220. *Modified Cinchona Alkaloids. Part II. The Action of Sulphuric Acid on Quinine and Quinidine.*

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Demethylation by 60% sulphuric acid, a process first used by Coulthard, Levene, and Pyman (*Biochem. J.*, 1933, **27**, 727), was applied by Suszko and collaborators (*Rec. trav. chim.*, 1933, **52**, 839, 847) to quinine and quinidine and a summary of their results was given in Part I (J., 1934, 1923), where the present authors showed that both these alkaloids yield complex mixtures of substances in this reaction, the principal products being apoquinine from quinine and *iso*apoquinidine from quinidine. The further investigation of this reaction is now described. The products fall into two groups: apo-bases (demethylated or phenolic bases) and isomerides of quinine and quinidine (undemethylated bases).

Apo-bases.—In describing apoquinine (Part I, p. 1927) it was pointed out that the mother-liquors of the acid sulphate, obtained in the process of purification, contained an isomeride of higher lævorotation. This substance, m. p. 275°, $[\alpha]_D^{15°}$ — 261·7° ($c = M/40$ in alcohol), which is produced in minute amount, has now been isolated in a pure condition. It is proposed to call it iso*apoquinine*, in spite of the fact that this name was used by Lippmann and Fleissner (*Monatsh.*, 1891, **12**, 327) for an ill-defined base, obtained by the action of potassium hydroxide in alcohol on iododihydroapoquinine, only the platinichloride being analysed, and no further work having been published. The alternative of adding a new item to the already unnecessarily extensive, trivial nomenclature of the modified cinchona alkaloids is not desirable.

A third apo-base, which proves to be *hydroxydihydroapoquinine*, m. p. 281—284°, $[\alpha]_D^{15°}$ — 205·4° ($c = M/40$ in $N/10$-sulphuric acid) has also been obtained. It is formed, no doubt, by the addition of the elements of a molecule of water to the side chain of apoquinine, since it is produced when pure apoquinine is boiled with 60% sulphuric acid. This substance should be the phenolic base corresponding to one of the constituents of Giemsa and Oesterlin's hydroxydihydroquinine (*Ber.*, 1931, **64**, 57).

From quinidine, in addition to the lævorotatory *iso*apoquinidine already described (Part I, p. 1929), a new dextrorotatory apo-base, m. p. 172°, $[\alpha]_D$ + 208·6° ($c = 1$ in alcohol) has been obtained, for which the name *apoquinidine* is proposed, since this substance is probably the chief constituent of the amorphous dextrorotatory mixtures which have hitherto been called " apoquinidine."

A third isomeride, provisionally named *base A*, has been obtained, but not yet in sufficient quantity to justify the assumption that it has been entirely freed from the other isomerides. No hydroxydihydroapoquinidine analogous with the apoquinine product referred to above has yet been isolated.

Isomerides of Quinine and Quinidine.—The undemethylated bases recovered in the case of quinine have so far yielded only one crystalline product, m. p. 183—185°, $[\alpha]_D^{15°}$ — 201·9° ($c = 0{\cdot}811$ in alcohol), which proves to be identical with the apoquinine methyl ether,

m. p. 183—185°, $[\alpha]_D^{15°}$ — 201·2° (c = 0·811 in alcohol) described in Part I (p. 1928), and is clearly the β-*iso*quinine of the earlier workers as suggested by Suszko and collaborators (*loc. cit.*). No α-*iso*quinine has been found so far.

The recovery of undemethylated products is always larger from quinidine than from quinine. From this material two well-defined isomerides have been isolated. The first is β-*iso*quinidine, m. p. 142°, $[\alpha]_D^{17°}$ — 9·7° (c = 1·4224 in alcohol), identical with the product described by Pfannl (*Monatsh.*, 1911, **32**, 341) and by Konopnicki and Suszko (*Bull. Inter. Acad. Polonaise*, 1929, *A*, 347), which had m. p. 139—140°, $[\alpha]_D^{20°}$ — 9·7° (c = 1·4424 in alcohol). β-*iso*Quinidine is now shown to be *iso*apoquinidine methyl ether.

The second isomeride is the methyl ether of the new apoquinidine. It is tempting to suggest that this is identical with the not very well-defined base, α-*iso*quinidine, described by Domanski and Suszko (*Bull. Inter. Acad. Polonaise*, 1933, *A*, 123), but there are differences, particularly in the values of the specific rotations, which make the identification doubtful without further investigation. α-*iso*Quinidine is described as crystallising from aqueous acetone in rhombohedra with $1H_2O$, m. p. 80°, $[\alpha]_D^{15°}$ + 111° (c = 0·7815 in alcohol). It could not be crystallised in the anhydrous form: the hydrochloride had m. p. 224°, $[\alpha]_D^{15°}$ + 16° (c = 0·8 in water). Apoquinidine methyl ether separates from ether in anhydrous crystals, m. p. 181°, and from aqueous acetone as a monohydrate in rhombic plates, m. p. 90—100°, $[\alpha]_D^{15°}$ + 193·2° (c = 0·7815 in alcohol); the hydrochloride has m. p. 267° and $[\alpha]_D^{15°}$ + 174·7° (c = 0·902 in water).

A possible third and dextrorotatory isomeride of quinidine has been obtained in such small yield that only a preliminary examination has been made so far.

Work is in progress on the constitution and inter-relationships of all the products described and, though some comments on these subjects could be made now, it seems desirable to reserve these until various gaps in the series have been filled and further experimental data are available.

Experimental.

The demethylation process was carried out and the products were worked up as described in Part I into (*a*) recovered undemethylated bases, (*b*) precipitated phenolic bases, and (*c*) ethereal extract of final carbonated liquors.

In the following account, the melting points are corrected and, unless otherwise stated, are also decomposition points. They vary with the rate of heating and are, therefore, of little diagnostic value. The specific rotations are recorded for the dry substance, unless stated otherwise, and where the solvent is not named or the value of c is not stated, the solvent is $N/10$-sulphuric acid and $c = M/40$. The combustion results are microanalyses and are recorded for the substance dried at 120° in a vacuum, unless other conditions are specified as in the case of apoquinidine base and salts.

Demethylation of Quinine.

iso*Apoquinine*.—This substance has now been obtained in a pure state by converting the mixture of bases recovered from apoquinine acid sulphate mother-liquors into the dihydrobromides and fractionally crystallising the latter from 96% alcohol, in which apoquinine dihydrobromide is sparingly soluble. The *iso*apoquinine salt accumulates in the mother-liquors and is recovered by taking the latter to dryness and recrystallising the residue from water. The base, regenerated from the pure dihydrobromide, crystallises from acetone, containing about 2% of alcohol, in faintly yellow, hard, spheroidal aggregates of needles, which begin to sinter at 170°, froth at about 190°, blacken at about 260°, and finally effervesce at 275°. It is sparingly soluble in acetone or ether, readily soluble in alcohol, and has $[\alpha]_D^{15°}$ — 356·7° or — 261·7° (dry alcohol). (Found: loss at 125° in a vacuum, 14·6. $C_{19}H_{22}O_2N_2,3H_2O$ requires $3H_2O$, 14·8. Found for dry substance: C, 73·4; H, 7·2; N, 8·85. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·0%). The *dihydrobromide* crystallises from water in stout, cream-coloured rods, m. p. 136—140°, $[\alpha]_D^{15°}$ — 230·2° (water) (Found: loss at 110° in a vacuum, 6·7. $C_{19}H_{22}O_2N_2.2HBr,2H_2O$ requires $2H_2O$, 7·1%. Found for dry salt: C, 48·3; H, 5·2; N, 5·6; Br, 33·9. $C_{19}H_{22}O_2N_2,2HBr$ requires C, 48·3; H, 5·1; N, 5·9; Br, 33·9%). Unlike apoquinine dihydrobromide, the *iso*apoquinine salt contains the calculated quantity of bromine and is not dissociated by the solvent from which it is crystallised. The *hydrochloride*, clusters of colourless needles from alcohol, has m. p. 271°, $[\alpha]_D^{15°}$ — 194·5° (water) or — 226·7° (dry alcohol) and is anhydrous (Found: C, 65·8; H, 6·7; N, 8·0; Cl, 10·3. $C_{19}H_{22}O_2N_2,HCl$ requires C, 65·75; H, 6·7; N, 8·1; Cl, 10·2%).

The *acid sulphate* forms small, cream-tinted, glistening plates from water, m. p. 202—205°, $[\alpha]_D^{15°}$ — 268·4° (water) (Found: loss at 110° in a vacuum, 8·2. $C_{19}H_{22}O_2N_2,H_2SO_4,2H_2O$ requires $2H_2O$, 8·1. Found for dry salt: C, 55·7; H, 5·9; N, 6·6; S, 7·25. $C_{19}H_{22}O_2N_2,H_2SO_4$ requires C, 55·8; H, 5·9; N, 6·9; S, 7·85%).

Hydroxydihydroapoquinine.—This substance is most readily obtained from the ethereal extract of the final carbonated liquors left after the precipitation of crude apoquinine (Part I, p. 1927). The yield of this product varies from 4 to 6%. On solution in 96% alcohol (1 g. in 3 c.c.) it furnishes about one-eighth to one-half of its weight of crystalline hydroxydihydroapoquinine, which can be purified by repeated crystallisation from boiling 90% alcohol (1 g. in 30 c.c.). It forms colourless needles, sinters at 277°, melts at 281—284°, and has $[\alpha]_D^{15°}$ — 205·4°. The base is sparingly soluble in ether, acetone or alcohol, but rather more soluble in methyl alcohol. On exposure to light it gradually acquires a canary-yellow colour, which is lost on recrystallisation. The freshly precipitated base is soluble in sodium carbonate solution and is on that account even more difficult than phenolic bases in general to recover from its salts. The best precipitant is a solution containing sodium carbonate (2%) and sodium hydrogen carbonate (4%), but even this leaves a considerable amount of alkaloid in solution, which can only be recovered by the tedious process of continuous extraction with ether. The air-dry base loses 14·3% at 115° in a vacuum (calc. for $3H_2O$, 14·1%) and regains 6·8% on exposure to air (calc. for $1H_2O$, 5·2%) (Found for dry substance: C, 69·6; H, 7·5; N, 8·6. $C_{19}H_{24}O_3N_2$ requires C, 69·5; H, 7·4; N, 8·5%). The *hydrochloride* crystallises from boiling water in cream-tinted, felted needles, m. p. 264—268°, $[\alpha]_D^{15°}$ — 177·3° (*N*/10-hydrochloric acid) or — 108·9° ($c = M/80$ in water) or — 110·4° ($c = M/80$ in alcohol). It is sparingly soluble in water or alcohol, but rather more soluble in mixtures of these solvents (Found: loss at 115° in a vacuum, 4·5. $C_{19}H_{24}O_3N_2,HCl,H_2O$ requires H_2O, 4·7. Found for dry salt: C, 62·8; H, 6·8; N, 7·6; Cl, 9·6. $C_{19}H_{24}O_3N_2,HCl$ requires C, 62·5; H, 6·9; N, 7·7; Cl, 9·7%). The *sulphate* crystallises from boiling 50% methyl alcohol in colourless, felted needles, m. p. 287—293°, $[\alpha]_D^{15°}$ — 175·5°, and is almost insoluble in water, ethyl or methyl alcohol, but somewhat more soluble in boiling 50% methyl alcohol [Found: loss at 120° in a vacuum, 2·1. $(C_{19}H_{24}O_3N_2)_2,H_2SO_4,H_2O$ requires H_2O, 2·3. Found for dry substance: C, 60·6; H, 6·6; N, 7·4; S, 4·7. $(C_{19}H_{24}O_3N_2)_2,H_2SO_4$ requires C, 60·4; H, 6·7; N, 7·4; S, 4·2%]. The *acid sulphate* crystallises from 60% alcohol in felted masses of needles, not quite so dull as those of the sulphate, does not melt, but begins to discolour at 215° and is quite black at 230°; $[\alpha]_D^{15°}$ — 154°. It is readily soluble in water, but almost insoluble in methyl or ethyl alcohol (Found: loss at 120° in a vacuum, 14·15. $C_{19}H_{24}O_3N_2,H_2SO_4,4H_2O$ requires $4H_2O$, 14·5. Found for dry salt: C, 53·6; H, 6·3; N, 6·4; S, 7·4. $C_{19}H_{24}O_3N_2,H_2SO_4$ requires C, 53·5; H, 6·1; N, 6·6; S, 7·5%). The *dihydrobromide* crystallises from 96% alcohol in colourless glistening needles, m. p. variable: it decomposes quietly to a tar at about 285° and froths at about 295°. It is very soluble in water, but sparingly in dry alcohol. It can be dissolved in boiling 96% alcohol (about 1 g. in 25 c.c.) and this solution, on concentration to 1 g. in 15 c.c., crystallises; $[\alpha]_D^{15°}$ — 130·6° (water) [Found: loss at 100° in a vacuum, 0·9 (re-absorbed on exposure to air). $C_{19}H_{24}O_3N_2,2HBr,0·25H_2O$ requires H_2O, 0·9. Found for dry salt: Br, 32·5. $C_{19}H_{24}O_3N_2,2HBr$ requires Br, 32·6%].

Recovered Undemethylated Base.—The crude product amounted to 1·8% of the quinine acid sulphate used. It was dissolved in boiling benzene (1 g. in 20 c.c.), and the solution kept for 48 hours to deposit resin. The residue left on evaporation of the filtrate crystallised from boiling acetone in snow-white masses of slender needles, m. p. 183—185°, $[\alpha]_D^{15°}$ — 295·9° or — 201·9° ($c = 0·811$ in alcohol) (Found: C, 74·0; H, 7·6; N, 8·5; MeO, 9·1. Calc. for $C_{20}H_{24}O_2N_2$: C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%). The hydrochloride crystallises with difficulty from dry alcohol on careful addition of dry acetone in spheroidal masses of minute colourless needles, m. p. 249—251°, $[\alpha]_D^{15°}$ — 174·0° (water) (Found: C, 66·4; H, 7·1; N, 7·5; Cl, 9·7; MeO, 8·0. Calc. for $C_{20}H_{24}O_2N_2,HCl$: C, 66·5; H, 7·0; N, 7·8; Cl, 9·8; MeO, 8·6%). The *sulphate* separates from 50% acetone in minute, dull, colourless needles, m. p. 220°, $[\alpha]_D^{15°}$ — 171·2° (water) [Found: loss at 120° in a vacuum, 7·5. $(C_{20}H_{24}O_2N_2)_2,H_2SO_4,3·5H_2O$ requires H_2O, 7·8. Found for dry salt: N, 7·15; MeO, 7·6; S, 4·3. $(C_{20}H_{24}O_2N_2)_2,H_2SO_4$ requires N, 7·5; MeO, 8·3; S, 4·3%]. The *dihydrobromide*, obtained by adding the calculated quantity of hydrobromic acid to the pure base, could only be induced to crystallise by rubbing the amorphous residue with dry alcohol. After a short time a streak of crystals appeared and the residue gradually became semi-solid. It formed minute, cream-coloured rosettes of needles, m. p. 125° (air-dry) or 219° (dry), $[\alpha]_D^{15°}$ — 196° (water) (Found: loss at 120° in a vacuum, 3·7. $C_{20}H_{24}O_2N_2,2HBr,H_2O$ requires H_2O, 3·6. Found for dry salt: C, 49·6; H, 5·6; N, 6·0; MeO, 5·6; Br, 32·5. $C_{20}H_{24}O_2N_2,2HBr$ requires C, 49·4; H, 5·4; N, 5·8; MeO, 6·4; Br, 32·9%).

These results are in good agreement with those recorded already for apoquinine methyl ether (Part I, p. 1928) and a mixed melting point of the two bases showed no depression. The figure now given for the specific rotation of the hydrochloride is — 174·0° in place of — 196° recorded previously for apoquinine methyl ether hydrochloride. The latter figure is calculated for the base and by a copying error was unfortunately given in the previous paper as calculated for the salt. Similarly the specific rotation of apoquinine ethyl ether hydrochloride in water should have been given as — 173·0° instead of — 191·7°. The identity of this substance with β-*iso*quinine has been referred to already (p. 967).

Demethylation of Quinidine.

The quinidine used was freed from dihydroquinidine in part by the method of Buttle, Henry, and Trevan (*Biochem. J.*, 1934, **28**, 434) and in part by the mercuric acetate process of Thron and Dirscherl (*Annalen*, 1935, **515**, 252). The two samples had $[\alpha]_D^{15°}$ + 333·2° and 333·7° respectively, both, within experimental error, in agreement with the figure + 334·2° previously recorded for pure quinidine (Buttle, Henry, and Trevan, *loc. cit.*). Pure quinidine has now been prepared by three entirely different processes and the specific rotations, found by four different observers, are in good agreement, so there can no longer be any reasonable doubt regarding the use of this constant as a criterion of the purity of quinidine.

Phenolic Bases.—The crude " apoquinidine " precipitate (yield, 67—80% of the quinidine used, depending mainly on the duration of the reaction), after treatment with acetone to remove insoluble mineral matter, is dissolved in 96% alcohol (1 g. in 2·5 c.c.) and neutralised by careful addition of concentrated hydrochloric acid, and the solution left over-night to deposit *iso*apoquinidine hydrochloride. The filtrate from this is evaporated in a vacuum, the residue dried for 15 minutes at 100°, dissolved in dry alcohol (1 g. in 1 c.c.), and left to crystallise. The crop is filtered off, and the process repeated on the filtrate three times, the united crops being recrystallised once from 96% alcohol, giving impure apoquinidine hydrochloride. The combined mother-liquors on long standing deposit further small quantities of the same salt, mixed with *iso*apoquinidine hydrochloride, and, when this process ceases, the calculated quantity of hydrochloric acid necessary to convert the remaining bases into dihydrochlorides is added, the liquors taken to dryness, and the dry residue dissolved in dry alcohol (1 g. in 1 c.c.). This solution deposits a mixture of dihydrochlorides of *iso*apoquinidine and the third phenolic base, already referred to as base A. The mixture is separated by conversion into neutral hydrochlorides and crystallisation from 96% alcohol, which yields a small crop of *iso*apoquinidine hydrochloride; the filtrate from this on evaporation to dryness and solution of the dry residue in dry alcohol (1 g. in 1·5 c.c.) furnishes impure base A hydrochloride. The combined mother-liquors from these processes are taken to dryness, and the residue converted into zincichlorides by solution in concentrated hydrochloric acid (1 g. in 1 c.c.) and addition of an equal weight of zinc chloride (1 g. in 1 c.c.). The crystalline crop of zincichlorides is not separable into its components by fractional crystallisation, but the mixture of clean bases recovered from it can be converted into the hydrochlorides and so separated as described above into apoquinidine and base A. The total yield of the three components, expressed as percentages of the crude " apoquinidine " used, are approximately as follows : *iso*apoquinidine, 38; apoquinidine, 21; base A, 9.

Apoquinidine.—The crude hydrochloride, isolated as described above, is purified by recrystallisation from boiling 96% alcohol and finally from water, and the base recovered from it by pouring an aqueous solution into excess of a solution of sodium hydroxide and passing carbon dioxide. The precipitate can be crystallised from alcohol or acetone and in each case tenaciously retains 1 mol. of the solvent. Thus, it separates from alcohol in needles or short prisms, m. p. 172°, which lose only 0·5—1% at 120° in a vacuum, but at 160° lose 13·1% (calc. for 1 mol. C_2H_5·OH, 12·9%), show signs of incipient decomposition, and then melt at 185—190°. At 150° in a vacuum the loss is 5·7%. The precipitated base dissolves easily in acetone and at once crystallises in minute hexagonal prisms, m. p. 178—180° (air-dry). This preparation loses 15·2% at 140° in a vacuum (calc. for $1C_3H_6O$, 15·8%). The product crystallised from chloroform and dried at 120° in a vacuum contains Cl, 4·1% ($C_{19}H_{22}O_2N_2$,$CHCl_3$ requires Cl, 24·8%). Combustions have been made of the base crystallised from alcohol and acetone and dried at 120°, 160°, and 150° in a vacuum [Found for base crystallised from alcohol (*a*) dried at 120° : C, 71·1; H, 8·0; N, 7·9; (*b*) dried at 160° : C, 74·0; H, 7·4; N, 8·9. Found for base crystallised from acetone and dried at 150° : C, 73·7; H, 7·2; N, 9·0. $C_{19}H_{22}O_2N_2$,C_2H_5·OH requires C, 70·8; H, 7·9; N, 7·9. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·0%]. The base crystallised from alcohol has $[\alpha]_D^{15°}$ + 253·9° or + 181·8° (c = 1 in alcohol) : these figures become + 291·4° and + 208·6° respectively calculated for the base dried at 160°.

The neutral salts show the same tendency to retain solvent. The *hydrochloride* crystallises from alcohol in plates or prisms, m. p. 183—185°, $[\alpha]_D^{15°}$ + 156·3° (water) or + 177·0° (calc. for salt free from alcohol) (Found for salt dried at 120° in a vacuum: C, 64·2; H, 7·55; N, 6·6; Cl, 9·2. $C_{19}H_{22}O_2N_2,HCl,C_2H_5{\cdot}OH$ requires C, 64·2; H, 7·4; N, 7·1; Cl, 9·0%). This alcoholate, on exposure to air, slowly changes in appearance and the m. p. rises to 235°, owing to replacement of the alcohol by two molecules of water. It dissolves easily in water and at once crystallises in small needles, m. p. 238—240°, $[\alpha]_D^{15°}$ + 178·3° ($C_{19}H_{22}O_2N_2,HCl,H_2O$ in water) or + 187·5° (calc. for $C_{19}H_{22}O_2N_2,HCl$) (Found: loss at 120° in a vacuum, 5·0. $C_{19}H_{22}O_2N_2,HCl,2H_2O$ requires $1H_2O$, 4·7%. Found for salt so dried: C, 62·2; H, 6·9; N, 7·85; Cl, 9·9. $C_{19}H_{22}O_2N_2,HCl,H_2O$ requires C, 62·5; H, 6·9; N, 7·7; Cl, 9·7%). The *sulphate* crystallises from alcohol in clusters of needles, m. p. 257—258° [Found: loss at 165° in a vacuum, 11·3. $(C_{19}H_{22}O_2N_2)_2,H_2SO_4,2C_2H_6O$ requires C_2H_6O, 11·4%. Found for salt dried at 120° in a vacuum: C, 62·75; H, 6·4; N, 7·6; S, 5·1. $(C_{19}H_{22}O_2N_2)_2,H_2SO_4,C_2H_6O$ requires C, 62·8; H, 6·9; N, 7·3; S, 4·2%]. Crystallised from water, it has m. p. 260° [Found for salt dried at 120° in a vacuum: C, 61·95; H, 6·55; N, 7·4; S, 4·3. $(C_{19}H_{22}O_2N_2)_2,H_2SO_4,H_2O$ requires C, 61·9; H, 6·6; N, 7·6; S, 4·4%]. $[\alpha]_D^{15°}$ + 242·4° or + 248·5° (calc. for anhydrous salt). The salt is very sparingly soluble in water. The *dihydrobromide* crystallises from water in needles, m. p. 280°, $[\alpha]_D^{15°}$ + 192·5° (water) (Found: loss at 120° in a vacuum, 3·6. $C_{19}H_{22}O_2N_2,2HBr,H_2O$ requires H_2O, 3·7%. Found for dry salt: C, 48·1; H, 5·1; N, 6·0; Br, 33·65. $C_{19}H_{22}O_2N_2,2HBr$ requires C, 48·3; H, 5·1; N, 5·9; Br, 33·9%). From alcohol, in which it is sparingly soluble, the salt crystallises in anhydrous, minute prisms. The *zinci-chloride* crystallises from 5% hydrochloric acid in colourless, anhydrous needles, m. p. 290°, $[\alpha]_D^{15°}$ + 175·3° (water) (Found: C, 44·2; H, 4·8; N, 5·0; Cl, 27·25. $C_{19}H_{22}O_2N_2,2HCl,ZnCl_2$ requires C, 43·9; H, 4·7; N, 5·4; Cl, 27·3%).

The methyl ether was obtained by treating the base in solution in alcohol with diazomethane (yield, 62%). It separated from ether in crystals, m. p. 185°, $[\alpha]_D^{15°}$ + 277·6°, and proved to be identical with one of the undemethylated bases described below.

Phenolic Base A.—The *base*, regenerated from the dihydrochloride, crystallises from alcohol in prisms, m. p. 250°, $[\alpha]_D^{15°}$ + 209·5° or + 139·5° (c = 1 in alcohol) (Found: C, 73·6; H, 7·3; N, 8·7. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·0%). The *hydrochloride* crystallises from alcohol in large, rectangular prisms, m. p. 115° (air-dry) or 180—190° (dried at 120°), $[\alpha]_D^{15°}$ + 139·3° (water) (Found: loss at 100° and finally at 120° in a vacuum, 11·1. $C_{19}H_{22}O_2N_2,HCl,C_2H_5{\cdot}OH$ requires $C_2H_5{\cdot}OH$, 11·7. Found for dry salt: N, 7·6; Cl, 10·1. $C_{19}H_{22}O_2N_2,HCl$ requires N, 8·1; Cl, 10·2%).

Recovered Undemethylated Bases.—The yield of this material varies from 15 to 20% by weight of the quinidine used, when the time of heating is 6 hours, and is proportionately larger for shorter periods. The crude product contains at least three substances. On exposure of a solution in moist ether (1 g. in 10 c.c.) in a refrigerator, about 25% of the product crystallises (β-*iso*quinidine), no further crops being obtained on concentration and cooling of the mother-liquor. The residue from the latter is dissolved in alcohol and neutralised with dilute sulphuric acid, yielding a crystalline crop (apoquinidine methyl ether sulphate) amounting to a further 20% of the crude product. The remaining mixed bases are precipitated from the mother-liquor and extracted with the minimum quantity of ether, from which, on cooling, a further crop of β-*iso*quinidine is obtained amounting to about 25% of the total crude product. The residual bases are converted into cuprichlorides and give a further 5% yield of β-*iso*quinidine in the form of the additive compound $B,2HCl,CuCl_2$. The bases recovered from the cuprichloride mother-liquors, on conversion into neutral sulphate, give a further 5% of apoquinidine methyl ether, and the residual bases from the sulphate mother-liquors, on solution in alcohol (1 g. in 1 c.c.), give a further 5% of crystalline material, which is a third isomeride of quinidine.

β-iso*Quinidine.*—This substance is best purified by crystallisation from moist ether, from which it separates in colourless, silky needles, m. p. 72° (air-dry) or 142° (dry) (Found: loss on drying over sulphuric acid in a vacuous desiccator, 14·05. Calc. for $C_{20}H_{24}O_2N_2,3H_2O$: loss, 14·3%. No further loss at 110° in a vacuum. Found for dry substance: C, 74·4; H, 7·5; N, 8·7; MeO, 9·3. Calc. for $C_{20}H_{24}O_2N_2$: C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%). The substance has $[\alpha]_D^{17°}$ + 29·0° or − 9·7° (c = 1·4424 in 96% alcohol). These results are in close agreement with those recorded for β-*iso*quinidine by previous workers and there can be no doubt of the identity of this substance with the *iso*quinidine of Pfannl (*loc. cit.*) and with the β-*iso*quinidine of Konopnicki and Suszko (*loc. cit.*). The neutral sulphate, $B_2,H_2SO_4,7H_2O$, differed from Pfannl's description only in having $[\alpha]_D^{15°}$ − 47·1° ($c = M/40$ in water) instead of − 35° (c = 1·4 in water). The *cuprichloride*, prepared by the general method (Buttle, Henry, and Trevan, *loc.*

cit.), forms small plates, m. p. 220° (Found : C, 45·1; H, 4·9; N, 5·5; Cl, 26·7; Cu, 11·8. $C_{20}H_{24}O_2N_2,2HCl,CuCl_2$ requires C, 45·1; H, 4·9; N, 5·3; Cl, 26·7; Cu, 12·0%).

On demethylation by boiling with 18*N*-sulphuric acid (20 c.c.) for 6 hours, β-*iso*quinidine (5 g.) yields about 10% of recovered undemethylated base and 90% of phenolic bases, of which about one-third is *iso*apoquinidine and the rest consists of dextrorotatory phenolic bases, from which about 4% of apoquinidine is isolated in the form of the hydrochloride and identified by its specific rotation and the characteristic melting point changes.

Conversion of iso*Apoquinidine into* β-iso*Quinidine.*—*iso*Apoquinidine (2 g.) in alcoholic solution, on treatment with diazomethane in ether, yielded 0·8 g. of methylated base, which on recrystallisation from moist ether had m. p. 70—75° (air-dry) or 142—143° (dried in a vacuous desiccator) and $[\alpha]_D^{15°}$ − 10° (c = 1 in alcohol). These constants agree well with those given above for β-*iso*quinidine, and identity of the two was confirmed by a mixed melting point determination. *iso*Apoquinidine is, therefore, the phenolic base corresponding to β-*iso*quinidine.

Apoquinidine Methyl Ether.—The crude sulphate, isolated as described above, can be recrystallised from boiling water (1 g. in 35 c.c.), but purification is best effected by recrystallising the regenerated base first from aqueous acetone (70%) and finally from 96% alcohol; this provides a small first crop of a substance which appears to be impure quinidine. The mother-liquor from this is taken almost to dryness, and the residue crystallised first from ether (1 g. in 1 c.c.) and finally from alcohol (1 g. in 1·5 c.c.), from which the base will not crystallise until it is pure. It separates from ether in minute, anhydrous needles or from alcohol in colourless prisms, m. p. 180—181°, $[\alpha]_D^{15°}$ + 278·8° (Found : loss at 120° in a vacuum, 12·1. $C_{20}H_{24}O_2N_2,C_2H_5{\cdot}OH$ requires $C_2H_5{\cdot}OH$, 12·4%. Found for dry substance : C, 74·1; H, 7·6; N, 8·3; MeO, 8·9. $C_{20}H_{24}O_2N_2$ requires C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%). From aqueous acetone it crystallises in rhombic plates, m. p. 90—100°, $[\alpha]_D^{15°}$ + 193·2° (c = 0·7815 in alcohol) (Found : loss at 80—115° in a vacuum, 7·1. Calc. for $1H_2O$, 5·3; for $2H_2O$, 10·0%). The constants found for this base are in good agreement with those recorded for apoquinidine methyl ether (p. 970) and a mixed melting point of the two confirmed this identification. The differences between it and α-*iso*quinidine have been referred to already (p. 967). The *hydrochloride* crystallises from water or 96% alcohol and has m. p. 267°, $[\alpha]_D^{15°}$ + 174·7° (c = 0·9 in water) (Found : loss at 120° in a vacuum, 4·9. $C_{20}H_{24}O_2N_2,HCl,H_2O$ requires H_2O, 4·8%. Found for dry substance : C, 66·5; H, 7·25; N, 7·8; Cl, 10·2; MeO, 8·3. $C_{20}H_{24}O_2N_2,HCl$ requires C, 66·5; H, 7·0; N, 7·8; Cl, 9·8; MeO, 8·6%). The *dihydrobromide* is much more soluble in water than quinidine dihydrobromide and crystallises from alcohol in prisms, m. p. 140° or 210—215° (dry), $[\alpha]_D^{15°}$ + 186·3° (water). The loss on drying at 120° in a vacuum varied in different specimens from 5 to 8%, owing to efflorescence. It was found impossible to dry the salt to constant weight and it was taken as dry at the point at which the drying curve began to flatten (Found for salt so dried : C, 49·8; H, 5·85; N, 5·5; Br, 32·3; MeO, 6·8. $C_{20}H_{24}O_2N_2,2HBr$ requires C, 49·4; H, 5·4; N, 5·8; Br, 32·9; MeO, 6·4%).

The Third Quinidine Isomeride.—The minute quantity of crude material separated as described above, on recrystallisation from alcohol (1 g. in 3 c.c.), forms large, triangular prisms, m. p. 90—93° (air-dry) or 120° (dry), $[\alpha]_D^{15°}$ + 233·5° or + 136·5° (c = 1 in alcohol) (Found : loss on drying, first at 55° and finally at 120° in a vacuum, 11·5. $C_{20}H_{24}O_2N_2,C_2H_5{\cdot}OH$ requires $C_2H_5{\cdot}OH$, 12·4%. Found for dry substance : C, 74·0; H, 7·4; N, 8·6; MeO, 9·3. $C_{20}H_{24}O_2N_2$ requires C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%).

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