol. When recrystallised from hot water, it remained unchanged and appeared as long rectangular plates melting at 255° with decomposition. It dissolved easily in dilute acids. When the finely powdered solid was treated with cold 10% aqueous sodium hydroxide and stirred for 15 minutes it underwent change into compound III. This was definitely proved when the product was washed free from alkali, recrystallised from alcohol and analysed. (Found: Cl, 16.6%; Compound III requires Cl, 16.9% and Compound IV 21.2%). Otherwise the reactions of IV in the solid form with boiling alkali or of this reagent on a solution of IV as well as the action of ammonium sulphide were quite similar to those given by Compound III.

α -Hydroxy-mercuri- β -hydroxydihydroquinine (V).—Quinine (3 g.) was dissolved in dilute acetic acid and treated with an aqueous solution of mercuric acetate (6 g.). The mixture was stirred well for about 15 minutes and then dilute sodium hydroxide was added (It should not be allowed to stand for a longer time in acid medium as oxidation of quinine occurs). First yellow mercuric oxide began to separate out and on further addition of the alkali a colourless substance appeared. The latter dissolved on the addition of excess of alkali leaving a yellow solid consisting mostly of mercuric oxide behind. The clear liquid (A) was decanted, the residual solid was dissolved in a very small amount of dilute acetic acid and then again rendered alkaline with aqueous sodium hydroxide. The clear liquid now obtained was added to (A) and the yellow mercuric oxide discarded. The collected alkaline solution was then titrated with dilute acetic acid till the maximum amount of a white precipitate was obtained. This occurred roughly at a pH of 9.0. Addition of a few drops of acid or alkali dissolved the compound and hence the titration should be done very carefully. The precipitate was allowed to settle during the course of a few hours and then filtered, washed with water and dried in air (2.2 g.). The filtrate was tested by adding a few drops of alkali or acid with a view to see if some more of the compound could be obtained. (Found: Hg, 32.7; C, 40.5%. $C_{20}H_{24}O_2N_2.OH.HgOH, 2 H_2O$ requires Hg, 33.7; C, 40.4%).

The substance was a crystalline looking powder but exhibited no definite structure under the microscope. Immediately after the preparation it was found to decompose at 115° whereas after drying for a few days in air the decomposition point was 166° and was not affected further. It was insoluble in all organic solvents and hence could not be crystallised. It was however readily soluble in dilute acids and alkalies including ammonia without decomposition. The solution in sulphuric acid exhibited fluorescence similar

to that of quinine. By the action of ammonium sulphide mercuric sulphide is not immediately produced from the solid compound or its solution in alkali; but on standing for a long time it is found to be formed gradually. However, a solution in dilute acid precipitates mercuric sulphide readily on passing hydrogen sulphide.

α-Acetoxymercuri-β-hydroxy dihydroquinine acetate (VI).—The above compound was dissolved in just enough of dilute acetic acid and the clear solution was evaporated on a water-bath in a porcelain basin. The solid residue was dissolved in water, filtered from any insoluble matter and again evaporated down to dryness. (Found: Hg, 28.6; C, 41.6%; $C_{20}H_{24}O_2N_2$, OH, HgO, CO, CH_3 , CH_3COOH , $2H_2O$ (or $C_{24}H_{36}O_9N_2Hg$) requires Hg, 28.8; C, 41.4%).

The product which was kept dry in a desiccator was found to be very hygroscopic, easily soluble in water and gave all the reactions given by compound V. It was difficult to handle and no melting or decomposition point could be determined.

Compounds of Cinchonine:

Cinchonine monomeric chloride (I) was prepared in the same way as the quinine compound and its properties were similar. It was obtained as a pale yellow crystalline solid (rhombic prisms) melting at 172° with decomposition. (Found: Hg, 36.1; $C_{19}H_{22}ON_2$, $HgCl_2$ requires Hg, 35.5%).

Cinchonine dimercuric chloride (II).—Using two molecular proportions of mercuric chloride and conducting the experiment as described for the quinine compound, a pale yellow solid of the following composition was obtained. (Found: Hg, 43.5%; $C_{19}H_{22}ON_2$, $2HgCl_2$ requires Hg, 48.0%). It was obvious that it was a mixture. The experiment was therefore repeated using three molecular proportions of mercuric chloride. The product was now found to contain 48.0% of mercury. Hence it is evident that excess of mercuric chloride is necessary for the preparation of the dimercuric chloride compound. It was microcrystalline in appearance and melted between $155-72^\circ$. It could be converted into compound IV by boiling with dilute hydrochloric acid.

Cinchonine mono-hydrochloride monomeric chloride (Cinchonine trichloro-mercurate III)—Cinchonine (2 g.) was suspended in water and to it was added the calculated quantity (1 molecular proportion) of hydrochloric acid. The clear solution thus obtained was treated with an aqueous solution of mercuric chloride (1.85 g.). Immediately a colourless precipitate began to separate. The mixture was kept overnight, filtered, washed with small amounts of alcohol and dried in air (3.0 g.). (Found: Cl, 18.0%; $C_{19}H_{22}ON_2$, HCl, $HgCl_2$ requires Cl, 17.7%).

It melted between 120–66°. It was soluble in cold water and hot alcohol and very easily soluble in hot water. Hot dilute hydrochloric acid gave compound IV.

Cinchonine dihydrochloride monomeric chloride (Cinchonine tetrachloro-mercurate IV).—This was prepared in the same way as the quinine compound. It crystallised out as colourless rectangular prisms from water and had an indefinite melting point 95–128° with decomposition. It contained water of crystallisation which was lost on drying at 100° C. (Found : in air dried sample: Cl, 20.4; C₁₉H₂₂ON₂, 2HCl, HgCl₂ 3H₂O requires Cl, 20.5%). Found : in sample dried at 100° C. : Cl, 21.7%; Hg 31.5%, C₁₉H₂₂ON₂, 2HCl, HgCl₂ requires Cl, 22.2; Hg, 31.5%). The use of a larger quantity of mercuric chloride did not produce any change in the product.

α-Hydroxymercuri-β-hydroxy-dihydrocinchonine (V).—The cinchonine compound was obtained in the same way as the quinine compound and had quite similar properties. It was a crystalline looking powder which on heating turned brown at 212° and finally melted at 235°. (Found : Hg, 36.3%; C₁₉H₂₂ON₂, OH. HgOH, H₂O requires Hg, 36.6%).

The corresponding acetate was also obtained.

Summary

The action of mercuric chloride and mercuric acetate on the alkaloids quinine and cinchonine has been investigated with a view to prepare organo-mercury compounds. The properties and constitutions of the compounds have been studied. Mercuric chloride forms combinations with the basic nitrogen atoms of the alkaloids whereas with mercuric acetate it is possible to produce compounds by addition at the ethylenic double bond. Some of these can be conveniently employed for therapeutic purposes.

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