254. *Modified Cinchona Alkaloids. Part III. Chlorodihydro-bases.*

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As part of a general chemical and biological investigation of natural anti-malarial drugs, including the cinchona alkaloids and their derivatives, now proceeding in these laboratories, the author set out to prepare the hydrogen chloride addition products of the four primary cinchona alkaloids, quinine, quinidine, cinchonidine, and cinchonine. Though a somewhat extensive literature on these products exists, only two of them have been more or less definitely characterised, *viz.*, " hydrochloroquinine " (Comstock and Koenigs, *Ber.*, 1887, **20**, 2517; Hesse, *Annalen*, 1893, **276**, 125) and the " chlorocinchonide " of Zorn (*J. pr. Chem.*, 1874, **8**, 284), which Konek (*Monatsh.*, 1895, **16**, 321) has shown is identical with " hydrochlorocinchonine " prepared by the method of Comstock and Koenigs (*loc. cit.*). As these products are chloro-derivatives of dihydroquinine and dihydrocinchonine respectively, it is proposed to rename them on this basis and to adopt analogous names for the corresponding derivatives of cinchonidine and quinidine.

In the addition of hydrogen chloride at the double bond in the vinyl group of cinchona alkaloids, should the chlorine become attached to the β-carbon atom, one chlorodihydro-base would be formed; if the chlorine entered the α-position, two stereoisomerides would be produced, and if addition of chlorine occurred on both the α- and the β-carbon atom, three compounds would result. No record of more than one chlorodihydro-base being formed by the direct addition of hydrogen chloride to a cinchona base has been found in the literature, although Rosenmund and Kittler (*Arch. Pharm.*, 1924, **262**, 18) have recorded the isolation of two isomerides having the composition of iododihydroquinine from the products of the action of hydrogen iodide on quinine, and Comstock and Koenigs (*loc. cit.*, p. 2515) and Christensen (*J. pr. Chem.*, 1905, **71**, 1) have noted the formation of two cinchonine dibromides by the action of bromine on cinchonine. If, as it seems reasonable to assume, bromine adds on at the vinyl group, the formation of two isomerides must be due to the bromine atom entering the α-position, with the formation of a new centre of asymmetry.

In the present investigation only two isomerides having the composition of *chlorodihydro-bases* have been isolated in each case from the products of the action of hydrogen chloride on quinine, cinchonine, cinchonidine, and quinidine, respectively, whether the reaction takes place under the conditions of Comstock and Koenigs (*loc. cit.*) or of Hesse (*loc. cit.*). Since, in the former method, the chlorine-containing bases are formed at room temperature, it appears justifiable to consider these as the products of addition of hydrogen chloride to the unaltered bases, and the production of two isomerides as due to the addition of the chlorine atom at the α-carbon atom, giving rise to two stereoisomerides. It is proposed to call the isomeride with the higher optical rotation the α-, and the other the α′-chlorodihydro-base. The quinine, cinchonine, and cinchonidine used were good commercial specimens. The quinidine was freed from dihydroquinidine by the process described recently by Buttle, Henry, and Trevan (*Biochem. J.*, 1934, **28**, 426), or by that of Thron and Dirscherl (*Annalen*, 1935, **515**, 252).

The *cuprichlorides* of the chlorodihydro-bases described exhibit two features of interest. Buttle, Henry, and Trevan have shown already (*loc. cit.*) that Cohen's view (J., 1933, 996) that cupric chloride is a specific precipitant for cinchona alkaloids containing the vinyl side chain intact, is untenable, and this is now confirmed by the preparation of cuprichlorides from these bases, in which the vinyl group has been saturated by the addition of hydrogen chloride. The chlorodihydrocinchonine cuprichlorides, unlike other products of this type, separate into their components on recrystallisation from concentrated hydrochloric acid, unless cupric chloride is also present in excess. All the cuprichlorides described are of the normal type, $B,2HCl,CuCl_2$, in this series, except those derived from α′-chlorodihydroquinine and α-chlorodihydrocinchonidine, which are representatives of the type $(B,2HCl)_2,CuCl_2$.

The two chlorodihydroquinines have been tested for anti-malarial activity in bird malaria by Drs. Buttle and Trevan of the Wellcome Physiological Research Laboratories. In doses of 5 mg. per 20 g. of bird, both isomerides were about as active as quinine, and a

little less active than dihydroquinine. These results are not significantly different from those of Giemsa, Weise, and Tropp (*Arch. Schiffs- u. Tropenhyg.*, 1926, **30**, 342) for " hydrochloroquinine." They indicate that chlorine in the α-position in the side-chain has very little dystherapeutic effect compared with chlorine replacing hydroxyl in the secondary alcohol group characteristic of the natural cinchona alkaloids, and that in these two isomerides the stereochemical difference implies no difference in anti-malarial action. As representative of the dextrorotatory pair of cinchona alkaloids, quinidine and cinchonine, the α- and α'-chlorodihydrocinchonines were examined: they were almost inactive, which is not unexpected since quinidine and cinchonine have been shown recently (Buttle, Henry, and Trevan, *loc. cit.*) to have about one-half and one-fifth respectively of the activity of quinine in bird malaria.

Experimental.

In the following account, the m. p.'s are corrected; the analyses are for material dried at 105° in a vacuum; and rotations are given for solutions in *N*-hydrochloric acid unless otherwise stated.

Quinine.—" Hydrochloroquinine," prepared by the method of Comstock and Koenigs (*loc. cit.*) by the action of hydrochloric acid, saturated at − 17° with dry hydrogen chloride, on quinine hydrochloride for many weeks at ordinary temperature, or by that of Hesse (*loc. cit.*) and Suszko (*Bull. Inter. Acad. Polonaise*, 1925, 129) by heating quinine hydrochloride in a sealed tube with concentrated hydrochloric acid (*d* 1·19) at 85° during 50 hours, is a mixture of α- and α'-chlorodihydroquinine.

The two methods gave similar yields, the former 67·9% and the latter 66·6% of the theoretical quantity of crude chlorodihydroquinine acid nitrate. Attempts to hasten the reaction by boiling quinine with concentrated hydrochloric acid under reflux during 7½ hours and 17½ hours were unsuccessful, the yield of crude acid nitrate being reduced to 23·2% and 9·6% respectively. Comstock and Koenigs (*loc. cit.*, p. 2518) have shown that " hydrochloroquinine " can be isolated from the reaction mixture as the sparingly soluble acid nitrate, which they assumed to be pure after three recrystallisations. It has now been found that this salt gradually changes in specific rotation and other properties on repeated recrystallisation. The base, on the other hand, is readily separated into a sparingly soluble and soluble fraction by crystallisation from methyl alcohol or ether.

By taking advantage of these properties, the " hydrochloroquinine " of Comstock and Koenigs has been separated into two isomerides. The bases regenerated from the reaction mixture were dissolved in slight excess of nitric acid (2%), and the acid nitrate of the chlorobases rapidly crystallised. Further crops of acid nitrate were obtained by redissolving the base recovered from the mother-liquor in slight excess of nitric acid (2%). The base regenerated from the crops of acid nitrate was dissolved in hot methyl alcohol, which soon deposited crystals of crude α-chlorodihydroquinine. This base was recrystallised from methyl alcohol until of constant rotation. The mother-liquors were concentrated and kept until no more sparingly soluble base separated. The methyl alcohol was removed, and the residue of crude α'-chlorodihydroquinine recrystallised several times as acid nitrate from dilute nitric acid, and finally as base from benzene. In case one or both of these bases were mixtures, their neutral tartrates were prepared and recrystallised, but no separation was effected. The two isomerides occur in the proportion of roughly 1 of α- to 3 of α'-chlorodihydroquinine.

α-*Chlorodihydroquinine* separates from methyl alcohol in anhydrous rhombs; sinters at 203°, m. p. 210°, froths at 215°; $[\alpha]_D^{20°}$ − 251·0° (*c* = 0·5) (Found: C, 66·9; H, 7·2; N, 8·0; Cl, 9·9; MeO, 9·0. $C_{20}H_{25}O_2N_2Cl$ requires C, 66·5; H, 7·0; N, 7·8; Cl, 9·8; MeO, 8·6%). The *acid nitrate* crystallises from water in anhydrous rhombohedral crystals; sinters at 209°, froths at 212°; $[\alpha]_D^{23°}$ − 196·6° (*c* = 0·5 in water); solubility 1 in *ca.* 91 of water at 19°; the solution has a blue fluorescence (Found: C, 49·5; H, 5·8; N, 11·4; Cl, 7·4; MeO, 6·5. $C_{20}H_{25}O_2N_2Cl,2HNO_3$ requires C, 49·3; H, 5·6; N, 11·5; Cl, 7·3; MeO, 6·4%). The *tartrate* crystallises as *heptahydrate* from 60% methyl alcohol in prisms (Found: loss at 105° in a vacuum, 12·6. Loss of $7H_2O$ requires 12·6%). The *anhydrous salt* sinters at 187°, froths at 198°; $[\alpha]_D^{22°}$ − 209·4° (*c* = 0·5) [Found: N, 6·4; Cl, 8·1; MeO, 7·1. $(C_{20}H_{25}O_2N_2Cl)_2,C_4H_6O_6$ requires N, 6·4; Cl, 8·1; MeO, 7·1%]. The *cuprichloride* crystallises from concentrated hydrochloric acid in greenish-yellow needles; sinters at 212°, froths at 215° (Found: C, 42·6; H, 4·9; N, 4·9; Cl, 31·3; Cu, 11·7. $C_{20}H_{25}O_2N_2Cl,2HCl,CuCl_2$ requires C, 42·2; H, 4·8; N, 4·9; Cl, 31·2; Cu, 11·1%).

α′-Chlorodihydroquinine is deposited from benzene in needles containing solvent of crystallisation, which is replaced by water on exposure to air. The solvent-free substance sinters at 184°, m. p. 194°, froths at 225°; $[\alpha]_D^{22°}$ — 168·1° (*c* = 0·5) (Found: C, 66·5; H, 7·1; N, 7·8; Cl, 9·9; MeO, 8·7. $C_{20}H_{25}O_2N_2Cl$ requires C, 66·5; H, 7·0; N, 7·8; Cl, 9·8; MeO, 8·6%). The *acid nitrate* separates from dilute nitric acid in anhydrous rhomboidal crystals; sinters at 219°, froths at 223°; $[\alpha]_D^{21°}$ — 132·8° (*c* = 0·5 in H_2O); solubility in water 1 in *ca.* 132 at 20°, giving a solution with blue fluorescence (Found: C, 49·5; H, 5·6; N, 11·5; Cl, 7·4; MeO, 6·5. $C_{20}H_{25}O_2N_2Cl,2HNO_3$ requires C, 49·3; H, 5·6; N, 11·5; Cl, 7·3; MeO, 6·4%). The *tartrate* crystallises from methyl alcohol in needles of the *dihydrate* (Found: loss at 105° in a vacuum, 4·1. Loss of $2H_2O$ requires 4·0%). The *anhydrous salt* sinters at 223°; froths at 228°; $[\alpha]_D^{22°}$ — 132·3° (*c* = 0·5) [Found: C, 60·6; H, 7·1; N, 6·5; Cl, 8·2; MeO, 7·1. $(C_{20}H_{25}O_2N_2Cl_2)_2,C_4H_6O_6$ requires C, 60·6; H, 6·5; N, 6·4; Cl, 8·1; MeO, 7·1%]. The *cuprichloride* crystallises from concentrated hydrochloric acid in yellow needles of the *trihydrate* (Found: loss at 105° in a vacuum, 5·4. Loss of $3H_2O$ requires 5·1%). The *anhydrous* substance sinters at 190°; froths at 198° [Found: C, 47·9; H, 5·6; N, 5·6; Cl, 28·1; Cu, 6·1. $(C_{20}H_{25}O_2N_2Cl,2HCl)_2,CuCl_2$ requires C, 47·9; H, 5·4; N, 5·6; Cl, 28·1; Cu, 6·3%].

Cinchonine.—Konek (*loc. cit.*) prepared Zorn's "chlorocinchonide" (*loc. cit.*) by several hours' heating of cinchonine hydrochloride in a sealed tube at 140—150° with hydrochloric acid saturated at — 17° with dry hydrogen chloride, and "hydrochlorocinchonine" by the method of Comstock and Koenigs, and stated that these substances are identical. This product has also been prepared by Hesse (*Annalen*, 1893, **276**, 109). From the description given, these substances are α-chlorodihydrocinchonine containing a little α′-isomeride. The methods of Comstock and Koenigs and of Hesse have now been found to yield the same two chloro-bases, the α-chlorodihydrocinchonine in greater amount. This base was separated from the reaction mixture as the sparingly soluble dihydrochloride, which was recrystallised until constant in optical rotation. The bases were liberated from the mother-liquors and dissolved in sufficient hot 5% methyl-alcoholic solution of tartaric acid to give a neutral solution. Crude α′-chlorodihydrocinchonine tartrate separated on standing, and was recrystallised until of constant rotation.

α-Chlorodihydrocinchonine forms anhydrous needles from much alcohol; sinters at 233°; froths at 236°; $[\alpha]_D^{20°}$ + 226·0° (*c*, 0·5) (Found: C, 69·2; H, 7·2; N, 8·6; Cl, 10·7. $C_{19}H_{23}ON_2Cl$ requires C, 69·0; H, 7·0; N, 8·5; Cl, 10·7%). The *dihydrochloride* separates from dilute hydrochloric acid in anhydrous prisms; sinters at 279°; froths at 283°; $[\alpha]_D^{22°}$ + 196·7° (*c*, 1 in water); solubility 1 in *ca.* 22 of water at 20°; much less soluble in dilute hydrochloric acid (Found: C, 56·6; H, 6·5; N, 7·1; Cl, 26·2. $C_{19}H_{23}ON_2Cl,2HCl$ requires C, 56·5; H, 6·2; N, 6·9; Cl, 26·4%). The *tartrate* crystallises from 50% methyl alcohol in matted needles of *dihydrate* (Found: loss at 105° in a vacuum, 4·0. Loss of $2H_2O$ requires 4·3%). The *anhydrous* salt sinters at 196° and froths at 204°; $[\alpha]_D^{21°}$ + 185·4° (*c* = 0·5) [Found: Cl, 8·7. $(C_{19}H_{23}ON_2Cl)_2,C_4H_6O_6$ requires Cl, 8·7%]. The *cuprichloride* separates from concentrated hydrochloric acid, containing excess of cupric chloride, in pale yellow prisms of *monohydrate* (Found: loss at 105° in a vacuum, 3·9. Loss of H_2O requires 3·2%). If it is dissolved in boiling hydrochloric acid, the dihydrochloride of the base crystallises on cooling. The *anhydrous* cuprichloride sinters at 228°, and froths at 234° (Found: C, 41·9; H, 4·8; N, 5·0; Cl, 32·9; Cu, 11·9. $C_{19}H_{23}ON_2Cl,2HCl,CuCl_2$ requires C, 42·4; H, 4·7; N, 5·2; Cl, 32·9; Cu, 11·8%).

α′-Chlorodihydrocinchonine forms minute anhydrous needles from much alcohol; sinters at 220°; froths at 223°; $[\alpha]_D^{22°}$ + 176·0° (*c* = 0·5) (Found: C, 69·1; H, 6·9; N, 8·4; Cl, 10·4. $C_{19}H_{23}ON_2Cl$ requires C, 69·0; H, 7·0; N, 8·5; Cl, 10·4%). The *dihydrochloride* crystallises from concentrated aqueous solution in anhydrous plates; sinters at 273°; froths at 276°; $[\alpha]_D^{22°}$ + 154·0° (*c* = 1 in water); solubility 1 in *ca.* 7·7 of water at 17·5° (Found: Cl, 26·9. $C_{19}H_{23}ON_2Cl,2HCl$ requires C, 26·4%). The *tartrate* separates from methyl alcohol as *dihydrate* in stellate groups of needles (Found: loss at 105° in a vacuum, 4·4. Loss of $2H_2O$ requires 4·3%). The *anhydrous salt* sinters at 209°; froths at 212°; $[\alpha]_D^{20°}$ + 142·0° (*c* = 0·5) [Found: C, 61·7; H, 6·5; N, 6·9; Cl, 8·3. $(C_{19}H_{23}ON_2Cl)_2,C_4H_6O_6$ requires C, 62·1; H, 6·5; N, 6·9; Cl, 8·7%]. The *cuprichloride* crystallises as *monohydrate* from concentrated hydrochloric acid containing excess of cupric chloride in yellow prisms (Found: loss at 105° in a vacuum, 3·5. Loss of H_2O requires 3·2%). The *anhydrous* substance sinters at 230°, froths at 235° (Found: C, 42·3; H, 5·0; N, 5·3; Cl, 32·3; Cu, 11·8. $C_{19}H_{23}ON_2Cl,2HCl,CuCl_2$ requires C, 42·4; H, 4·7; N, 5·2; Cl, 32·9; Cu, 11·8%).

Cinchonidine.—The chlorodihydrocinchonidines can be separated from the chlorine-free products of the action of hydrochloric acid on cinchonidine as acid sulphates or as tartrates,

but it was found impracticable to separate the two chloro-bases by crystallisation of these salts; this was, however, effected by recrystallisation of the dihydrobromides from hot alcohol, in which the α′-dihydrobromide is very sparingly soluble. From the mother-liquor, concentrated until no more dihydrobromide was deposited, the bases were liberated, and α-chlorodihydrocinchonidine separated by recrystallisation from alcohol. The former is produced in greater quantity.

α-*Chlorodihydrocinchonidine* separates from alcohol in small anhydrous crystals; sinters at 229°, froths at 231°; $[\alpha]_D^{23°}$ − 135·6° (*c* = 0·5) (Found : C, 69·5; H, 7·1; N, 8·4; Cl, 10·6. $C_{19}H_{23}ON_2Cl$ requires C, 69·0; H, 7·0; N, 8·5; Cl, 10·7%). The *cuprichloride* crystallises from concentrated hydrochloric acid in anhydrous orange prisms; sinters at 218°, froths at 220° (Found : Cu, 12·0. $C_{19}H_{23}ON_2Cl,2HCl,CuCl_2$ requires Cu, 11·8%).

α′-*Chlorodihydrocinchonidine* is deposited from much alcohol in small anhydrous crystals; sinters at 244°, froths at 246°; $[\alpha]_D^{23°}$ − 62·5° (*c* = 0·5) (Found : C, 69·4; H, 7·0; N, 8·2; Cl, 10·6. $C_{19}H_{23}ON_2Cl$ requires C, 69·0; H, 7·0; N, 8·5; Cl, 10·7%). The *hydrogen sulphate* crystallises from dilute acetone in thick tetragonal plates of *trihydrate* (Found : loss at 105° in a vacuum, 10·8. Loss of $3H_2O$ requires 11·2%). The *anhydrous* substance sinters at 162° and froths at 176°; $[\alpha]_D^{22°}$ − 59·5° (*c* = 1 in water) (Found : C, 53·2; H, 6·1; N, 6·5; Cl, 8·1; S, 7·4. $C_{19}H_{23}ON_2Cl,H_2SO_4$ requires C, 53·3; H, 5·9; N, 6·5; Cl, 8·3; S, 7·5%). The *tartrate* separates from alcohol in long prisms; sinters at 210°, froths at 212°; $[\alpha]_D^{22°}$ − 52·4° (*c* = 0·5) [Found : Cl, 8·2. $(C_{19}H_{23}ON_2Cl)_2,C_4H_6O_6$ requires Cl, 8·7%]. The *dihydrobromide* crystallises from alcohol in tetragonal plates; sinters at 256°, froths at 257°; $[\alpha]_D^{21°}$ − 50·4° (*c* = 1 in water) (Found : C, 46·5; H, 5·1; N, 5·7; Cl, 7·2; Br, 32·5. $C_{19}H_{23}ON_2Cl,2HBr$ requires C, 46·4; H, 5·1; N, 5·7; Cl, 7·2; Br, 32·4%). The *cuprichloride* is deposited as *heptahydrate* from concentrated hydrochloric acid in clusters of yellow needles. The *anhydrous* substance sinters at 175°, froths at 185° [Found : loss in air-dried substance substance at 105° in a vacuum, 11·5. $(C_{19}H_{23}ON_2Cl,2HCl)_2,CuCl_2,7H_2O$ requires $7H_2O$, 11·8. Found, in dry substance : Cu, 7·3. $(C_{19}H_{23}ON_2Cl,2HCl)_2,CuCl_2$ requires Cu, 6·8%].

Quinidine.—α-*Chlorodihydroquinidine* was isolated by crystallisation of the dihydrobromide of the reaction mixture from alcohol and the α′-base was removed from the bases contained in the mother-liquor as neutral tartrate. The former is obtained in greater amount.

α-Chlorodihydroquinidine crystallises from 70% alcohol in needles of the *dihydrate* (Found : loss at 105° in a vacuum, 9·2. Loss of $2H_2O$ requires 9·1%). The *anhydrous* base sinters at 198°; m. p. 206°; froths at 225°; $[\alpha]_D^{24°}$ + 276·3° (*c* = 0·5) (Found : C, 66·8; H, 7·0; N, 7·3; Cl, 9·8; MeO, 8·3. $C_{20}H_{25}O_2N_2Cl$ requires C, 66·5; H, 7·0; N, 7·8; Cl, 9·8; MeO, 8·6%). The *dihydrobromide* separates from alcohol in pale yellow, anhydrous needles; sinters at 250°, froths at 253°; $[\alpha]_D^{22°}$ + 200·0° (*c* = 1 in water) (Found : Cl, 6·7; Br, 30·3. $C_{20}H_{25}O_2N_2Cl,2HBr$ requires Cl, 6·7; Br, 30·6%). The *tartrate* separates as *dihydrate* from dilute alcohol in rhomboidal crystals (Found : loss at 105° in a vacuum, 4·2. Loss of $2H_2O$ requires 4·0%). The *anhydrous* salt sinters at 157°, froths at 162°; $[\alpha]_D^{25°}$ + 224·7° (*c* = 0·5) [Found : Cl, 7·9; MeO, 7·0. $(C_{20}H_{25}O_2N_2Cl)_2,C_4H_6O_6$ requires Cl, 8·1; MeO, 7·1%]. The *cuprichloride* crystallises from concentrated hydrochloric acid in deep yellow, anhydrous needles; sinters at 230°, froths at 233° (Found : Cu, 11·2. $C_{20}H_{25}O_2N_2Cl,2HCl,CuCl_2$ requires Cu, 11·1%).

α′-*Chlorodihydroquinidine* crystallises from dilute alcohol in needles of the *trihydrate* (Found : loss at 105° in a vacuum, 12·9. Loss of $3H_2O$ requires 13·0%). The *anhydrous* base sinters at 195°, m. p. 200°, froths at 229°; $[\alpha]_D^{22°}$ +240·7° (*c* = 0·5) (Found : Cl, 9·7; MeO, 8·4. $C_{20}H_{25}O_2N_2Cl$ requires Cl, 9·8; MeO, 8·6%). The *tartrate* crystallises from 30% alcohol in plates of *undecahydrate* (Found : loss at 105° in a vacuum, 18·6. Loss of $11H_2O$ requires 18·5%). The *anhydrous* substance sinters at 152°, froths at 196°; $[\alpha]_D^{21°}$ + 203·0° (*c* = 0·5) [Found : Cl, 8·2. $(C_{20}H_{25}O_2N_2Cl)_2,C_4H_6O_6$ requires Cl, 8·1%]. The *cuprichloride* is deposited from concentrated hydrochloric acid in anhydrous orange prisms; sinters at 230°, froths at 236° (Found : Cu, 11·5. $C_{20}H_{25}O_2N_2Cl,2HCl,CuCl_2$ requires Cu, 11·1%).

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