133. *Modified Cinchona Alkaloids. Part IV. Constitution.*

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The substances described in this and Parts I and II (J., 1934, 1923; 1935, 966; Part III, Goodson, J., 1935, 1094) as produced by the action of boiling 60% sulphuric acid on quinine and quinidine are of three kinds: (1) isomerides of the two alkaloids, (2) demethylated (phenolic) bases corresponding to these isomerides, and (3) hydration products of (1) and (2). Sufficient information has now been obtained to warrant discussion of the formulæ to be assigned to these substances. The authors have confined their attention to the products formed by the action of sulphuric acid, but similar products are obtained when the cinchona alkaloids are treated with other mineral acids, as well as by the dehalogenation, by alkalis or silver salts, of the halogeno-dihydro-bases formed by the addition of a molecule of one of the halogen acids, usually hydrogen bromide or iodide, to the vinyl side chain of any one of the normal cinchona alkaloids.

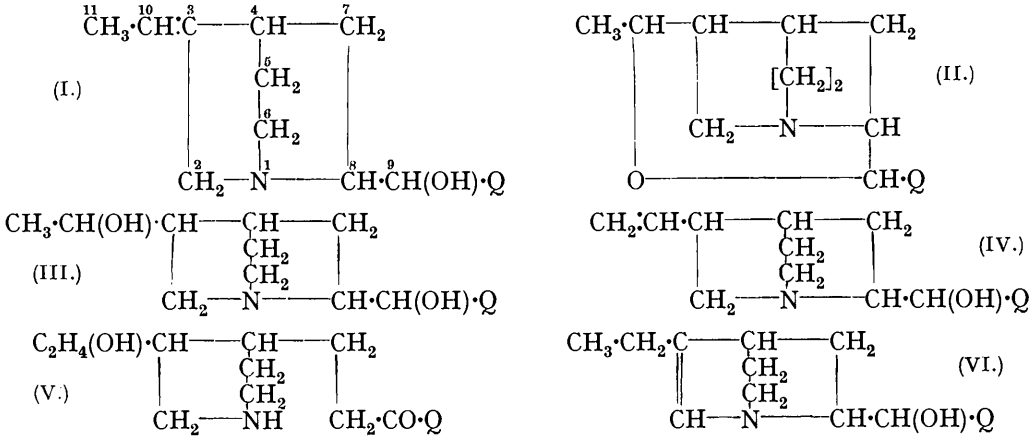
It is possible to account for the reactions of many of these substances on the basis of formulæ (I) to (III), which are accepted for certain transformation products of cinchonidine and cinchonine. A detailed account of the investigations which resulted in the development of these formulæ has been published by Jungfleisch and Léger (*Ann. Chim.*, 1920, **14**, 59).

An inspection of these formulæ will show that substances of type (I) should exist in two geometrically isomeric forms; those of type (II), which are found only in the dextrorotatory series, in two epimeric forms about the new centre of asymmetry at carbon atom **10**; and those of type (III) in two stereoisomeric forms. Most of these forms are now known for the four alkaloids under consideration, but only one form of type (I) and one of type (III) are known for cinchonine and cinchonidine respectively. Quinidine yields a third isomeride of type (II) and an isomeride of a new type; these two unexpected forms are discussed later.

The experimental portion of the paper is concerned mainly with (1) the methods by which assignment of each transformation product of quinine and quinidine to its particular type has been made, (2) an investigation of the nature of the side chain in each of the three types, and (3) descriptions of certain of the transformation products now isolated for the first time. In discussing these substances the notation suggested by Rabe and Riza (*Annalen*, 1932, **496**, 152) with the addition of the numbers **10** and **11** for the two-carbon side chain, as shown in formula (I), has been used. The principal data required for the classification of the transformation products have been assembled in a table (p. 593) in which the name of each *apo-* or phenolic base is placed under the name of the methyl ether to which it is related when this is known. For the sake of simplicity these *apo-* or phenolic bases are ignored in the following discussion, except where they exhibit some peculiarity.

In obtaining these data the authors have used methods differing from those employed by their predecessors. Acylation of cinchona alkaloids is unsatisfactory, as the products are often amorphous, and Zerewitinoff determinations of replaceable hydrogen (RH), which in these cases can only mean hydrogen in hydroxyl groups, have been used instead. No difficulty was experienced in deciding by this means between type (I) (RH = 1), type (II) (RH = 0) and type (III) (RH = 2) so far as this factor is concerned. With the *apo-*

or phenolic bases, which are insoluble in the ethereal solvents usually used in this process, pyridine had to be used as a solvent and as this, even after rigorous drying, gave an



undesirably large yield of methane in blank experiments, an unusually large quantity (0·5 to 1·0 g.) of the phenolic base had to be used to get trustworthy results.

Name of alkaloid.	Hydroxyl, % (Zerewitinoff). Found.	Calc.	*C*-Me, % (Kuhn–Roth). Found.	Calc.	$[\alpha]_D^{15°}$.	Structural type.
Quinine	6·3	1 = 5·2	nil	nil	− 284·5°	IV
Cupreine	—	—	—	—	− 283·5	,,
α-*iso*Quinine	5·15	1 = 5·2	7·7	1 = 8·3	− 364·3	I
*isoapo*Quinine	10·5	2 = 10·9	—	—	− 356·7	,,
β-*iso*Quinine	6·0	1 = 5·2	8·6	1 = 8·3	− 295·9	,,
*apo*Quinine	11·1	2 = 10·9	—	—	− 281·0	,,
α-Hydroxydihydroquinine	9·3	2 = 9·9	5·2	1 = 7·9	− 197·5	III
α-Hydroxydihydro*apo*quinine	14·9	3 = 15·5	—	—	− 205·4	,,
β-Hydroxydihydro*apo*quinine [a]	14·0	3 = 15·5	9·4	1 = 8·2	− 205·1	,,
Quinidine [b]	6·2	1 = 5·2	nil	nil	+ 334·2	IV
*apo*Quinidine methyl ether	5·0	1 = 5·2	7·9	1 = 8·3	+ 277·6	I
*apo*Quinidine	10·7	2 = 10·9	—	—	+ 291·4	,,
*neoiso*Quinidine	5·5	1 = 5·2	8·0	1 = 8·3	+ 197·2	,,
*neoapo*Quinidine	10·7	2 = 10·9	—	—	+ 206·2	,,
ψ-Quinidine [b]	5·3	1 = 5·2	6·5	1 = 8·3	+ 249·2	VI
α-*iso*Quinidine [b]	nil	nil	6·9	1 = 8·3	+ 125·2	II
β-*iso*Quinidine	nil	nil	6·0	1 = 8·3	+ 29·0	,,
*isoapo*Quinidine	5·9	1 = 5·5	—	—	+ 25·0	,,
γ-*iso*Quinidine [b]	nil	nil	6·3	1 = 8·3	+ 67·8	,,
α-Hydroxydihydroquinidine	—	—	—	—	+ 241·5	III
α-Hydroxydihydro*apo*quinidine	14·7	3 = 15·5	—	—	+ 252·6	,,
Hydroxydihydroquinidine	9·5	2 = 9·9	4·9	1 = 7·9	+ 225·3 [c]	,,
β-Hydroxydihydro*apo*quinidine	17·1	4 [d] = 18·2	—	—	+ 224·6 [c]	,,

[a] Corresponding methyl ether unknown.
[b] Corresponding phenolic base unknown.
[c] In alcohol. [d] One hydroxyl due to retained alcohol.

Catalytic hydrogenation of substances of type (I) should add on one molecule of hydrogen at C_3–C_{10}, producing, *e.g.*, dihydroquinine from α- and β-*iso*quinines and dihydroquinidine from the two quinidine isomerides of this type. In this process carbon atom 3 becomes a centre of asymmetry, as it is in the normal cinchona alkaloids (IV), so that the dihydro-base formed should be a mixture of two epimerides about carbon atom 3. This proved to be the case. Thus α- and β-*iso*quinine yielded dihydroquinine and *epi*-C_3-dihydroquinine, while *apo*quinidine methyl ether gave dihydroquinidine and *epi*-C_3-dihydroquinidine. Both *neoiso*quinidine and ψ-quinidine similarly yielded dihydroquinidine, but the C_3-epimeride has not been isolated in a pure state in these cases.

In the hydrogenation of the quinine and quinidine isomerides of type (I), it is the dihydro-

base of higher rotation which is formed in predominant quantity, *viz.*, the C_3-epimeride from the quinine isomerides and dihydroquinidine from those of quinidine.

This is the first instance in which substances are described which are stereoisomeric with the natural cinchona alkaloids and differ from them only in respect of the relative configuration of C_3 to C_4. Rabe *et al.* (*Annalen*, 1932, **492**, 242) have obtained the C_8- and C_9-epimerides, such as "*epi*hydroquinine" and "*epi*hydroquinidine," in which the configuration at C_3 and C_4 is identical with that of the parent alkaloids, and have synthesised the complete enantiomorphs, *d*-dihydroquinine and *l*-dihydroquinidine (Rabe and Schultze, *Ber.*, 1933, **66**, 120), in which C_3 and C_4 taken together have the opposite configuration. The present results, therefore, showing as they do that in dihydroquinine and dihydroquinidine, as probably also in the other natural cinchona alkaloids, carbon atom 3 must be dextrorotatory, constitute the first evidence of the configuration at one of these atoms taken by itself.

The nature of the side chain in the transformation products of all three types has been investigated by Kuhn's method for the estimation of methyl groups attached to carbon (Kuhn and Roth, *Ber.*, 1933, **66**, 1274; Kuhn and L'Orsa, *Z. angew. Chem.*, 1931, **44**, 847). With one exception each of the quinine and quinidine isomerides of type (I) gave results clearly indicating the presence of one such group, and supporting the representation of the side chain in type (I) as $:CH{\cdot}CH_3$. Confirmation of this result was attempted by an ozonisation experiment in which it was expected that acetaldehyde would be produced. The result was disappointing, only a small yield of the aldehyde being obtained. ψ-Quinidine, the unexpected third isomeride of quinidine, gave a low result in the Kuhn–Roth estimation. Since it also produces a mixture of dihydroquinidine and *epi*-C_3-dihydroquinidine on catalytic hydrogenation, C_3 must be the centre of asymmetry produced in the hydrogenation, and it is suggested that this third isomeride should be represented by formula (VI), with the ethylenic linkage between C_3 and C_2, the side chain becoming $CH_3{\cdot}CH_2$. This accounts for the one replaceable hydrogen found, the formation of two epimeric dihydroquinidines on hydrogenation, and for the low result of the Kuhn–Roth *C*-Me estimation, as it has been found that dihydroquinine and dihydroquinidine, where the side chain is also $\cdot CH_2{\cdot}CH_3$, give by the Kuhn–Roth method values for *C*-Me of about the same order.

Formula (II) has been generally accepted as representing the stereoisomeric α- and β-*iso*cinchonines. In investigating the validity of this formula for α-*iso*cinchonine, Rabe and Böttcher (*Ber.*, 1917, **50**, 128) showed that this substance undergoes the normal Pasteur conversion into hydroxydihydrocinchonicine (V), but were unable to decide between the structures (i) $R<^{CH{\cdot}CH_3}_{O}$ and (ii) $R<^{CH_2}_{-O-}>CH_2$ for the side chain C_{10}—C_{11}. The three substances of type (II) now dealt with, α-, β-, and γ-*iso*quinidines, showed all the characteristics of the type: relative stability to potassium permanganate, absence of replaceable hydrogen, and failure to hydrogenate. In the Kuhn–Roth estimations the three isomerides gave results, which, though unexpectedly low, favour the side chain (i) rather than (ii).

Domański and Suszko (*Rec. trav. chim.*, 1935, **54**, 481), who first obtained γ-*iso*quinidine, point out its great similarity to α-*iso*quinidine (*Bull. Inter. Acad. Polonaise*, 1933, *A*, 119) and suggest that these are epimerides about carbon atom 3, both belonging to type (II), to which Konopnicki and Suszko (*ibid.*, 1929, *A*, 340) were the first to assign β-*iso*quinidine. In making this suggestion, the Polish authors recognise the difficulties of such an assumption as pointed out in another connection by Rabe *et al.* (*Annalen*, 1932, **492**, 251). In the present authors' view the information available is insufficient to decide the question, but in this connection the following table is interesting.

	$[\alpha]_D^{15°}$.	Assumed direction of asymmetry. Carbon atom 10.	Carbon atom 9.
β-*iso*Quinidine	+ 29·0°	−	−
γ-*iso*Quinidine	+ 67·8	+	−
α-*iso*Quinidine	+ 125·2	−	+

There is evidence that carbon atom 9 makes the largest contribution to the total value of the specific rotation of any one alkaloid in this group: thus epimerisation about this

centre changes the specific rotation of quinidine, + 243·5°, to that of *epi*quinidine, + 102·4° (Rabe *et al.*, *ibid.*, p. 252). The small dextro-contribution made by carbon atoms 3 and 4 to the total dextrorotation of quinidine is evidenced by the fall in rotation, + 243·5° (alcohol) to + 38° (chloroform), when quinidine is converted into quinicine, in which asymmetry at carbon atoms 8 and 9 disappears. It seems possible, therefore, that the large changes in rotation produced by the conversion of quinidine into α-, γ-, and β-*iso*quinidines are due in the first place to lævorotation at carbon atom 10, in the second to lævorotation at carbon atom 9, and in the third to both these changes. It is not unreasonable to suppose that epimerisation can occur at C_9 under the conditions of these experiments, since Rabe, Haeuszler, and Hochstätter (*Annalen*, 1934, **514**, 63) have shown that Emde's supposed "hydrocinchonicine," produced by the action of 25% hydrochloric acid on dihydrocinchonidine (*Helv. Chim. Acta*, 1932, **15**, 557), is in reality *epi*dihydrocinchonidine (*epi*-C_9-dihydrocinchonidine) and Fiedzuiszko and Suszko found that dihydrocinchonine can be epimerised about C_9 in the same manner (*Bull. Inter. Acad. Polonaise*, 1934, *A*, 415). Further, there is at present no evidence that in all these isomerides of type (II) the ether-oxide linkage is between carbon atoms 9 and 10. It is possible that in one of them it is at C_3—C_9.

Although somewhat unsatisfactory, the results of the Kuhn–Roth estimation of ·CMe· groups for the hydration products (type III) clearly indicate that in these substances the side chain is of the form CH_3·CH·OH.

It has not been possible in all cases to obtain both the phenolic bases and their methyl ethers, because *O*-methylation of the former gives small yields and demethylation of the latter usually leads to mixtures, so that considerable quantities of material are necessary for the establishment of such relationships. It has, however, been possible to relate the phenolic base to its methyl ether in most cases, and in this connection it is of interest to mention that α-*iso*quinine, discovered by Böttcher and Horowitz a quarter of a century ago (*Monatsh.*, 1911, **32**, 793), is now shown to be the methyl ether of *isoapo*quinine (Part II, p. 967).

"allo*Quinidine*."—While this paper was in preparation Ludwiczac and Suszko published (*Bull. Inter. Acad. Polonaise*, 1936, *A*, 276) a description of a supposed new isomeride of quinidine, produced by the action of 70% sulphuric acid on quinidine at 60—70° for 100 hours. This product is named *allo*quinidine and is stated to have m. p. 249—250° and $[\alpha]_D$ + 230° (c = 1, alcohol). A specimen of this material has been prepared by the present authors by the prescribed process. It had m. p. 248—250°, $[\alpha]_D$ + 219·3° (c = 1, alcohol), but on recrystallisation from alcohol the m. p. gradually rose to 256—257° and the specific rotation to + 224·6° (c = 1, alcohol), which are the constants of hydroxydihydroquinidine (p. 598), and a mixture with that substance showed no depression of melting point. *allo*-Quinidine appears therefore to be merely impure hydroxydihydroquinidine, and the Polish authors' description of the base, as appreciably soluble in water, and giving low carbon results for $C_{20}H_{24}O_2N_2$ on combustion, is in harmony with that view.

Experimental.

In the following account the combustion results are in all cases from micro-analyses. Unless stated otherwise, the specific rotations are for $c = M/40$ for the dry substance: the solvent is N/10-sulphuric acid for bases, and water for salts.

Quinidine Transformation Products. Type (I).

Two substances of this group have been described already, *viz.*, *apo*quinidine and its methyl ether (Part II, pp. 969, 971). Two more are now dealt with, *viz.*, neoapo*quinidine* and its methyl ether, neoiso*quinidine*.

ψ-Quinidine (type VI) is dealt with at the end of this group, from which it differs only in the position of the ethylenic linkage. The *apo*-base corresponding to ψ-quinidine has not been obtained.

neoapo*Quinidine* (type I; Q = 6-hydroxyquinolyl).—A preliminary description of this substance was given in Part II (p. 970) under the name "phenolic base A." It is best isolated as the hydrochloride from the mother-liquors obtained in the purification of *apo*quinidine (Part II, p. 969), and is then recrystallised, first from water and finally from alcohol (96%).

From this salt the base is recovered as usual. The yield is about 4% of the crude "*apo*quinidine" obtained, which is equivalent to 3% of the quinidine used. neoapo*Quinidine* crystallises from ether or alcohol in needles, m. p. 260°, $[\alpha]_D^{15°}$ + 206·2° or + 120·7° (*c* = 1, alcohol) (Found : C, 73·5; H, 6·9; N, 8·8. $C_{19}H_{22}O_2N_2$ requires C, 73·5; H, 7·2; N, 9·0%). The *hydrochloride* crystallises from alcohol (96%) in hexagonal prisms or from water in rectangular prisms. Both forms have m. p. 197° and $[\alpha]_D^{15°}$ + 110·4° (Found : loss at 120° in a vacuum, 4·7. $C_{19}H_{22}O_2N_2,HCl,H_2O$ requires H_2O, 4·9%. Found for dry salt : N, 7·5; C, 10·3. $C_{19}H_{22}O_2N_2$, HCl requires N, 8·1; Cl, 10·2%). The *dihydrochloride* separates from water in small rectangular prisms, m. p. 255° (decomp.) with some sintering at 190°, $[\alpha]_D^{15°}$ + 167·0° (Found : loss on drying at 120° in a vacuum, 9·9%. Found for dry salt : N, 7·2; Cl, 17·3. $C_{19}H_{22}O_2N_2,2HCl$ requires N, 7·3; Cl, 18·5%). Combustion results for carbon in these two salts were persistently low : figures for chlorine were also low for the dihydrochloride, probably owing to dissociation on recrystallisation from water, as has been noticed in other cases in this series (Part I, p. 1928; Part II, p. 967). The *nitrate* crystallises from dry alcohol in colourless prisms, becomes yellow on exposure to light, has m. p. 100° (air-dry, decomp.), but after drying begins to discolour at 135° and is completely decomposed at 160°; $[\alpha]_D^{15°}$ + 102·2° (Found : loss on drying first at 90° and finally at 115° in a vacuum, 18·6%. Found for dry salt : C, 61·2; H, 6·1; N, 11·1. $C_{19}H_{22}O_2N_2,HNO_3$ requires C, 61·1; H, 6·2; N, 11·3%). The *neutral sulphate* crystallises from alcohol in bright yellow leaflets, m. p. 80° or 218—220° (dry, decomp.) [Found for salt dried in a vacuum first at 60°, then at 120° : C, 61·8; H, 6·0; N, 7·1; S, 4·9. $(C_{19}H_{22}O_2N_2)_2,H_2SO_4,H_2O$ requires C, 61·9; H, 6·5; N, 7·6; S, 4·4%].

With diazomethane *neoapo*quinidine gave an 80% yield of the methyl ether, m. p. 83—84°, $[\alpha]_D^{15°}$ + 197·2° (Found : loss on drying in a vacuum at 45°, 10·4. Calc. for $C_{20}H_{24}O_2N_2,2H_2O$: loss, 10·0%), identical with *neoiso*quinidine described in the next paragraph.

neoiso*Quinidine* (Type I; Q = 6-methoxyquinolyl).—This isomeride of quinidine was referred to in a preliminary manner in Part II (p. 971). The crude material then obtained has now been found to be a mixture of two substances, neoiso*quinidine* and *ψ-quinidine*, which were separated by crystallisation of the neutral sulphates from dry alcohol (1 g. in 2 c.c.), and of the final residues from water (1 g. in 1 c.c.), the separation being controlled polarimetrically. *neoiso*-Quinidine crystallises from ether in long prisms, m. p. 83°, $[\alpha]_D^{15°}$ + 198·6° or + 98·7° (*c* = 1, alcohol) (Found : loss on drying at 45° in a vacuum, 10·1. $C_{20}H_{24}O_2N_2,2H_2O$ requires H_2O, 10·0%. Found in dry base : 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%). A mixed m. p. determination with *neoapo*quinidine methyl ether (previous paragraph) showed no depression. The *nitrate* separates from water in prisms. The air-dry substance has m. p. 115° and re-melts at 218°; the dry substance has m. p. 220° (decomp.), $[\alpha]_D^{15°}$ + 100·6° (Found : loss on drying at 120° in a vacuum, 4·8. $C_{20}H_{24}O_2N_2,HNO_3,H_2O$ requires loss, 4·4%. Found for dry salt : C, 62·5; H, 6·3; N, 10·9; MeO, 7·8. $C_{20}H_{24}O_2N_2,HNO_3$ requires C, 62·0; H, 6·5; N, 10·85; MeO, 8·0%).

ψ-Quinidine (Type VI; Q = 6-methoxyquinolyl).—This substance occurs with *neoiso*-quinidine as described above, and is separated by taking advantage of the lower solubility in dry alcohol of its neutral sulphate. For final purification the latter is converted into the nitrate, and this recrystallised from boiling alcohol (1 g. in 4 c.c.). The *base* recovered from the pure nitrate crystallises from boiling alcohol (1 g. in 3 c.c.) in colourless prisms, m. p. 85—90° (air-dry) or 150—155° (dried at 80—115° in a vacuum), $[\alpha]_D^{15°}$ + 249·4° (Found : loss in a vacuum, first at 80° and finally at 115°, 12·0. $C_{20}H_{24}O_2N_2,C_2H_5{\cdot}OH$ requires loss, 12·4%. Found for dry substance : C, 74·2; H, 7·7; N, 8·4; MeO, 9·2. $C_{20}H_{24}O_2N_2$ requires C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%). The *hydrochloride* crystallises from water in anhydrous prisms, m. p. 269° (decomp.) (Found : C, 66·6; H, 7·1; N, 7·8; Cl, 9·9; MeO, 8·5. $C_{20}H_{24}O_2N_2,HCl$ requires C, 66·6; H, 6·9; N, 7·8; Cl, 10·0; MeO, 8·6%). The *nitrate* separates from boiling alcohol in anhydrous rhombic prisms, m. p. 217—218° (decomp.) (Found : C, 62·5; H, 6·6; N, 10·5; MeO, 7·8. $C_{20}H_{24}O_2N_2,HNO_3$ requires C, 62·0; H, 6·5; N, 10·85; MeO, 8·0%).

Hydrogenation of Quinidine Isomerides (Types I and VI).—Preliminary experiments showed that *apo*quinidine hydrochloride and *neoapo*quinidine dihydrochloride could be hydrogenated in *N*/10-sulphuric acid solution in the presence of Adams's platinic oxide as catalyst. The reduced product was in each case converted into the neutral hydrochloride, which after a single crystallisation from water had in the two cases m. p. 238—240°, $[\alpha]_D^{15°}$ + 188·9° and m. p. 239—240°, $[\alpha]_D^{15°}$ + 180·4°. These figures approximate to those of dihydrocupreidine hydrochloride, m. p. 231—233°, $[\alpha]_D^{15°}$ + 194°, but, as the dihydrocupreidines proved less easy to separate than their methyl ethers, recourse was had to hydrogenation of the methyl ethers of these *apo*-bases.

Hydrogenated under these conditions, *apo*quinidine methyl ether absorbed about 1% more than the calculated amount of hydrogen. The product, isolated in the usual manner, and crystallised once from alcohol, had m. p. 167° and $[\alpha]_D^{15°}$ + 286·9°. After three further crystallisations (1 g. in 5 c.c.) the m. p. was 171—172° and $[\alpha]_D^{15°}$ + 298·3°. The product then showed no depression of m. p. on admixture with dihydroquinidine, m. p. 171—172°, $[\alpha]_D^{15°}$ + 299·0°. The mother-liquors gave more dihydroquinidine on concentration, the total yield being 63% of the crude product. From the final mother-liquors there was obtained in small yield by crystallisation from ether a substance, m. p. 112° (air-dry) or 151—152° (dry), $[\alpha]_D^{15°}$ + 233·8° (Found: loss on drying at 120° in a vacuum, 7·0%. Found for dry base: C, 73·8; H, 8·2; N, 8·4; MeO, 9·6. $C_{19}H_{26}O_2N_2$ requires C, 73·6; H, 8·0; N, 8·6; MeO, 9·5%). This, as already stated, must be epi-C_3-*dihydroquinidine*.

*neoiso*Quinidine (0·6 g.), reduced under similar conditions, furnished an initial product, which after one crystallisation from alcohol had m. p. 168°, $[\alpha]_D^{15°}$ + 290·4°, and yielded after two further crystallisations, dihydroquinidine, m. p. 171—172°, $[\alpha]_D^{15°}$ + 297·5°. *ψ*-Quinidine (0·53 g.) similarly yielded a crude product, m. p. 170°, $[\alpha]_D^{15°}$ + 292·0, from which dihydroquinidine, m. p. and mixed m. p. 171—172°, $[\alpha]_D$ + 296·6°, was obtained, but in this case and that of *neoiso*quinidine (see above) the C_3-epimeride was too small in amount to be isolated from the residual mother-liquors.

Quinidine Transformation Products. Type (II).

Of the three quinidine isomerides of this group, β-*iso*quinidine has been described already (Part II, p. 970) and its position established as the methyl ether of *isoapo*quinidine (Part I, p. 1929). These results have been confirmed by Ludwiczak and Suszko (*Bull. Inter. Acad. Polonaise*, 1935, *A*, 65), who, however, re-named the phenolic base β-*iso*cupreidine.

Under the conditions used by the present authors, *viz.*, boiling quinidine with 60% sulphuric acid, α- and γ-*iso*quinidines are not found in the reaction mixture, but according to Domański and Suszko (*ibid.*, p. 465), when quinidine is digested with 70% sulphuric acid (*d* 1·615) at 60—70° during 20 hours, β- and γ-*iso*quinidines are produced. On repeating this experiment, the present authors were able to isolate all three isomerides together with some hydroxydihydroquinidine. With 50% sulphuric acid (*d* 1·40) at 65—70° for 20 hours, the whole of the quinidine was recovered unchanged. At 100° for the same period and the same strength of acid, about 40% of the quinidine can be recovered and the reaction products are, as with 70% acid at 60—70°, α-, β- and γ-*iso*quinidines with hydroxydihydroquinidine.

It appears that, as Domański and Suszko found, α- and γ-*iso*quinidines are less stable to sulphuric acid than β-*iso*quinidine and that the survivals in this reaction depend more on the temperature than upon the strength of the acid used.

The Polish authors (*loc. cit.*; *Rec. trav. chim.*, 1935, **54**, 481) have also prepared α- and γ-*iso*quinidines by dehalogenating the crude hydrogen chloride or hydrogen bromide addition products of quinidine with potassium hydroxide in alcohol. The following method of isolating and separating the two isomerides is shorter and gives better yields than that described by them. The largely amorphous hydriodide precipitate, prepared from the crude mixture of bases, is dissolved in alcohol (1 g. in 1 c.c.) and left to deposit quinidine hydriodide. The mixed bases are recovered from the alcoholic mother-liquor and converted into cuprichlorides (1 g. of base, 1 g. of cupric chloride, 5 c.c. of concentrated hydrochloric acid), from which the bases are recovered in the usual way (Buttle, Henry, and Trevan, *Biochem. J.*, 1934, **28**, 435), dried in a vacuum, and dissolved in diluted acetone (1 g. in 1 c.c. + 0·5 c.c. of water). From this solution, nearly pure α-*iso*quinidine crystallises (yield, 57% of the quinidine used). The residue left on removal of the solvent from the mother-liquors, on solution in cold 10% nitric acid, gives γ-*iso*quinidine acid nitrate, of which a further quantity is obtained by dissolving the bases recovered from the cuprichloride mother-liquors in 10% nitric acid (yield, 15%). Additional quantities can be recovered by repeating the process with the residual bases, which also yield a little of Suszko's niquidine and about 3% of *apo*quinidine methyl ether.

α-iso*Quinidine*.—The base is purified by crystallisation from boiling acetone (1 g. in 2 c.c.) twice, from which it separates in anhydrous prisms, m. p. 136—137°, or from 66% aqueous acetone in rhombohedra containing $2H_2O$, m. p. 77°, $[\alpha]_D^{15°}$ + 125·2° or + 109·0° (*c* = 1, alcohol) (Found: loss on drying at 45° in a vacuum, 10·1; calc. for $2H_2O$, 10·0%. Found for dry substance: C, 74·2; H, 7·4; N, 8·4; MeO, 9·1. Calc. for $C_{20}H_{24}O_2N_2$: C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%). Domański and Suszko give for the product crystallised from aqueous acetone and containing $1H_2O$, m. p. 80° or 130—133° from dry acetone, and $[\alpha]_D^{15°}$ + 111° (*c* = 0·7815, 96% alcohol). The hydrochloride, $B,HCl,4H_2O$, had m. p. 88—90° or 237° (dry)

and $[\alpha]_D^{15°}$ + 20·3°; Domański and Suszko give m. p. 224°, $[\alpha]_D^{15°}$ + 16° (*c* = 0·8, water). α-*iso*Quinidine could not be hydrogenated in presence of Adams's platinic oxide catalyst.

γ-*iso*Quinidine acid nitrate, isolated as described, was purified by recrystallisation from boiling water (1 g. in 8 c.c.); the base recovered from it crystallised from wet ether in long prisms, m. p. 83—84° (air-dry), $[\alpha]_D^{15°}$ + 67·8° or + 51° (alcohol) (Found : loss on drying at 120° in a vacuum, 10·25. Calc. for $C_{20}H_{24}O_2N_2,2H_2O$: loss, 10·0%. Found for dry substance : C, 74·3; H, 7·45; N, 8·7; MeO, 9·6. Calc. for $C_{20}H_{24}O_2N_2$: C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%). The neutral hydrochloride has m. p. 163—165°, $[\alpha]_D^{15°}$ − 12·6° (water) (Found : loss on drying at 120° in a vacuum, 6·3. Calc. for $C_{20}H_{24}O_2N_2,HCl,1·5H_2O$: loss, 6·9%). The dinitrate crystallises from boiling water in anhydrous needles, m. p. 213° (decomp.), $[\alpha]_D^{15°}$ + 53·3° (water). Domański and Suszko (*loc. cit.*) give for γ-*iso*quinidine, needles, m. p. 70°, $[\alpha]_D^{15°}$ + 51·1° (*c* = 0·9, alcohol); dinitrate, needles, m. p. 196°, $[\alpha]_D^{16°}$ + 50° (water). γ-*iso*Quinidine, like the α-and β-isomerides, resisted catalytic hydrogenation.

Quinidine Transformation Products. Type (III).

The products so far obtained are α-hydroxydihydro*apo*quinidine and its methyl ether, and β-hydroxydihydro*apo*quinidine, with what is possibly its methyl ether, though the two have not yet been definitely related.

α-*Hydroxydihydro*apo*quinidine* (III; Q = 6-hydroxyquinolyl).—This substance is best prepared from the ethereal extract of the carbonated precipitation liquors as described for the analogous derivative of quinine (Part II, p. 968). The extract amounts to about 4% by weight of the quinidine used. On solution in alcohol (1 g. in 1 c.c.) and neutralisation by dilute hydrochloric acid (10%), it yielded a crop of neutral hydrochloride, which was purified by crystallisation from alcohol, water, and 40% alcohol in succession. The *base* was recovered by pouring a solution of the salt in dilute hydrochloric acid into excess of sodium hydroxide solution, passing carbon dioxide into the liquid, and subjecting the latter to prolonged automatic extraction with ether. It crystallises from ether in prisms, which after drying in a vacuum, first at 60° and finally at 120°, swell at 170° and melt to a clear liquid at 205°, $[\alpha]_D^{15°}$ + 252·6° or + 204·7° (*c* = 1, alcohol) (Found : loss on drying at 120° in a vacuum, 11·1%. Found for dry substance : C, 69·7; H, 7·6; N, 8·1. $C_{19}H_{24}O_3N_2$ requires C, 69·5; H, 7·4; N, 8·5). The *hydrochloride* forms small needles, m. p. 203—204°, $[\alpha]_D^{15°}$ + 165·3° (Found : loss on drying at 120° in a vacuum, 4·9. $C_{19}H_{24}O_3N_2,HCl,H_2O$ requires H_2O, 4·7%. Found for dry salt : N, 7·3; Cl, 9·5. $C_{19}H_{24}O_3N_2,HCl$ requires N, 7·7; Cl, 9·7%). With diazomethane the base gave a poor yield (30%) of methyl ether, crystallising from acetone, or alcohol–ether, in prisms, m. p. 145—150°, $[\alpha]_D^{15°}$ + 241·5° (Found : loss on drying at 120° in a vacuum, 4·9%). This methyl ether has not been found among the quinidine transformation products.

β-*Hydroxydihydro*apo*quinidine* (III; Q = 6-hydroxyquinolyl).—The mother-liquors from the separation of the neutral hydrochloride of the α-hydroxy-base are rendered just acid to Congo-red paper with hydrochloric acid and evaporated to dryness, and the residue of acid hydrochloride dissolved in the minimum quantity of boiling absolute alcohol. The crop is a mixture of acid hydrochlorides of the two hydroxy-bases. It is reconverted into neutral hydrochloride, and recrystallised once from alcohol, and then from water (1 g. in 4 c.c.) until the specific rotation is constant. The *base* crystallises from alcohol in small prisms, m. p. 190° (decomp.), $[\alpha]_D^{20°}$ + 197° (*c* = 0·5, alcohol), which is equivalent to + 224·6° for the base free from the retained molecule of alcohol. It loses nothing on drying at 115° in a vacuum, but the analytical results indicate that it still retains one mol. of alcohol (Found : C, 67·3; H, 8·4; N, 7·2. $C_{19}H_{24}O_3N_2,C_2H_5·OH$ requires C, 67·4; H, 8·1; N, 7·5%). The *hydrochloride* crystallises from water in anhydrous prisms, m. p. 300° (decomp.), $[\alpha]_D^{16°}$ + 201·0° (water) (Found : C, 63·0; H, 7·0; N, 7·3; Cl, 9·65. $C_{19}H_{24}O_3N_2,HCl$ requires C, 62·5; H, 6·9; N, 7·7; Cl, 9·7%).

The quantity of β-hydroxydihydro*apo*quinidine available is so small that its methylation has not been attempted.

Hydroxydihydroquinidine (III; Q = 6-methoxyquinolyl).—This substance occurs in the precipitation liquors obtained in the preparation of *iso*quinidines by the action of 70% sulphuric acid (p. 597). It was isolated by long-continued automatic extraction of the liquors with ether. The crude extract obtained, on solution in boiling acetone (1 g. in 2 c.c.), gave a crystalline crop, which was recrystallised twice from alcohol. The *base* separates from alcohol in small anhydrous prisms, m. p. 257°, $[\alpha]_D$ + 298·5° or + 225·3° (*c* = 1, alcohol) (Found : C, 70·6; H, 7·8; N, 8·2; MeO, 8·9. $C_{20}H_{26}O_3N_2$ requires C, 70·1; H, 7·6; N, 8·2; MeO, 9·1%). The hydrochloride crystallises from boiling absolute alcohol (1 g. in 3 c.c.) in prisms, m. p. 277° (decomp.), $[\alpha]_D^{15°}$ + 198·6°. This substance may be the methyl ether of β-hydroxydihydro*apo*quinidine.

Relative Stability of Quinidine Transformation Products to Potassium Permanganate.—To 5 c.c. of a 2% solution in water of the acid sulphate of the alkaloid, 0·3 c.c. of *N*-sulphuric acid was added, followed by 0·5 c.c. of *N*/50-potassium permanganate. With quinidine isomerides of types (I) and (VI), as well as with hydroxydihydroquinidine, the colour disappeared immediately; with isomerides of type (II) it was discharged in 3—3·5 minutes, and with dihydroquinidine the colour persisted for about 10 minutes.

Transformation Products of Quinine. Type (I).

The products of this type described already are *apo*quinine (Part I, p. 1927), its methyl ether, β-*iso*quinine (Part II, p. 968), and *isoapo*quinine (Part II, p. 967). The following account relates to experiments with the two last-mentioned substances.

Methylation of isoapo*Quinine to* α-iso*Quinine* (isoapo*Quinine Methyl Ether*).—*isoapo*Quinine gave with ethereal diazomethane in cold methyl-alcoholic solution a 44% yield of the crude methyl ether, which on recrystallisation from benzene or acetone (charcoal) formed glistening masses of colourless needles, m. p. 192—194° (with some sintering at 188—189°), $[\alpha]_D^{15°}$ — 364·3° or — 253·4° (alcohol) (Found: C, 74·3; H, 7·6; N, 8·45; MeO, 9·45. Calc. for $C_{20}H_{24}O_2N_2$: C, 74·0; H, 7·5; N, 8·6; MeO, 9·6%). These results leave no doubt of its identity with α-*iso*quinine, for which Böttcher and Horowitz (*Monatsh.*, 1912, **33**, 567) record m. p. 196·5°, $[\alpha]_D^{18°}$ — 245° (c = 1) and — 248° (c = 0·5) in alcohol. In agreement with these authors' results the air-dry hydrochloride loses 2·3% on drying at 120° in a vacuum and re-gains 1·9% on exposure to air (Calc. for $C_{20}H_{24}O_2N_2,HCl,1/3H_2O$: H_2O, 1·6%. Found for dry substance: Cl, 9·8. Calc. for $C_{20}H_{24}O_2N_2,HCl$: Cl, 9·8%). The tartrate forms minute granules from aqueous alcohol as the alcohol is evaporated, and is less soluble in water or alcohol than β-*iso*quinine (*apo*quinine methyl ether) tartrate; m. p. 207—210° (corr., decomp.), $[\alpha]_D^{15°}$ — 206·5° ($c = M/80$; dry alcohol) [Found: C, 65·7; H, 7·1; N, 7·1. Calc. for $(C_{20}H_{24}O_2N_2)_2,C_4H_6O_6$: C, 66·1; H, 6·8; N, 7·0%].

Hydrogenation of β-iso*Quinine.* epi-C_3-*Dihydroquinine.*—β-*iso*Quinine, on catalytic hydrogenation in the manner described for the quinidine isomerides (p. 596), gave a crude product, m. p. 165°, $[\alpha]_D^{15°}$ — 255·7°, which after cleaning by a single crystallisation as the neutral sulphate, was freed from dihydroquinine by repeated crystallisation of the dihydrobromide from hot water, to constant optical rotation, $[\alpha]_D^{15°}$ — 184°, which is equivalent to — 275·4° for the base. The *dihydrobromide* crystallises in glistening colourless rosettes of flattened needles, which become bright yellow on drying in a vacuous desiccator and decolourise in a few minutes on re-exposure to air. The salt sinters from 225° and is completely decomposed at 234° (Found: loss on drying at 120° in a vacuum, 9·6. $C_{20}H_{26}O_2N_2,2HBr,3H_2O$ requires loss, 9·9%. Found for dry salt: C, 49·5; H, 6·2; N, 5·6; Br, 32·4; MeO, 6·3. $C_{20}H_{26}O_2N_2,2HBr$ requires C, 49·1; H, 5·8; N, 5·7; Br, 32·7; MeO, 6·3%).

The *base* recovered from the dihydrobromide crystallises on evaporation of the ether used for extraction and shows no change of m. p., 169°, on recrystallisation from benzene (Found for substance dried at 120° in a vacuum: C, 73·6; H, 8·2; N, 8·6. $C_{20}H_{26}O_2N_2$ requires C, 73·6; H, 8·0; N, 8·6%). As already pointed out (p. 593), this substance must be *epi*-C_3-dihydroquinine. Though the dihydrobromide provided a ready means of separating the isomeride of higher rotation, it was much less satisfactory for the isolation of the second component, since, like most salts of dihydroquinine except the sulphate, it was very soluble in water. By persistent recrystallisation of the middle fractions and accumulation of the ultimate residues a small fraction of slightly coloured but well-crystallised material was obtained having $[\alpha]_D^{16°}$ — 158·3°. Dihydroquinine dihydrobromide has $[\alpha]_D^{16°}$ — 157·5°. This and similar small fractions were mixed and converted into the neutral sulphate, which was obtained in the characteristic colourless, hair-like needles of dihydroquinine sulphate. The specimen lost 11·9% on drying in a vacuum at 120° and had $[\alpha]_D^{16°}$ — 206°, which is equivalent to $[\alpha]_D^{16°}$ — 237° for the base. Dihydroquinine sulphate, $(C_{20}H_{26}O_2N_2)_2,H_2SO_4,6H_2O$, requires loss on drying, 12·6% and has $[\alpha]_D$ — 204·6°, equivalent to — 235·4° for the base.

Hydrogenation of α-iso*Quinine.*—Reduction and the separation of the components were effected as described in the preceding paragraph. The initial base, purified through the sulphate, had $[\alpha]_D^{15°}$ — 253·8°. The dihydrobromide of highest rotation obtained had $[\alpha]_D^{16°}$ — 184·0° and agreed in characters with the *epi*-C_3-dihydroquinine dihydrobromide described above. The sulphate prepared from the ultimate mother-liquors had $[\alpha]_D^{15°}$ — 206·4° and had the characteristics of dihydroquinine sulphate.

Ozonisation of n-*Butyl*apo*quinine.*—A preliminary ozonisation experiment with *apo*quinine having given unpromising results, the experiment was repeated with *n*-butyl*apo*quinine, of

which a considerable quantity had been prepared for another purpose. The ether (3 g.) in chloroform (60 c.c.) was ozonised at 0° during 4½ hours. The yellowish product (3·3 g.) which separated during the operation was collected and hydrolysed with boiling water in an apparatus arranged for distillation; the distillate was collected in fractions, each of which was treated with *p*-nitrophenylhydrazine (cf. Reynolds and Robinson, J., 1934, 594). An orange-coloured crystalline precipitate formed in minute amount (0·05 g.). This had m. p. 118—122° after a single crystallisation from dilute alcohol. An authentic specimen of acetaldehyde-*p*-nitrophenylhydrazone had m. p. 124—127° and a mixture of the two had m. p. 121—125°. A second crystallisation failed to raise the m. p. (Found: C, 54·2; H, 5·4; N, 23·6. Calc. for acetaldehyde-*p*-nitrophenylhydrazone, $C_8H_9O_2N_3$: C, 53·6; H, 5·0; N, 23·5%. Calc. for formaldehyde-*p*-nitrophenylhydrazone, $C_7H_7O_2N_3$: C, 50·9; H, 4·25; N, 25·4%).

Transformation Products of Quinine. Type (III).

*Hydroxydihydro*apo*quinines* (*Hydroxydihydrocupreines*).—One of these isomerides has been described already (Part II, p. 968). It is proposed to distinguish that form as α-hydroxydihydro*apo*quinine. The process already described (Part I, p. 1927) for the isolation of the components of crude " apoquinine " has been improved by repeating the solution of the mixture in sodium hydroxide solution and reprecipitation by the passage of carbon dioxide several times, usually five. The final precipitate consists almost wholly of *apo*quinine and *isoapo*quinine, which can be separated by fractional crystallisation of the dihydrobromides from alcohol, in which the *apo*quinine salt is the less soluble, and from water, in which the *isoapo*quinine salt is the less soluble.

The hydroxydihydro*apo*quinines remain dissolved in the alkaline, carbonated precipitation liquors and are recovered by the following method. The liquors are neutralised with acid, concentrated to low bulk, again made alkaline, and treated with carbon dioxide until precipitation ceases. The filtrate is extracted with ether in a continuous-extraction apparatus, usually for 7 days, and the extract added to the precipitate. The product on solution in alcohol deposits α-hydroxydihydro*apo*quinine as already described (Part II, p. 968). The residual bases, on conversion into dihydrobromides, furnish a crystalline deposit from boiling alcohol, consisting largely of minute leaflets (A) suspended in the mother-liquor and a small quantity of crystalline crusts (B) adhering to the sides of the flask. Though product (A) is somewhat less soluble than (B), it has proved impossible to separate them by crystallisation, but fortunately they can readily be separated mechanically. They are both hydroxydihydro*apo*quinines and it is proposed to distinguish them as β- and γ-. The γ-isomeride has not yet been obtained in sufficient quantity for description.

β-*Hydroxydihydro*apo*quinine*.—The purification of the crude β-dihydrobromide is effected by repeated crystallisation from alcohol (10—15 times may be necessary) and is controlled polarimetrically. The base remains dissolved when liberated from solutions of its salts even under conditions which usually lead to precipitation of phenolic bases. Its recovery can be effected as follows. The dihydrobromide, dissolved in water, is poured into a known slight excess of a solution of sodium hydroxide, and *N*-hydrochloric acid carefully added; precipitation begins after the known excess of alkali is neutralised but before the whole of the sodium presumably in combination with the phenolic base has been converted into sodium chloride, and the careful addition of *N*-hydrochloric acid is continued until precipitation ceases. The precipitate is filtered off, and the rest of the base recovered by extraction of the filtrate in a continuous-extraction apparatus. The *base* so recovered is dried, packed in a Soxhlet apparatus, and extracted by dry ether; it gradually accumulates in the flask as a buff-coloured, amorphous powder, which is very sparingly soluble in all ordinary solvents except alcohol. It melts indefinitely, and after some effervescence at about 120°, and has $[\alpha]_D^{15°}$ — 205·1°. The base loses 4·1% on drying in a vacuum at 95° and regains 2·9% on re-exposure to air (Found for dry base: C, 69·0; H, 7·85; N, 8·0. $C_{19}H_{24}O_3N_2$ requires C, 69·45; H, 7·4; N, 8·5%).

The *dihydrobromide* crystallises from alcohol or water in glistening, greyish or cream-tinted rectangular plates. It begins to decompose at 235° and froths at 245°, has $[\alpha]_D^{15°}$ — 141·9°, and is readily soluble in water, sparingly in alcohol (Found for substance dried at 110° in a vacuum: C, 47·15; H, 5·65; N, 5·6; Br, 31·5. $C_{19}H_{24}O_3N_2$,2HBr requires C, 46·5; H, 5·35; N, 5·7; Br, 32·6%). The salt is deficient in bromine, as has been noticed with other dihydrobromides in this series. The *hydrochloride* crystallises from alcohol in small, colourless needles. It darkens from about 200°, shrinks at about 240°, and froths at 255° to 260°. The salt becomes slightly discoloured on drying in a vacuum at 120° and loses less than 1% by weight (Found: C, 62·5; H, 6·9; N, 7·4; Cl, 9·7. $C_{19}H_{24}O_3N_2$,HCl requires C, 62·5; H, 6·9; N, 7·7; Cl, 9·7%).

The *sulphate* crystallises from a concentrated aqueous solution in yellowish leaflets; it melts in its own water of crystallisation below 100°, but the dry salt has m. p. 265—270° (decomp.) [Found: loss on drying in a vacuum at 120°, 16·8. $(C_{19}H_{24}O_3N_2)_2,H_2SO_4,8{\cdot}5H_2O$ requires loss, 16·9%. Found for dry salt: C, 60·4; H, 6·8; N, 7·25; S, 4·1. $(C_{19}H_{24}O_3N_2)_2,H_2SO_4$ requires C, 60·45; H, 6·7; N, 7·4; S, 4·3%]. The *d*-tartrate, $B_2,C_4H_6O_6$, separates from water in colourless needles with $2H_2O$ or from alcohol with $1C_2H_6O$. It decomposes at 235—240° and has $[\alpha]_D^{15°}$ − 99·5° (c = 0·5, alcohol). The acid dianisoyltartrate, $B,C_{20}H_{18}O_{10}$, crystallises from alcohol in colourless needles, m. p. 194—197° (decomp.), $[\alpha]_D^{15°}$ − 141·5° (c = 0·24, alcohol). The base could not be hydrogenated catalytically and on treatment with diazomethane gave an amorphous product, with a small amount of a crystalline substance, which appeared to be a quaternary compound.

*Methylation of α-Hydroxydihydro*apo*quinine* (Part II, p. 968).—The crude product resulting from the interaction of α-hydroxydihydro*apo*quinine (5 g.) in methyl alcohol (200 c.c.) and diazomethane (*ex* nitrosomethylurethane, 10 c.c.) in ether (125 c.c.) during 2 hours was crystallised once from alcohol–acetone to remove some tar, and then worked up as usual, being finally crystallised from boiling methyl alcohol. The *base* separated in felted, lustrous masses of needles, m. p. 247—249° (corr.), $[\alpha]_D^{15°}$ − 197·5° or − 119·1° ($c = M/40$, dry alcohol). It is almost insoluble in ether, benzene, or chloroform but dissolves in hot ethyl alcohol, the solution gelatinising on cooling (Found for substance dried at 120° in a vacuum: C, 70·2; H, 7·6; N, 8·1; MeO, 9·1. $C_{20}H_{26}O_3N_2$ requires C, 70·1; H, 7·7; N, 8·2; MeO, 9·1%). The *hydrochloride* crystallises from dilute methyl alcohol in silky needles, m. p. 255—259° (corr., decomp.), $[\alpha]_D^{15°}$ − 94·6° ($c = M/40$, dry alcohol) (Found: loss on drying at 120° in a vacuum, 10·5. $C_{20}H_{26}O_3N_2,HCl,2{\cdot}5H_2O$ requires H_2O, 10·6%. Found for dry substance: C, 63·3; H, 7·2; N, 7·3; Cl, 9·4; MeO, 7·8. $C_{20}H_{26}O_3N_2,HCl$ requires C, 63·4; H, 7·2; N, 7·4; Cl, 9·4; MeO, 8·2%). The *nitrate* crystallises from boiling water (1 g. in 20 c.c.) in matted, long needles, m. p. 226° (corr., decomp.) with previous sintering, $[\alpha]_D^{15°}$ − 103·8° ($c = M/40$, dry alcohol) (Found: loss on drying at 120° in a vacuum, 4·0. $C_{20}H_{26}O_3N_2,HNO_3,H_2O$ requires H_2O, 4·2%. Found for dry substance: N, 9·9. $C_{20}H_{26}O_3N_2,HNO_3$ requires N, 10·4%).

The results of protozoicidal and bactericidal tests with these substances and an extensive series of *apo*quinine ethers, for which we are indebted to Drs. Trevan and Buttle of the Wellcome Physiological Research Laboratories, will be published in full elsewhere, but it may now be pointed out that, whereas isomerides of type (I) have in general anti-malarial action comparable in kind and degree with that of the parent alkaloids (type IV), isomerides of type (II) and the hydration products (type III) exhibit no anti-malarial activity.

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