422. *Modified Cinchona Alkaloids. Part I. Apoquinine and Apoquinidine.*

By Thomas A. Henry and William Solomon.

When quinine is treated with any of the ordinary demethylating agents it yields, not the corresponding phenolic alkaloid cupreine, but an ill-defined amorphous substance, which was first prepared nearly 60 years ago and named apoquinine (Hesse, *Annalen* 1880, **205**, 322) and about which an extensive but inconclusive literature has accumulated. In the hope of clearing up the chemistry of this interesting, modified, cinchona alkaloid, the authors have investigated in detail the products resulting from the action on quinine of two demethylating agents, aluminium chloride and 60% sulphuric acid. Aluminium chloride was first used as a demethylating agent by Hartmann and Gattermann (*Ber.*, 1892, **25**, 3521) and the process has already been applied to quinine by Oberlin (*Arch. Pharm.*, 1927, **265**, 269), who found that it yielded apoquinine, $C_{19}H_{22}O_2N_2$, free from chlorine. The present authors, on the contrary, find that the crude "apoquinine," prepared by this process and isolated by Oberlin's method, invariably contains non-ionisable chlorine and is, in fact, mainly a mixture of apoquinine, $C_{19}H_{22}O_2N_2$, and *chlorodihydroapoquinine*, $C_{19}H_{23}O_2N_2Cl$ (suggested as a more accurate name than hydrochloroapoquinine, generally used for this substance). This is a typical instance of the confusion obtaining in the literature regarding the composition of apoquinine, which seems to be due to the facts that the alkaloid has not until now been obtainable with certainty in a pure and crystalline condition, and that the mixtures which have hitherto been regarded as apoquinine can be made to yield certain salts and derivatives of approximately constant composition. Thus, the authors find that Oberlin's "apoquinine" furnishes a "dihydrochloride,"

$$C_{19}H_{22}O_2N_2,C_{19}H_{23}O_2N_2Cl,4HCl,$$

m. p. 225°, $[\alpha]_D^{20°}$ — 204·1°, and a "zincichloride," $C_{19}H_{22}O_2N_2,C_{19}H_{23}O_2N_2Cl,4HCl,2ZnCl_2$, m. p. 242°, which can both be crystallised to constancy in composition (as represented by the foregoing formulæ) and physical characters, from concentrated hydrochloric acid. On the other hand this equimolecular proportion of the two components is disturbed when this crude "apoquinine," or certain salts made from it, is crystallised from other solvents. Thus, repeated crystallisation of the acetone-insoluble portion of crude "apoquinine" from hot methyl alcohol by addition of acetone leads to the accumulation of a fraction rich in the chloro-compound, and this is also true of the acid sulphate, whilst crystallisation of the acid dianisoyl-*d*-tartrate provides fractions in which the chlorine-free apoquinine salt accumulates. Although these methods furnish poor yields, it has been possible by them to isolate small specimens of apoquinine and chlorodihydroapoquinine sufficiently pure for comparison with these substances made in other ways, and so to establish their identity beyond any reasonable doubt. It will be noticed, however, that, whilst there is good general agreement in properties, and admixture of the two preparations in each case causes no depression in melting point, there are differences in specific rotation : below the correct value in the case of the apoquinine and above it in the case of the chlorodihydroapoquinine, isolated from the product prepared by Oberlin's method. In considering the validity of this comparison, it must be borne in mind that these demethylation processes are

drastic, and present considerable possibilities of racemisation, and that the addition of the elements of hydrogen chloride to the unsaturated side chain of apoquinine may give rise to isomerides. For these reasons, complete identity, *e.g.*, in specific rotation, in products prepared in different ways is hardly to be expected. Now that pure apoquinine is readily obtainable, it will be possible to investigate these points of detail and for the present it is merely intended to settle the question of the composition of " apoquinine " prepared by the aluminium chloride process.

Demethylation by boiling with 60% sulphuric acid has been applied to quinine by Jarzyński, Ludwiczakówna, and Suszko (*Rec. trav. chim.*, 1933, **52**, 839) and to quinidine by Ludwiczakówna, Suszko, and Zwierzchowski (*ibid.*, p. 847). In the case of quinine the Polish authors obtained apoquinine, which they were unable to crystallise, but from which they succeeded in preparing a number of crystalline derivatives, including a neutral hydrochloride, m. p. 236—237°, $[\alpha]_D^{20°}$ — 145° (c = 1 in water). The only analytical figure given is for chlorine, 10·08 (calc., 10·23%). Although the present authors believe Suszko and his co-workers to be mistaken in the view that this amorphous " apoquinine " is a pure substance, it should be recorded that this product is a great improvement on most of the " apoquinines " previously described, and is a material from which, as shown below, it is possible to prepare pure crystalline apoquinine in any desired quantity.

On repeating this work the authors always obtained a crystalline hydrochloride, m. p. 265°, $[\alpha]_D^{20°}$ — 154·5° (c = 0·9 in water), and this on complete analysis invariably gave results nearly 1% low in carbon. They, therefore, had recourse to other salts and it was found that the best salt for purification is the acid sulphate, which crystallises well, gives satisfactory analytical results, and from which, for the first time, apoquinine base has been obtained easily and in quantity in well-defined crystals. From it a series of well-crystallised salts, including the pure neutral hydrochloride, m. p. 272·5°, $[\alpha]_D^{20°}$ — 163·8°, has been prepared.

The base regenerated from the crude crystalline hydrochloride first obtained, yields two acid sulphates, the one referred to above having $[\alpha]_D^{20°}$ — 223·0° and a second having $[\alpha]_D^{20°}$ — 235°. This second salt is still under investigation, but sufficient data have been obtained to indicate that it may be the acid sulphate of an isomeride of apoquinine.

In spite of the hitherto ill-defined character of apoquinine a constitutional formula has been proposed for the alkaloid by Suszko *et al.* (*loc. cit.*; *Bull. Inter. Acad. Polonaise*, 1925, 129) which may be written in linear form as follows :

$$\underset{\text{Quinine}}{MeO\cdot C_9H_5N\cdot CH(OH)\cdot C_7H_{11}N\cdot CH{:}CH_2} \longrightarrow \underset{\text{Apoquinine}}{HO\cdot C_9H_5N\cdot CH(OH)\cdot C_7H_{10}N{:}CH\cdot CH_3}$$

As apoquinine has now been obtained in a satisfactory condition for investigation, and as it seems possible that at least two species are already obtainable, the authors propose to reserve any comments regarding this and other possible formulæ until they have accumulated a broader basis of experimental data.

Though apoquinidine has received less attention than apoquinine, there has hitherto been no reason to suppose that quinidine differs from quinine by undergoing simple demethylation, without further intramolecular change. The observation of Suszko and his collaborators (*loc. cit.*) that quinidine, on demethylation with boiling 60% sulphuric acid, yields the hitherto unknown cupreidine, a dextro-isomeride of cupreine, was therefore surprising. The chief item of evidence upon which this view is based is that cupreidine on simple methylation regenerates quinidine, just as its analogue, cupreine, on similar treatment yields quinine. For convenience of comparison the m. p.'s and specific rotations of cupreidine, dihydrocupreidine, quinidine, dihydroquinidine, and the methyl ether of cupreidine have been assembled in the following table.

	Cupreidine.		Dihydrocupreidine.		Quinidine.	Dihydro-quinidine.	Cupreidine methyl ether.
	Base.	B,HCl.	Base.	B,HCl.	Base.	Base.	Base.
M. p.	186—190°	215—216°	185—195°	230—232°	173·5°	169·5°	169·0°
Sp. rot.	+219·4° (c = 1·116; EtOH)	+190° (c = 1; H_2O)	+227·2° (c = 1·116; EtOH)	+194·0° (c = 0·872; H_2O)	+266·1° (c = 1; EtOH)	+230·8° (c = 1; EtOH)	+234·1° (c = 0·994 EtOH)

The comparable data available are scanty, but so far as they go they indicate a close resemblance between the constants of the supposed cupreidine with those of dihydrocupreidine, whilst the characters of the methyl ether of the supposed cupreidine agree much better with those of dihydroquinidine, the methyl ether of dihydrocupreidine, than with those of quinidine.

It is not well known that the well-crystallised and apparently pure quinidine of commerce usually contains about 20% and may contain as much as 30% of dihydroquinidine (Buttle, Henry, and Trevan, *Biochem. J.*, 1934, **28**, 434). On demethylation, commercial quinidine yields a product containing much dihydrocupreidine, and this, on re-methylation, will yield dihydroquinidine, and it seems possible that the substance described by Suszko and his collaborators as cupreidine may be in reality largely dihydrocupreidine, and its methyl ether, not quinidine, but dihydroquinidine. The present authors have repeated the work of the Polish investigators, using as a starting material quinidine purified by a method already described (Buttle, Henry, and Trevan, *loc. cit.*) and of 99·5% purity as measured by its capacity for hydrogen absorption. This, on demethylation by boiling 60% sulphuric acid, yields two products, neither of which has been described previously. The first, $C_{19}H_{22}O_2N_2$, it is proposed to call iso*apoquinidine*, because it is lævorotatory, and probably represents a greater change in the quinidine molecule than the second substance, which is dextrorotatory; further, all the "*apoquinidine*" hitherto obtained has been amorphous and markedly dextrorotatory and it seems desirable to reserve the name apoquinidine for the second and dextrorotatory product of this reaction.

*iso*Apoquinidine differs markedly from "cupreidine," having m. p. 245° and $[\alpha]_D^{20°}$ −12·6° ($c = 1$ in alcohol): its neutral salts are also lævorotatory, but the acid salts are dextrorotatory.

The second product, apoquinidine, is crystalline, yields well-crystallised salts and is dextrorotatory, but it is not yet possible to say whether it has been freed entirely from *iso*apoquinidine.

As by-products of the action of 60% sulphuric acid on quinine and quinidine, two non-phenolic bases have been obtained in small quantity; these are still under investigation and appear to be isomerides of the two starting materials.

In the preparation of crude apoquinine, by precipitation with carbon dioxide from solution in aqueous sodium hydroxide, some alkaloid remains in solution, and can be recovered by long-continued extraction of the alkaline liquor with hot ether. This product is being accumulated for examination. No analogous product is found at the corresponding stage in the preparation of crude apoquinidine.

Experimental.

In the following account the m. p.'s are corrected and, unless otherwise stated, are also decomposition points; they are of little diagnostic value, as they vary with the rate of heating. The specific rotations are recorded for the dry substance and, unless stated otherwise, the solutions are $M/40$ and the solvent is water for the salts and $N/10$-sulphuric acid for the bases. Except in one case (p. 1926) the combustion results are recorded for the substance dried in a vacuum at an appropriate temperature, usually 120°. With the exception of *iso*apoquinidine, none of the phenolic bases dry to constant weight, but ultimately reach a stage at which there is a constant minute loss. In these cases the substance has been taken as anhydrous at the point at which the drying curve begins to flatten.

Many cinchona alkaloidal salts are either efflorescent or hygroscopic and consequently show great variation in loss of weight on drying. For that reason, the losses found are not usually represented by a definite number of molecules of water or other solvent, unless special precautions are taken. The authors have, therefore, merely recorded the percentage loss found in the particular preparation used for analysis. It was quite frequently different in other preparations of the same substance.

Action of Aluminium Chloride on Quinine.—Crude "apoquinine," prepared and isolated by Oberlin's method (*loc. cit.*), is a pale yellow or cream-coloured powder (yield, 70%), appreciably soluble in water, sparingly soluble in benzene or ether, more so in acetone, and readily in chloroform or alcohol; m. p. 175°, $[\alpha]_D^{18°}$ − 177° ($c = 0·514$ in methyl alcohol) (Found: Cl,

5·3; MeO, 0·5. Calc. for the equimolecular mixture $C_{19}H_{22}O_2N_2 + C_{19}H_{23}O_2N_2Cl$: Cl, 5·4%). Oberlin (*loc. cit.*) found no chlorine and Jarzyński, Ludwiczakówna, and Suszko (*loc. cit.*) confirm this by stating that " apoquinine " prepared by this method is the same as that made by the sulphuric acid process (p. 1927). As a similar discrepancy is recorded for Hesse's " apoquinine," obtained by the action of hydrochloric acid (*d* 1·125) at 140° on quinine (Hesse, *loc. cit.*; *Ber.*, 1895, **28**, 1301; Lippmann and Fleissner, *Monatsh.*, 1895, **16**, **34**; Lippmann, *Ber.*, 1895, **28**, 1971; Fränkel and Buhlea, *Ber.*, 1925, **58**, 559), a specimen of this material was prepared; it closely resembled Oberlin's product but contained less chlorine (2·6%).

This equimolecular proportion of apoquinine and chlorodihydroapoquinine is preserved through several salts. When the crude product (1 g.) is dissolved in hot concentrated hydrochloric acid (2 c.c.), the solution, on cooling, deposits slender colourless needles. This substance, on recrystallisation in like manner till colourless, has m. p. 225° (dry), $[\alpha]_D^{20°}$ — 204·1° (Found : C, 56·3; H, 6·3; N, 6·5; Cl, 22·5. $C_{19}H_{22}O_2N_2,2HCl + C_{19}H_{23}O_2N_2Cl,2HCl$ requires C, 56·8; H, 6·15; N, 7·0; Cl, 22·1%). Similarly, when crude " apoquinine " (1 g.) in hot hydrochloric acid (2 c.c.) is mixed with a solution of zinc chloride (1 g.) in the same solvent (2 c.c.), a mixture of zincichlorides crystallises on standing, and this on recrystallisation from hot hydrochloric acid forms pale yellow needles, m. p. 242° [Found : C, 42·2; H, 4·8; N, 5·2; Cl (total), 29·5; Cl (non-ionisable), 3·15; Zn, 12·45. $C_{19}H_{22}O_2N_2,2HCl,ZnCl_2 + C_{19}H_{23}O_2N_2Cl,2HCl,ZnCl_2$ requires C, 42·4; H, 4·5; N, 5·2; Cl (total), 29·7; Cl (non-ionisable), 3·3; Zn, 12·2%]. This mixture, on repeated crystallisation from hot hydrochloric acid, becomes sticky and the m. p. falls. It cannot be crystallised from water or alcohol.

Out of many methods tried, three ways have been found of isolating the two chief components of crude " apoquinine " and though none of these is of practical value, the yields being so poor, two of them are now described briefly, as the results confirm the view expressed above as to the composition of this mixture. When crude " apoquinine " is boiled with acetone (1 g. in 10 c.c.) it dissolves and almost immediately deposits a white powder (40%), which when air-dry has m. p. 175°. When dried at 105° in a vacuum, it loses 7·6% by weight after 11 hours, and at this stage contains Cl 7·0% and has $[\alpha]_D^{20°}$ — 188·4° (*c* = 0·484 in methyl alcohol). It continues to lose weight on further drying, but gradually turns black. On solution in warm methyl alcohol (1 g. in 2 c.c.) and addition of acetone (2 c.c.) the product deposits clusters of prismatic crystals and, by repeated crystallisation in this manner, a 10% yield of a substance, m. p. 182—183°, $[\alpha]_D^{20°}$ — 200·0° (*c* = 0·625, air-dry substance in methyl alcohol), is obtained. This behaves like the anterior product on drying, and was analysed in an air-dry condition, in which it appears to contain one molecule of acetone (Found : C, 65·7; H, 7·2; N, 7·2; Cl, 9·0. $C_{19}H_{23}O_2N_2Cl,C_3H_6O$ requires C, 65·2; H, 7·2; N, 6·9; Cl, 8·8%). The substance is, therefore, chlorodihydroapoquinine. A series of salts was prepared, of which the *acid sulphate* may be described : aggregates of transparent yellow plates, sinters at 192°, darkens at 195° and liquefies at 205°, $[\alpha]_D^{15°}$ — 206·7° (*c* = 0·556 in water), becomes anhydrous over sulphuric acid in a vacuous desiccator; loss 8·7—9·4% (Found : C, 51·2; H, 6·0; N, 6·4; Cl, 7·7; S, 7·2. $C_{19}H_{23}O_2N_2Cl,H_2SO_4$ requires C, 51·3; H, 5·7; N, 6·3; Cl, 8·0; S, 7·2%).

For comparison a specimen of chlorodihydroapoquinine was made by Zorn's method (*J. pr. Chem.*, 1871, **4**, 44; 1873, **8**, 279) and converted into the same series of salts. The only difference noted was that the base now described and its salts had higher specific rotations than the corresponding Zorn base and its salts. The acid sulphate, for example, showed the same characters as those just described, but had $[\alpha]_D^{15°}$ — 198·6° (*c* = 0·556 in water), a discrepancy for which an explanation has been suggested already (p. 1923).

When hot solutions in alcohol of crude " apoquinine " and of excess of dianisoyl-*d*-tartaric acid (Rabe and Meyer, *Annalen*, 1932, **492**, 265) are mixed, a white, crystalline powder separates as the mixture cools. This substance is insoluble in all ordinary solvents and can only be recrystallised by solution in boiling glacial acetic acid (1 g. in 10 c.c.), concentration of the solution in a vacuum to 2·5 c.c., and dilution with dry alcohol (12 c.c.). Each crystallisation reduces the quantity available by 50—75%, but the 5% of chlorine contained in the crude product is reduced in 2 or 3 crystallisations to 0·5%. The best specimen obtained consisted of minute colourless granules, m. p. 242° (Found : C, 63·9; H, 5·8; N, 4·3; Cl, 0·2; MeO, 9·1. $C_{19}H_{22}O_2N_2,C_{20}H_{18}O_{10}$ requires C, 64·3; H, 5·5; N, 3·85; Cl, nil; MeO, 8·5%). This only differs from pure apoquinine acid dianisoyltartrate (p. 1928) in containing 0·2% of chlorine, but the base recovered from it has m. p. 180° (no depression on admixture with pure apoquinine), and $[\alpha]_D^{15°}$ — 196·5° (*c* = 0·579 in methyl alcohol), whereas pure apoquinine froths at 184° and has $[\alpha]_D^{15°}$ — 212° (*c* = 0·6585 in methyl alcohol), the reason for this discrepancy being no doubt that already stated (p. 1923).

Action of Sulphuric Acid (60%) *on Quinine.*—Commercial quinine contains cinchonidine and dihydroquinine, from which it is easily purified by recrystallisation of the acid sulphate (Buttle, Henry, and Trevan, *loc. cit.*). For that reason quinine acid sulphate was employed as a starting material. The process used was that described by Suszko *et al.* (*loc. cit.*) with the exception that the alkaline solution of the crude phenolic base was shaken out with ether to remove any remaining undemethylated base (1·3—8%). The latter does not appear to be quinine and is still under investigation. The yield of crude apoquinine is difficult to state, since the moisture content after drying in a vacuous desiccator varied considerably, but is probably about 80% of the theoretical. The carbonated liquors left after the precipitation of apoquinine, still contain alkaloid, which can be recovered by long-continued treatment with ether (about 100 hours) in a continuous-extraction apparatus. The product, which does not appear to be apoquinine, is being accumulated for examination (yield, 6%).

The crude apoquinine is dissolved in hot acetone (1 g. in 25 c.c.), the solution filtered to remove inorganic material, concentrated to low bulk, diluted with sufficient alcohol to form a clear solution, and neutralised with *N*-hydrochloric acid. Water is then added, and the bulk of the organic solvents removed by distillation in a vacuum. The neutral hydrochloride crystallises as the solution cools, and a second crop is obtained by evaporating the mother-liquor to dryness in a vacuum and boiling the residue with dry alcohol. The whole of the crude hydrochloride is boiled with dry alcohol (1 g. in 5 c.c.) to remove coloured impurities and finally recrystallised by solution in 50% alcohol (1 g. in 10 c.c.) and removal of about half the solvent by distillation in a vacuum. It then has m. p. 265°, $[\alpha]_D^{20°}$ — 154·5° (c = 0·9 in water) (Found : C, 64·8; H, 6·7; N, 7·9; Cl, 9·9; OMe, nil. $C_{19}H_{22}O_2N_2$,HCl requires C, 65·75; H, 6·7; N, 8·1; Cl, 10·2%). No matter what method of purification was adopted this deficiency of 1% in carbon could not be overcome. Suszko *et al.* (*loc. cit.*) give for their hydrochloride prepared from crude apoquinine and repeatedly recrystallised, m. p. 236—237°, $[\alpha]_D$ — 145° (c = 1 in water) and Cl, 10·08% and provide no further analytical data. Though the hydrochloride so obtained is impure, its preparation is necessary as a preliminary means of purification. The base is then recovered from it and converted into the acid sulphate by solution in methyl alcohol and addition of the calculated quantity of *N*-sulphuric acid. The residue left on evaporation of the solution in a vacuum is redissolved several times in methyl alcohol and taken to dryness each time, to remove as much water as possible, and is finally dissolved in hot methyl alcohol (1 g. in 20 c.c.), from which it crystallises on cooling. Further crops are obtained with difficulty on concentration of the mother-liquor. The whole of the crops are recrystallised from methyl alcohol and then yield pure apoquinine acid sulphate. Six fractions of such material, obtained by the recrystallisation of 10 g. from water, had $[\alpha]_D^{20°}$ ranging only from 221·25° to 223·25°. Apoquinine base is prepared by pouring a saturated aqueous solution (2% approx.) of this salt into excess of a saturated aqueous solution of sodium carbonate in presence of ether (100 c.c. per g. of base) and shaking vigorously until all the alkaloid has been extracted, more ether being used if necessary. The ethereal solution is dried for a short time only (to avoid crystallisation of the base at this stage) over anhydrous sodium sulphate, and the solvent removed by slow distillation. As concentration proceeds, apoquinine crystallises in a pure condition.

The combined methyl-alcoholic mother-liquors, which have ceased to deposit apoquinine acid sulphate, are taken to dryness in a vacuum, and the residue dissolved in hot water. This solution deposits an acid sulphate, closely resembling apoquinine acid sulphate, but having a higher specific rotation, $[\alpha]_D^{20°}$ — 235°, which, so far, it has not been found possible to alter by fractional crystallisation. The base recovered from this salt crystallises well and is also mainly distinguished from apoquinine by its higher specific rotation. It may be one of the numerous possible stereoisomerides of apoquinine and is still under examination.

Apoquinine crystallises in small, colourless, transparent, triangular prisms, is readily soluble in ethyl or methyl alcohol and sparingly soluble in ether or acetone. It froths at 184° and has $[\alpha]_D^{20°}$ — 281° (c = 0·784 in N/10-sulphuric acid), or — 214·8° (c = 0·775 in alcohol). Crystals of apoquinine have been obtained, apparently with difficulty, twice previously. Lippmann and Fleissner (*loc. cit.*) record m. p. 210° with shrinkage at 160°, $[\alpha]_D$ — 217° (c = 0·7877 in alcohol), whilst Fränkel and Buhlea (*loc. cit.*) give m. p. 160° and $[\alpha]_D$ — 196·37° (c = 0·7995 in alcohol). No more recent author appears to have succeeded in crystallising apoquinine. Miura (*Japan J. Med. Sci.*, 1930, **5**, 1) states that amorphous apoquinine, prepared by a new method, not yet described, sinters at 170°, melts at 210°, and has $[\alpha]_D^{13°}$ — 216·1°, and Suszko *et al.* (*loc. cit.*), for their amorphous base, give m. p. 190—195° and $[\alpha]_D^{20°}$ — 188·7—191·7° (c = 1 in water). The crystalline base described above does not dissolve appreciably in water. These discrepancies

in m. p. are no doubt mainly due to differences in purity of materials, but may also in part be due to the fact that pure apoquinine froths at 184° and, on continued heating the froth becomes transparent at about 205°, and observers may record either or both of these points. Apoquinine crystals lose nothing when dried at 120° in a vacuum, but the finely powdered base loses 7% by weight after 8 hours at 110—135° (Found: C, 73·4; H, 7·6; N, 8·9. Calc. for $C_{19}H_{22}O_2N_2$: C, 73·5; H, 7·2; N, 9·0%).

The hydrochloride forms clusters of colourless needles, m. p. 272·5°, $[\alpha]_D^{15°}$ — 163·8°. Aqueous solutions are pale yellow: the colour is intensified by heat and is discharged by addition of acid. Solutions in alcohol are colourless. The salt is sparingly soluble in alcohol or water, but readily soluble in mixtures of the two solvents. It is anhydrous (Found: C, 65·8; H, 6·7; N, 8·2; Cl, 10·2. Calc. for $C_{19}H_{22}O_2N_2$,HCl: C, 65·75; H, 6·7; N, 8·1; Cl, 10·2%). The *dihydrochloride* crystallises from dry alcohol in colourless spherical nodules, m. p. 261°, $[\alpha]_D^{20°}$ — 224·4°. It loses 8·7% by weight in a vacuum at 110°, is hygroscopic, and appears to be readily dissociated, all the samples examined being slightly deficient in chlorine (Found: Cl, 17·7. $C_{19}H_{22}O_2N_2$,2HCl requires Cl, 18·5%). The *hydrobromide* forms colourless needles, m. p. 284°, from dilute alcohol (Found: Br, 20·7. $C_{19}H_{22}O_2N_2$,2HBr requires Br, 20·4%). The *dihydrobromide* crystallises from dry alcohol in colourless or faintly yellowish-grey spangles, m. p. 255°, $[\alpha]_D^{15°}$ — 180·9°, and, like the dihydrochloride, seems to dissociate, being always slightly deficient in bromine (Found: C, 48·05; H, 5·5; N, 5·8; Br, 32·1 to 33·2. $C_{19}H_{22}O_2N_2$,2HBr requires C, 48·3; H, 5·1; N, 5·9; Br, 33·9%).

The *acid sulphate* crystallises in two forms: (*a*) from methyl alcohol in thin, soft, lemon-yellow platelets, and (*b*) stout, hard, almost colourless, thin, hexagonal plates from water. The two forms lose 10·7 and 8·0% by weight respectively on drying and re-absorb these amounts on exposure to air. The salt is sparingly soluble in water (2% approx.) or methyl alcohol. The (*a*) form sinters at 90° when rapidly heated, and at 170—190° when heated slowly, then darkens and finally froths at 200°. The (*b*) form melts sharply at 203° to 208° depending on the rate of heating, $[\alpha]_D^{20°}$ — 223° (Found: C, 55·7; H, 6·0; N, 6·9; S, 7·7. $C_{19}H_{22}O_2N_2,H_2SO_4$ requires C, 55·8; H, 5·9; N, 6·9; S, 7·85%). The sesquioxalate crystallises from alcohol in pale yellow needles, is sparingly soluble in water or alcohol, has m. p. 224·5—226°, $[\alpha]_D^{20°}$ — 193·6° (c = 0·212 in water) [Found: C, 59·55; H, 5·8; N, 6·3. Calc. for $(C_{19}H_{22}O_2N_2)_2,3H_2C_2O_4$: C, 59·3; H, 5·7; N, 6·3%]. Suszko (*Bull. Inter. Acad. Polonaise*, 1925, 143) gives m. p. 228°, $[\alpha]_D$ — 168—170° (c = 0·84 in water) to a sesquioxalate of "apoquinine" prepared from either quinine or β-*iso*quinine by Hesse's method (*loc. cit.*).

The *acid dianisoyl*-d-*tartrate* prepared for comparison with the chlorine-free component of Oberlin's "apoquinine" (p. 1926) is a colourless crystalline powder, has m. p. 235·5°, and is anhydrous (Found: C, 64·3; H, 5·7; N, 4·0; MeO, 8·8. $C_{19}H_{22}O_2N_2,C_{20}H_{18}O_{10}$ requires C, 64·3; H, 5·5; N, 3·85; MeO, 8·5%).

Apoquinine methyl ether was obtained in poor yield by the action of diazomethane on the base, and after treatment with sodium hydroxide solution to remove unchanged phenolic base, was converted into *hydrochloride*, which was recrystallised from dry alcohol, by addition of acetone and a little ether. The salt separated in hemispherical aggregates of colourless needles, m. p. 249—251°, $[\alpha]_D^{15°}$ — 196°, was readily soluble in water or alcohol but sparingly in acetone, and was anhydrous (Found: C, 66·5; H, 7·0; N, 7·6; Cl, 9·8. $C_{20}H_{24}O_2N_2$,HCl requires C, 66·5; H, 7·0; N, 7·8; Cl, 9·8%). The base regenerated from the hydrochloride crystallised from benzene in anhydrous, colourless, aggregates of needles, m. p. 183—185° after sintering at 180° (*no decomp.*), $[\alpha]_D^{15°}$ — 201·2° (c = 0·811 in alcohol). Miura (*loc. cit.*) gives m. p. 175—176°, $[\alpha]_D^{13°}$ — 201·5°, and Suszko *et al.* (*loc. cit.*), m. p. 186—187°, $[\alpha]_D$ — 192° (c = 1 in alcohol).

Apoquinine ethyl ether, prepared by the use of ethyl sulphate, gave a *hydrochloride*, which crystallised from hot acetone (1 g. in 10 c.c.) in anhydrous, short, colourless needles, m. p. 247—250°, $[\alpha]_D^{15°}$ — 191·7° (Found: C, 67·6; H, 7·45; N, 7·45; Cl, 9·45. $C_{21}H_{26}O_2N_2$,HCl requires C, 67·2; H, 7·3; N, 7·5; Cl, 9·5%). The base regenerated from this and crystallised from benzene had m. p. 195—197°, after sintering at 189° (*no decomp.*) and $[\alpha]_D^{15°}$ — 199·7° (c = 0·846 in alcohol). Previous figures for the ethyl ether are: m. p. 195—196°, $[\alpha]_D^{13°}$ — 174·7° (Miura, *loc. cit.*); m. p. 182° (Lippmann and Fleissner, *loc. cit.*); m. p. 183° (Giemsa and Bonath, *Ber.*, 1925, **58**, 95).

Action of Sulphuric Acid (60%) *on Quinidine.*—The quinidine used was purified through the cuprichloride and dihydrochloride as already described (Buttle, Henry, and Trevan, *loc. cit.*) and was 99·5% pure, as estimated by absorption of hydrogen in presence of colloidal palladium. It was converted into crude apoquinidine by the method described under apoquinine (p. 1927), the recovery of undemethylated base being 15·0% and the yield of crude apoquinidine 77·0%.

The amount of alkaloid left in the final carbonated liquors was negligible. The crude apoquinidine, after treatment with dry acetone to remove inorganic matter, was dissolved in alcohol, neutralised with hydrochloric acid, the solution taken to dryness at 100° in a vacuum, and the residue crystallised from boiling alcohol. Two recrystallisations gave a 30% yield of pure *iso*apoquinidine hydrochloride.

The mother-liquors from this salt, on concentration, deposit crops of a mixture of *iso*-apoquinidine hydrochloride with the hydrochloride of a dextrorotatory phenolic base, which has proved difficult to isolate in a pure state and is still under investigation. For the reasons already given (p. 1925), the name *apoquinidine* is reserved for this substance.

iso*Apoquinidine*, prepared from the pure hydrochloride by solution in excess of aqueous sodium hydroxide, precipitation of the base with carbon dioxide, and solution in dry alcohol to remove inorganic impurities, crystallises from alcohol in colourless hexagonal prisms, m. p. 245° (*no decomp.*), has $[\alpha]_D^{15°}$ + 25·6° (*c* = 0·78 in *N*/10-sulphuric acid) or −12·6° (*c* = 1 in alcohol), and loses 16·8% at 120° in a vacuum (Found : C, 73·3; H, 7·1; N, 9·0. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·0%).

The *hydrochloride* crystallises from alcohol in rosettes of colourless needles, m. p. 255°, $[\alpha]_D^{15°}$ − 40·2°, and is sparingly soluble in alcohol (1 in 75 c.c. cold, or 1 in 10 c.c. boiling) or water : the aqueous solution is lemon-yellow in colour. The salt shows no appreciable absorption of hydrogen in presence of palladium or platinic oxide as catalysts (Found : C, 65·8; H, 6·7; N, 7·9; Cl, 10·9. $C_{19}H_{22}O_2N_2$,HCl requires C, 65·75; H, 6·7; N, 8·1; Cl, 10·2%). The hydrobromide forms colourless needles from alcohol, m. p. 252°, $[\alpha]_D^{15°}$ − 35·8°.

The *dihydrobromide* crystallises from boiling alcohol (1 g. in 85 c.c.) in yellowish rectangular prisms, which are anhydrous, m. p. 280°, $[\alpha]_D^{15°}$ + 18·6° (Found : C, 48·6; H, 5·2; N, 5·9; Br, 33·8. $C_{19}H_{22}O_2N_2$,2HBr requires C, 48·3; H, 5·1; N, 5·9; Br, 33·9%). The *acid sulphate* is very soluble in water, but separates from boiling dry alcohol in pale yellow crystals, which intensify in colour on drying at 120° in a vacuum with a loss of 7·7%. The dry salt sinters at 220° and decomposes at 235—240°, $[\alpha]_D^{15°}$ + 17·6° (Found : C, 56·4; H, 6·4; N, 6·6; S, 7·5. $C_{19}H_{22}O_2N_2$,H_2SO_4 requires C, 55·8; H, 5·9; N, 6·9; S, 7·85%).

The dihydrocupreidine used for the constants given in the comparative table (p. 1924) was made by demethylating specially prepared dihydroquinidine by the sulphuric acid process and was isolated in the same fashion as the apo-bases described above (yield, 62%). It was converted into the hydrochloride, the latter recrystallised till pure, and the base recovered and recrystallised from acetone. The two products had the following constants.

Dihydrocupreidine base : undried substance, m. p. 170°; dried at 90° in a vacuum (loss 3%), m. p. 175°; dried at 120° in a vacuum (loss 10·5%), m. p. 185—195°. The base does not dry to constant weight; at 120° it turns yellow, $[\alpha]_D^{20°}$ + 227·2° (*c* = 1·116 in alcohol).

Dihydrocupreidine hydrochloride : the salt is anhydrous, m. p. 230—232°, $[\alpha]_D^{20°}$ + 193·9°.

Jacobs and Heidelberger (*J. Amer. Chem. Soc.*, 1919, **41**, 817) state that the base softens at 170° and is completely melted at 195°, $[\alpha]_D$ + 253·4° (*c* = 1·422 in alcohol), and record for the hydrochloride m. p. 231—233°, $[\alpha]_D^{24°}$ + 194·2° (*c* = 0·618 in water).

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WELLCOME CHEMICAL RESEARCH LABORATORIES,
LONDON, N.W. 1.

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