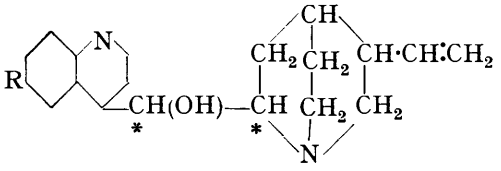
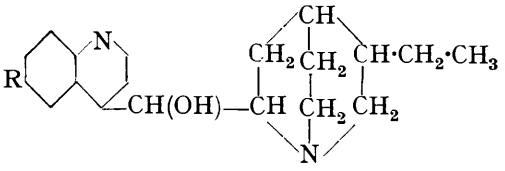
235. *Alkaloidal Cuprichlorides. The Specific Precipitation by Cupric Chloride of Cinchona Alkaloids containing the Vinyl Group.*

By Aaron Cohen.

It is well known that commercial samples of the alkaloids with the general formula (I)—quinine (R = MeO), quinidine (R = MeO), cinchonine (R = H), and cinchonidine (R = H), stereoisomeric differences being omitted—contain appreciable quantities of the corre-



(I.)



(II.)

sponding naturally occurring dihydro-derivatives (II) in which the vinyl is replaced by an ethyl group, and although the latter may be readily obtained by catalytic hydrogenation of the former (D.R.P. 252,136; B.P. 3948, 1912), yet the purification of the alkaloids containing the vinyl group (I) is very difficult, entailing repeated fractional crystallisation of their salts. The author therefore examined the possibility of obtaining alkaloidal derivatives which would facilitate such a separation.

The desiderata of such a derivative are (1) ease of preparation, (2) considerable difference of solubility between series (I) and (II), and (3) reversibility, the alkaloid being readily regenerated from its derivative. Complex salts were therefore examined, since alkaloids readily form such compounds with metallic salts; and it is believed those with cupric chloride, of the types $M^{I}CuCl_3$ and $M_2^{I}CuCl_4$, meet the requirements. These two types predominate among compounds derived from alkylammonium chlorides and cupric chloride (Remy and Laves, *Ber.*, 1933, **66**, 401).

On mixing concentrated solutions of quinine and cupric chloride in concentrated hydrochloric acid, a brick-red crystalline *compound* is obtained in excellent yield, of the composition $Q,2HCl,CuCl_2$, where Q represents the quinine molecule. Similarly quinidine yields an orange-coloured, cinchonine a green, and cinchonidine a yellowish-green *compound*, the compositions of which are all analogous to that of the quinine salt. On the other hand, no complex salts are precipitated when the corresponding dihydro-bases are treated with cupric chloride under exactly the same conditions, even after several weeks at − 4°.

These alkaloidal cuprichlorides are readily purified by recrystallisation from concentrated hydrochloric acid, the only solvent found suitable for this purpose; they are readily decomposed by water, the characteristic colour being discharged, with formation of a blue solution, similar to that of cupric chloride but quite distinct from the yellowish-green solutions in concentrated hydrochloric acid. From the aqueous solution the alkaloid is readily recovered by removing the copper by precipitation with hydrogen sulphide, and basifying the filtrate.

In attempting to formulate these compounds, regard has been taken of the behaviour of a few simple quinoline derivatives when treated with cupric chloride under the conditions described above. Quinaldine and 5-nitro-6-methoxyquinoline yield complex *salts* of the type $(Q,HCl)_2,CuCl_2$ or $B_2^{I}CuCl_4$ (B^{I} = univalent organic kation), quinoline gives a *compound* of the type $B^{I}CuCl_3$, and 6-methoxyquinoline yields an equimolecular addition *compound* of these two types. All the cinchona alkaloidal salts, however, have the composition $B^{II}CuCl_4$ (B^{II} = bivalent organic kation). Assuming, by analogy, that the quinolinium nitrogen

$$\underset{\text{(III.)}}{Cl\cdot B^{II}\cdot[CuCl_3]} \qquad \underset{\text{(IV.)}}{B^{II}\cdot[CuCl_4]} \qquad \underset{\text{(V.)}}{\{B^{II}\cdot[CuCl_4]\}_n}$$

is involved in the formation of the alkaloidal cuprichlorides, these may be formulated as (III), (IV), or (V), which may be written in the expanded forms (III*a*), (IV*a*), (V*a*), in which

the symbol . . . N_P–N_Q . . . represents the kation and indicates more clearly the attachment of the respective anions to the nitrogen of the bridged piperidine system (N_P) and the

$Cl{\cdot}N_P{-}N_Q{\cdot}CuCl_3$ (III*a*.) $\quad$ $N_P{\cdot}CuCl_4{\cdot}N_Q$ (IV*a*.) $\quad$ . . . $N_P{-}N_Q{\cdot}CuCl_4{\cdot}N_P{-}N_Q{\cdot}CuCl_4$ . . . (V*a*.)

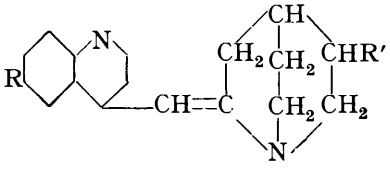
quinolinium nitrogen (N_Q). In (III*a*) N_P is associated with a chlorine anion and N_Q with a $CuCl_3'$ anion, whilst (IV*a*) represents a bivalent $CuCl_4''$ anion held between N_P and N_Q of the same kation. Remy and Laves (*loc. cit.*) have pointed out that, in accordance with theoretical considerations, more than 60% of the complex salts of cupric chloride described in the literature and 75% of the salts they obtained from alkylammonium chlorides contain the complex bivalent ion $CuCl_4''$, whilst the univalent ion $CuCl_3'$ occurs to the extent of 27% in the literature and 14% in the compounds described by them. Although these facts favour (IV) as the correct formulation of the alkaloidal cuprichlorides, an objection to it arises from inspection of a model of the quinine molecule, for it is difficult to accommodate a planar $CuCl_4''$ anion between N_P and N_Q. The objection appears to be overcome by formula (V*a*), representing a larger molecule containing n units of $B^{II}[CuCl_4]$ with the anion associated with N_Q of one kation and N_P of the next. This would admit of various ways of building up the crystal lattice, but the actual method would have to be determined by crystallographic and *X*-ray methods.

The optical rotations of the cuprichlorides (see table) indicate that the ionisation is similar in extent to that of the corresponding dihydrochloride, and hence that the rotation is due mainly to the optically active kation, and not to intact cuprichloride or a compound with cupric chloride linked to the vinyl group. The figures represent the observed rotations ($l = 1$) of equimolecular amounts ($c = 1{\cdot}00$, expressed as free base) of dihydrochloride and cuprichloride of each alkaloid in aqueous, methyl-alcoholic, and concentrated hydrochloric acid solution, respectively.

	α_D.		
	Water.	MeOH.	Conc. HCl.
Cinchonine dihydrochloride	+2·59°	+2·33°	+2·05°
Cinchonine cuprichloride	+2·51	+2·21	+2·07
Cinchonidine dihydrochloride	−1·71	−1·325	−1·05
Cinchonidine cuprichloride	−1·76	−1·33	−1·05
Quinine dihydrochloride	−2·80	—	−2·00
Quinine cuprichloride	−2·72	—	−1·915
Quinidine dihydrochloride	+3·26	—	+2·56
Quinidine cuprichloride	+3·25	—	+2·54

The properties of the alkaloidal cuprichlorides appear to indicate that their existence is confined to the crystalline solid state, and that their isolation depends on their ability to satisfy the requirements of the formation of a unit crystal pattern. The failure to obtain cuprichlorides from the dihydro-alkaloids (II) must therefore be ascribed to their inability to form a unit crystal pattern. That such a profound difference in behaviour should exist between the two types of alkaloid is remarkable, since they only differ in respect of the vinyl and the ethyl group, both groups constituting only a small part of the respective molecules.

Some light is thrown on the problem of this difference by the results obtained with quinene (VI; R = MeO, R′ = CH:CH_2), cinchene (VI; R = H, R′ = CH:CH_2), and dihydroquinene (VI; R = MeO, R′ = Et). Each of these substances contains an ethylenic



(VI.)

linking between the quinoline and quinuclidine systems, but in dihydroquinene the group R′ is saturated. In spite of this, the base behaves, together with quinene and cinchene,

as an alkaloid of type (I), readily yielding a cuprichloride of analogous composition to those already described. These facts may be co-ordinated by supposing that in the case of the alkaloids containing the vinyl group the cuprichlorides pack readily to form the unit crystal pattern. Owing to the larger volume occupied by the ethyl group, the dihydro-bases are unable to do this. In the " ene " compounds (VI), packing is possible in both types of alkaloid, since the presence of the ethylenic linking in the centre of the molecule has caused a contraction in molecular volume.

Another possible reason for the difference between alkaloids of types (I) and (II) is suggested by the behaviour of dihydroquinene. In alkaloids containing the ethyl group (II) this side chain may exert a spatial effect on the basic centre N_Q which inhibits crystallisation of the cuprichloride, and, in fact, a model shows that, by virtue of rotation about the linkings between the quinoline and the quinuclidine system, the ethyl group can pass readily through a position in close proximity to N_Q. The inhibition postulated depends on the possibility of rotation, and when this is prevented by a double bond in a suitable position, as in dihydroquinene (cf. VI), inhibition does not occur, and the cuprichloride is obtained. It is admitted that if this hypothesis applies, *e.g.*, to the behaviour of dihydrocinchonine, it could not be applied with equal validity to dihydrocinchonidine on account of the configurational differences of the carbon atoms marked with an asterisk in this pair of alkaloids. The same must be admitted with regard to the pair, dihydroquinine and dihydroquinidine. The different models constructed, having regard to the stereoisomerism associated with the two carbon atoms, do show, however, that the ethyl group may approach N_Q much more closely than is possible with an ethylenic linking between these carbon atoms.

The use of cupric chloride as a precipitant of certain cinchona alkaloids has proved of value in the preparation of some of the well-known derivatives of the natural bases. For instance, the crude products obtained in the preparation of quinene, cinchene, and dihydroquinene are readily purified through their cuprichlorides, from which they are quickly isolated as crystalline solids, and from experiments now in progress, it appears that the isolation of the desoxy-compounds will be equally facilitated by the use of this reagent.

For the separation of mixtures of alkaloids of types (I) and (II), the vinyl fraction is precipitated as cuprichloride, from which the base is later recovered, while the unprecipitated fraction is freed from copper and worked up for the recovery of the dihydro-base. The latter may be readily recognised and distinguished from the precipitated fraction by its stability to potassium permanganate in dilute sulphuric acid solution. It is, of course, impossible to effect complete precipitation of the vinyl fraction from the 1 : 1 mixtures used; but the proportion left in solution is very small, as is shown by comparative tests with permanganate and by the readiness with which the dihydro-fraction could be crystallised. Further, the aim of the separation is to obtain a specimen of vinyl base free from the base of the ethyl type, rather than to purify the latter, for this can be done by other means, *e.g.*, by destruction of the former by permanganate.

A manufacturer's sample of cinchonine, stated to contain 10% of dihydrocinchonine, was fractionated, and an amount of the latter corresponding to *ca.* 7·5% of the original material was isolated. Details are given below of the separation of the four chief cinchona alkaloids from considerable proportions of respective dihydro-analogues. The behaviour of other alkaloids towards cupric chloride under similar conditions has been examined, and the crystalline compounds obtained from strychnine, brucine, morphine, and papaverine are being investigated.

Experimental.

Preparation of the Cuprichlorides.—The compounds described below are best prepared by mixing warm solutions of the base and cupric chloride dihydrate, each in 2·5 parts by volume of concentrated hydrochloric acid. The product separates on cooling as a thick felt of crystals, which are filtered off, washed with a small quantity of cold concentrated hydrochloric acid, and air-dried on porous plate. For recrystallisation, the concentrated acid was used throughout.

Analysis. Chlorine was determined gravimetrically by precipitation as silver chloride from a dilute nitric acid solution of the compound. The determination of copper by precipitation as cuprous thiocyanate from dilute hydrochloric acid solution was unsatisfactory, as the precipitates were discoloured and appeared to contain organic matter. A semi-micro-method was adopted. About 80 mg. of substance were oxidised by heating in a micro-Kjeldahl flask with 0·6 c.c. of concentrated sulphuric acid, hydrogen peroxide being added at intervals until a clear green solution was obtained. This was diluted to 15 c.c. with distilled water, and the copper in 5 c.c. portions determined in duplicate by the micro-electrodeposition method of Pregl, which gives consistent results.

Quinine cuprichloride (86% yield) forms brick-red granular aggregates of small needles, m. p. 210° (decomp.) (Found : Cl, 26·7; Cu, 11·75. $C_{20}H_{24}O_2N_2,2HCl,CuCl_2$ requires Cl, 26·7; Cu, 11·96%). *Quinidine cuprichloride* (94·5% yield), orange plates, m. p. 208—209° (decomp.) (Found : Cl, 26·6; Cu, 11·76. $C_{20}H_{24}O_2N_2,2HCl,CuCl_2$ requires Cl, 26·7; Cu, 11·96%). *Cinchonine cuprichloride* (88% yield) crystallises as a *sesquihydrate* in long, flat, green needles, m. p. 130—132° (decomp.) (Found : H_2O, 5·39. $C_{19}H_{22}ON_2,2HCl,CuCl_2,1\frac{1}{2}H_2O$ requires $1\frac{1}{2}H_2O$, 5·1%. Found, in anhydrous material : Cl, 28·0; Cu, 12·3. $C_{19}H_{22}ON_2,2HCl,CuCl_2$ requires Cl, 28·3; Cu, 12·68%). *Cinchonidine cuprichloride* (89·7% yield) crystallises as a *dihydrate* in sheaves of yellowish-green, narrow, hexagonal plates, m. p. 128—129° (decomp.) (Found : H_2O, 7·6. $C_{19}H_{22}ON_2,2HCl,CuCl_2,2H_2O$ requires $2H_2O$, 6·7%. Found, in anhydrous material : Cl, 28·0; Cu, 12·61. $C_{19}H_{22}ON_2,2HCl,CuCl_2$ requires Cl, 28·3; Cu, 12·68%).

Quinene cuprichloride (80% yield), yellowish-green feathery needles, decomp. 125—130° (Found : Cl, 27·97; Cu, 12·67. $C_{20}H_{22}ON_2,2HCl,CuCl_2$ requires Cl, 27·7; Cu, 12·37%). *Cinchene cuprichloride* (86% yield), orange-yellow needles, which darken on heating and decompose at 185—187° (Found : Cl, 29·2; Cu, 12·92. $C_{19}H_{20}N_2,2HCl,CuCl_2$ requires Cl, 29·4; Cu, 13·15%). *Dihydroquinene cuprichloride* (88% yield), yellow needles, decomp. 195° (Found : Cl, 27·8; Cu, 12·12. $C_{20}H_{24}ON_2,2HCl,CuCl_2$ requires Cl, 27·6; Cu, 12·34%).

5-Nitro-6-methoxyquinoline cuprichloride (95% yield) crystallises as a *monohydrate* in large orange needles, greenish-gold in the anhydrous form, which effervesce at 187—189° (Found : H_2O, 3·3. $C_{20}H_{16}O_6N_4,2HCl,CuCl_2,H_2O$ requires H_2O, 2·84%. Found, in anhydrous material : Cl, 22·92; Cu, 10·6. $C_{20}H_{16}O_6N_4,2HCl,CuCl_2$ requires Cl, 23·07; Cu, 10·33%). *Quinaldine cuprichloride* (70% yield), orange, diamond-shaped tablets, m. p. 175—178° (decomp.) (Found : Cl, 28·66; Cu, 12·67. $C_{20}H_{18}N_2,2HCl,CuCl_2$ requires Cl, 28·77; Cu, 12·89%). *Quinoline cuprichloride* (76% yield), small brown needles, which darken and gradually decompose above 185° (Found : Cl, 35·44; Cu, 21·0. $C_9H_7N,HCl,CuCl_2$ requires Cl, 35·5; Cu, 21·2%).

An equimolecular *compound* of 6-methoxyquinoline cupritri- and cupritetra-chloride is obtained in excellent yield, and crystallises in chocolate-coloured needles of constant composition, m. p. 157—159°, when anhydrous (Found : Cl, 28·6, 28·64; Cu, 14·73; Cl : Cu = 3·48 : 1. $C_{10}H_{10}ON,HCl,CuCl_2 + C_{20}H_{20}O_2N_2,2HCl,CuCl_2$ requires Cl, 28·9; Cu, 14·8; Cl : Cu = 3·5 : 1); it forms a hydrate containing 4·1% H_2O.

Separation of Mixtures.—" Purified " cinchonine (1 g.), said to contain 10% of dihydrocinchonine, was treated with cupric chloride (1 g.) in 10 c.c. of concentrated hydrochloric acid and cooled at 0° for some hours. The complex salt, yield 1·28 g., m. p. 128—130° (decomp.), was collected and the filtrate diluted with water, treated with hydrogen sulphide, filtered, boiled to remove excess of gas, and basified. The precipitated alkaloid crystallised from alcohol in prismatic needles (0·075 g.), m. p. 262°, not depressed in admixture with a specimen of dihydrocinchonine of m. p. 267—268°. The product was quite stable to 2% acidified permanganate.

Cinchonine–dihydrocinchonine (1 : 1). The mixture (2 g., in HCl, 10 c.c.) was treated as above ($CuCl_2$, 2 g.; HCl, 6 c.c.) and chilled at − 4° over-night. The yield of cuprichloride was 1·6 g. The filtrate, treated as above, yielded 0·9 g. of dihydrocinchonine; the base was treated with acidified permanganate until a coloration persisted (very little was required), then recovered (0·85 g.) and crystallised from alcohol, m. p. 267—268°, $[\alpha]_D^{21°}$ + 203° (c = 1·00 in alcohol–chloroform, 1 : 2 by vol.). The cuprichloride was dissolved in water, and the cinchonine recovered (1 g.); prisms, m. p. 260°, $[\alpha]_D^{21°}$ + 221·5° (c = 1·00 in the same mixture), from alcohol.

Quinidine–dihydroquinidine (1 : 1). The mixture (2 g.) was treated as above, the total volume of acid being 14 c.c. The theoretical yield of quinidine cuprichloride was obtained (1·6 g.), from which quinidine was recovered (0·9 g.), m. p. 170—171°, $[\alpha]_D^{21°}$ + 273·3° (c = 1·00 in alcohol–chloroform, as above). The mother-liquor was worked up for the recovery of dihydroquinidine, which was obtained (1 g.) in prismatic needles, m. p. 167° when anhydrous, $[\alpha]_D^{21°}$ + 222·5° (c = 1·00 in alcohol).

Cinchonidine–dihydrocinchonidine (1 : 1). The mixture (4 g.), dissolved in 30 c.c. of concentrated hydrochloric acid, was separated into fractions : (i) 2·1 g. (consuming very little permanganate), which crystallised in long leaflets from alcohol, m. p. 228—230° (not depressed by admixture with dihydrocinchonidine), $[\alpha]_D^{21°}$ — 96·7° (c = 1·00 in alcohol) ; (ii) 1·8 g., m. p. 202—203°, $[\alpha]_D^{21°}$ — 107·5° (c = 1·00 in alcohol–chloroform, as before).

Quinine–dihydroquinine (1 : 1). The yield of cuprichloride from the quinine fraction was lower than usual (2·6 g. from 4 g. of mixture). The quinine left in solution was isolated with the dihydroquinine as a fraction of 2·4 g., which was freed from quinine by oxidation of the latter with permanganate, yielding 1·85 g. of dihydroquinine, m. p. 170°.

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