19. *Modified Cinchona Alkaloids. Part VIII. Niquine.*

By William Solomon.

Niquine, niquidine, and "δ-cinchonine," transformation products of quinine, quinidine, and cinchonine respectively, form a distinct class of analogously constituted, modified cinchona alkaloids. The first two are now shown to be stereoisomerides, and a study of the oxidation products of *dihydroniquine*, parallel with one which was carried out with dihydroniquidine (Part VII), confirms the structure, which, already assigned to the latter, must be common to both substances.

The action of mineral acids on the four typical cinchona alkaloids, (I), produces substances which are for the most part either structural isomerides or hydration products of the parent bases or of their demethylation products (Part IV, J., 1937, 592). Similar results are obtained in dehalogenating the halogenodihydro-compounds obtained by the addition of hydrogen halide to the vinyl group. In this case, however, the products include a different type of substance (II), in the formation of which the quinuclidine ring is ruptured with the production of a secondary amino-group; examples of this kind are the conversion of quinine into niquine (Skraup, *Ber.*, 1892, **25**, 2909; *Monatsh.*, 1893, **14**, 428), of cinchonine into δ-cinchonine (Jungfleisch and Léger, *Compt. rend.*, 1894, **118**, 30), afterwards recognised as an analogue of niquine (Langer, *Monatsh.*, 1901, **22**, 157), and of quinidine into niquidine (Domanski and Suszko, *Bull. Acad. Polonaise*, 1935, *A*, 457). It is not certain that any modification of the fourth alkaloid, cinchonidine, belongs to this class. These substances are formed in pairs of geometrical isomers; *e.g.*, "δ-cinchonine" is the α-cinchonhydrine of Léger (*Compt. rend.*, 1919, **169**, 797), and is accompanied by a β-isomer; "niquidine" is a mixture of niquidine and *iso*niquidine (Part VI, J., 1939, 240); and Skraup claimed an "*iso*niquine," but the present author has been unable to isolate this substance.

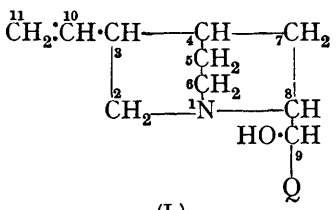
The recognition that these bases are analogous amongst themselves implies their stereochemical correspondence, and it seems probable that niquidine is 6-methoxy-α-cinchonhydrine and *iso*niquidine has the configuration of the β-isomer. That niquine

and one of the niquidines must be stereoisomers is now verified by the interconversion of their dihydro-derivatives (p. 82).

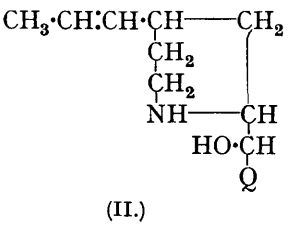
Until the results of the work on niquidine were obtained (Part VI, *loc. cit.*; Part VII, J., 1939, 1294), the constitution of these bases remained unsettled. Skraup observed that a reducing substance, now known to be formaldehyde, was produced in the reaction which gave rise to niquine, and proposed for the latter the formula $C_{19}H_{24}O_2N_2$, which contains one carbon atom less than quinine and is now known to be correct.

The information accumulated prior to 1939 may be summarised as follows: (*a*) niquine and its analogues retain intact the (methoxy)quinoline nucleus and central hydroxyl group of their parent alkaloids, and (*b*) the quinuclidine nitrogen atom becomes secondary, indicating rupture at one of three points. Confirmation of the splitting of a carbon atom as formaldehyde (Part VI) and the isolation of β-propylglutaric acid from the products of oxidation of dihydroniquidine with hydrogen peroxide (Part VII) sufficed to formulate niquidine as (II). The position of the forgotten double bond (see Léger, *loc. cit.*; *Ann. Chim.*, 1920, **14**, 59, 129) was confirmed in the case of niquidine (Part VI) and is now once more verified with niquine, by showing the presence of one *C*-methyl group (Kuhn–Roth). The existence of geometrical isomerides, which could be hydrogenated to one and the same dihydro-derivative, also supported the view that the double bond had shifted from the terminal carbon atom.

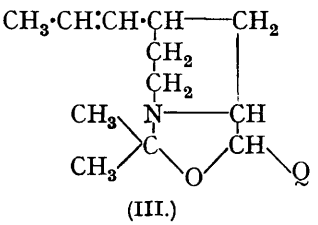
For the work now described, quinine was transformed into niquine in *ca.* 33% yields, concentrated hydriodic acid being used as the hydrohalogenating agent, and aqueous alcoholic potassium hydroxide for the dehalogenation. A further 33% of the quinine



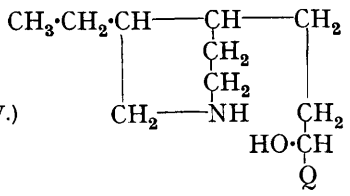
(I.)



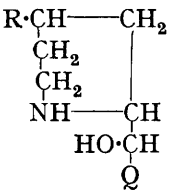
(II.)



(III.)



(V.)



(IV.)

Q = 4-Quinolyl or 6-methoxy-4-quinolyl.

was isolated as β-*iso*quinine; the remainder was uncrystallisable. In spite of the findings of several authors single attempts to de-iodinate with silver nitrate or with ammonia gave lower yields of niquine. This modified quinine alkaloid is now fully characterised. On catalytic hydrogenation it takes up two atoms of hydrogen, furnishing *dihydroniquine* (IV; R = propyl), which on boiling in dilute acetic acid is stereochemically converted into a mixture from which dihydroniquidine and *epi*-C_9-dihydroniquidine (Part VI) have been isolated, and which does not give the toxin reaction of Bachstez and Caro (*Arch. exp. Path. Pharm.*, 1932, **164**, 316); it seems that the modified cinchona alkaloids of this class are incapable of undergoing the Pasteur reaction to toxins (compare Part VI, and Suszko, *Bull. Acad. Polonaise*, 1925, *A*, 129, but contrast Domanski and Suszko, *loc. cit.*), but epimerise on boiling with dilute acetic acid. In view of the present results, moreover, this epimerisation seems to involve both carbon atoms 8 and 9, and a fourth epimeride, *epi*-C_9-dihydroniquine, probably remains undiscovered in the crude products obtained both from dihydroniquine and from dihydroniquidine.

Dihydroniquine, like dihydroniquidine, has now furnished quininic acid and β-propylglutaric acid on oxidation with hydrogen peroxide.

When niquine is heated with acetone, iso*propylideneniquine* (III) is formed. This substance does not react with methylmagnesium iodide in hot or cold anisole solution (Zerewitinoff), and thus differs from niquine, which furnishes one molecule of methane from the hydroxyl group in the cold and a further molecule from the imino-group at 130°. These results not only afford further evidence of the presence of both hydroxyl and the imino-group in niquine, but also show that (III) must be the formula of *iso*propylideneniquine. This compound, which is analogous to the acetone derivatives in the sugar series rather than to those formed by certain *iso*quinoline alkaloids, such as berberine-acetone and anhydrocotarnineacetone, is very unstable in acid solution, being readily hydrolysed to niquine and acetone, and attempts to prepare its salts furnish only the corresponding niquine salts and free acetone. It appears to be unusual for acetone to condense in this way with compounds having, not two adjacent hydroxyl groups, but one hydroxyl and one amino-group. Attempts to prepare the corresponding methylene derivative by treating niquine with formaldehyde gave inconclusive results.

Although the constitutions of niquine and its analogues have now been elucidated, the nature of the remarkable reaction which gives rise to these modified cinchona alkaloids remains obscure.

In bird malaria niquine and niquidine show a degree of activity almost equal to that of quinine (*Biochem. J.*, 1938, **32**, 47). This result is in good agreement with the theory of King and his co-workers (*Proc. Roy. Soc.*, 1938, *B*, **125**, 49, 60; J., 1940, 1307, 1315), according to which antiplasmodial activity is exhibited by 6-methoxyquinoline carbinolamines of the type (IV; R = H) or, more generally, of the type Q·CH(OH)·CH(NR′R″)·, to which the natural cinchona alkaloids belong. Inactivity results if the basic centre is removed to a remote position in the side chain, as in the dihydroquinicinols (V), which are of the type Q·CH(OH)·$[CH_2]_4$·CH(NR′R″)·. Niquine (IV; R = propenyl) and dihydroniquine (IV; R = propyl) clearly belong to the first of these two categories.

Experimental.

The m. p.'s are corrected. The optical rotations refer to M/40-solutions and were carried out with or are calculated for the anhydrous material.

Iododihydroquinine Dihydriodide (compare Skraup, *loc. cit.*; Schubert and Skraup, *Monatsh.*, 1891, **12**, 669).—Anhydrous quinine (20 g.) was heated with hydriodic acid (120 c.c., *d* 1·65—1·7, decolorised by heating with red phosphorus) for 1·5 hours on a water-bath. The yellow crystalline product was cooled, filtered off, and washed with alcohol (yield, 35 g.). The salt began to decompose at about 220° and frothed at 238°.

De-iodination of Iododihydroquinine (Skraup, *loc. cit.*).—A solution of the foregoing dihydriodide (35 g.) in hot aqueous alcohol was treated with a hot aqueous solution of potassium hydroxide (54 g.) (total alcohol, 300 c.c.; total water, 250 c.c.) and refluxed for 1 hour. No formaldehyde was detected (dimedon bubbler) even after concentration of the solution to low bulk under diminished pressure. The product, consisting essentially of β-*iso*quinine and niquine, separated as a pale yellow oil, which, with progressive removal of alcohol, thickened to a plastic mass, becoming brittle on cooling. The separated mass was dissolved in hot alcohol (40 c.c.), and a warm solution of crystallised oxalic acid (14 g.) in acetone (50 c.c.) added. The crystalline niquine acid oxalate was filtered off and washed with alcohol; it contained potassium oxalate and the average yield was 10—15 g., corresponding to 6·5—9·5 g. of dry base. The salt was dissolved in dilute mineral acid and introduced in a slow thin stream into a well-stirred solution of caustic alkali. The resulting precipitate was crystalline, and was reconverted into the acid oxalate in aqueous alcoholic solution. Final purification was effected either by repeating this process a third time or by crystallising the base from ether or acetone. The original crude oxalate filtrate, when steam-distilled, furnished formaldehyde (isolated as the dimedon compound, m. p. and mixed m. p. 190—192°), and after treatment with sodium hydroxide yielded to ether a base, which crystallised (later fractions from acetone) and consisted of crude β-*iso*quinine, m. p. *ca.* 175° (total crystalline yield, about 7 g.) (see Part II, J., 1935, 968).

Niquine.—A solution of the base in ether, treated with a few drops of water, deposits a dense mass of feathery needles, m. p. *ca.* 100° (Found: loss in a vacuum over sulphuric acid, 9·0. Calc. for $C_{19}H_{24}O_2N_2,2H_2O$: H_2O, 10·3%); on prolonged heating it sinters at lower temperatures. The base crystallises from acetone in colourless needles, anhydrous when the

solvent is dry, but usually containing up to $1H_2O$. When solutions of niquine in acetone are kept or subjected to prolonged heating, some *iso*propylideneniquine (III) is formed (see below). Anhydrous niquine has m. p. 137° after sintering at 130°; it is very readily soluble in alcohol, readily in warm acetone, fairly readily in warm, dry ether, but sparingly in cold acetone and very sparingly in cold or moist ether or in water. Its solutions are colourless and show a blue fluorescence in dilute sulphuric acid. The solid base, which shows no tendency to turn yellow on exposure, dissolves in semicarbazide acetate solution without the production of an insoluble derivative, and crystallises unchanged from liquid phenylhydrazine. The base has $[\alpha]_D^{15°}$ — 248·0° (0·1N-sulphuric acid), or — 132·2° (alcohol) [Found for the anhydrous base: C, 73·3; H, 7·7; N, 9·0; OMe, 10·0; CMe (Kuhn–Roth), 8·4; OH (Zerewitinoff in anisole), 5·4; NH (temperature raised to 130° after preceding determination), 4·5. Calc. for $C_{19}H_{24}O_2N_2$: C, 73·0; H, 7·75; N, 9·0; OMe, 9·9; CMe, 8·65; OH, 5·4; NH, 4·8%]. Niquine hydrochloride crystallises from water or alcohol in yellowish needles, m. p. 197° (sinters), $[\alpha]_D^{15°}$ — 147·9° (water), or — 216·1° (0·1N-hydrochloric acid). The last figure corresponds to — 242° when recalculated for base. The air-dried salt contains a little less than $1H_2O$. The neutral sulphate crystallises from water, alcohol, or aqueous alcohol; it is sparingly soluble in cold water, more readily in alcohol or hot water, and crystallises best from water in thin platelets or flakes, which melt in their own water of crystallisation at about 65°, re-solidify, and then melt again at 160—170°. This salt separates from alcohol or aqueous alcohol in fluffy masses of needles, m. p. 160—170°. The acid sulphate crystallises from water in colourless needles, which sinter at 75° and melt at 165—168° (Found: loss at 65—70° in a vacuum, 23·0. Calc. for $C_{19}H_{24}O_2N_2,H_2SO_4,7H_2O$: H_2O, 23·5%). The anhydrous salt on exposure reabsorbs $2H_2O$. Skraup states that this salt contains 3·5 H_2O. It has $[\alpha]_D^{15°}$ — 187·5° (water), and this corresponds to — 246·4° for the base. *Niquine dihydrobromide* crystallises from water or alcohol in almost colourless, anhydrous needles, readily soluble in cold water, very readily in hot water, and sparingly in alcohol. It decomposes at 242—244° after darkening from about 190° onwards, and has $[\alpha]_D^{15°}$ — 161·7°, — 164·1° (water), equivalent to — 245·5° and — 249·2° expressed as base (Found: C, 48·2; H, 5·6; N, 5·9; Br, 33·5. $C_{19}H_{24}O_2N_2,2HBr$ requires C, 48·1; H, 5·5; N, 5·9; Br, 33·7%). Niquine acid oxalate crystallises from hot alcohol in colourless felted needles, m. p. 198—200° (decomp.) with previous darkening. It is very sparingly soluble in water, alcohol, and acetone (Found: C, 56·4; H, 5·8; N, 5·9. Calc. for $C_{19}H_{24}O_2N_2,2C_2H_2O_4$: C, 56·1; H, 5·7; N, 5·7%). The *acid dianisoyl*-d-*tartrate* separates from acetone in soft needles which sinter and decompose between 100° and 150°, $[\alpha]_D^{15°}$ — 153·0° (alcohol) (Found for air-dried salt: loss at 95° in a vacuum, 4·1. Found for salt so dried: C, 64·1; H, 6·05; OMe, 13·5. $C_{19}H_{24}O_2N_2,C_{20}H_{18}O_{10},2H_2O$ requires H_2O, 4·7%. $C_{19}H_{24}O_2N_2,C_{20}H_{18}O_{10}$ requires C, 64·1; H, 5·8; OMe, 12·7%). Niquine nitrate crystallises from 20% alcohol in colourless, tough, square plates of a stratified structure, m. p. 134—139°. It is soluble in alcohol but very sparingly in water.

iso*Propylideneniquine* (III) was prepared by heating niquine (1 g.) with acetone (10 c.c.) in a sealed tube at 105° for 7 hours and crystallising the product from acetone. It was also found in the mother-liquors from crystallisations of niquine from acetone, particularly when these had stood for some time. It separates from acetone in stout, transparent, faintly coloured, prismatic rods, unsymmetrically pointed at their ends, and of unsymmetrical heptagonal cross-section; when allowed to crystallise slowly, these may exceed 1 cm. in length. The substance, which tends to develop a faint pink tinge in solution or when ground, has m. p. 158—160°, $[\alpha]_D^{16°}$ — 123·3° (alcohol) or — 216° (0·1N-sulphuric acid), and undergoes no loss when heated at 115° in a vacuum [Found: C, 74·9; H, 7·8; N, 7·9; OMe, 8·9; CMe (Kuhn–Roth), 5·0; OH (Zerewitinoff in anisole), 0·4; NH (temperature raised to 120° after preceding determination), 0·05. $C_{22}H_{28}O_2N_2$ requires C, 74·95; H, 8·0; N, 7·95; OMe, 8·8; CMe, 7·6%]. No acetone distils from alcoholic solutions of *iso*propylideneniquine, but when such solutions are neutralised with aqueous mineral acids, or when the solid base is dissolved in dilute mineral acids, the resulting solutions contain free acetone which can be distilled off. The acetone was detected in the distillate by the Legal nitroprusside test and was isolated as the *p*-nitrophenylhydrazone, m. p. 146—150°, which, when mixed with an authentic specimen, m. p. 150—152°, showed mixed m. p. 147—151°. Such neutralised or acidified solutions of the base contain also free niquine, the salts of which crystallise when these solutions are evaporated. In view of this behaviour of *iso*propylideneniquine in acid solution, it is hardly surprising that its specific rotation in 0·1N-sulphuric acid should be lower than the corresponding figure for niquine very nearly in proportion of the molecular weights of the two bases, but there is no perceptible mutarotation which might have signified hydrolysis during the actual deter-

mination. *iso*Propylideneniquine in alcoholic solution absorbs one molecule of hydrogen in presence of Adams's platinic oxide catalyst, but the product has not been isolated; when neutralised, the reduced solution furnishes salts of dihydroniquine. An attempt to prepare " methyleneniquine " by heating niquine (2 g.) with 40% aqueous formaldehyde (20 c.c.) in a sealed tube at 95—105° for 7 hours furnished an amorphous, ether-soluble base (1·46 g.), which in alcoholic solution absorbed 117 c.c. of hydrogen in presence of Adams's platinic oxide catalyst. The reduced compound was itself amorphous, and was expected, by analogy, to furnish on neutralisation salts of dihydroniquine. Unlike the latter, however, the substance would not crystallise as hydrochloride, sulphate, or dihydrobromide.

Dihydroniquine (IV; R = $CH_3 \cdot CH_2 \cdot CH_2$) was prepared by hydrogenating a solution of niquine (10 g.) in 5% hydrochloric acid (200 c.c.) in the presence of Adams's platinic oxide catalyst (0·1 g.). The reduction proceeded rapidly, particularly if the niquine solution was first filtered through kieselguhr, and was complete in 3 hours. After removal of the catalyst, the base was discharged to ether by sodium hydroxide solution; it crystallised from ether in tufts of soft, feathery needles, which sintered at 50°, became translucent at 65°, and gradually melted to a colourless oil at 85°. The needles, $[\alpha]_D^{16°}$ — 210·1° (0·1N-sulphuric acid), contain $1·5H_2O$, which can be expelled in a vacuum over sulphuric acid, $1H_2O$ being re-absorbed on exposure (Found: C, 72·1; H, 8·2; N, 8·7. $C_{19}H_{26}O_2N_2$ requires C, 72·6; H, 8·3; N, 8·9%). The *hydrochloride* crystallises from water in colourless, brittle needles, m. p. 185°, $[\alpha]_D$ — 190° to — 192° (0·1N-hydrochloric acid), sparingly soluble in water, more easily in alcohol (Found: loss at 110° in a vacuum, 3·7—4·2. $C_{19}H_{26}O_2N_2,HCl,H_2O$ requires H_2O, 4·9%. Found in salt so dried: C, 64·5; H, 8·0; N, 7·95; Cl, 10·1. $C_{19}H_{26}O_2N_2,HCl$ requires C, 65·0; H, 7·8; N, 8·0; Cl, 10·1%). The *sulphate* crystallises from aqueous alcohol or from water in colourless feathery needles, m. p. 172° (decomp.) after softening, and seems to have the composition $B_3,2H_2SO_4$. It is sparingly soluble in alcohol and very sparingly in water. Its water content is variable, and drying figures at temperatures ranging from 100° to 150° in a vacuum include 7·45 as a minimum, and 16·3% as a maximum, corresponding to $B_3,2H_2SO_4,5H_2O$ and $B_3,2H_2SO_4,12·5H_2O$ respectively (Found in anhydrous salt: C, 59·85; H, 7·3; N, 7·45. $3C_{19}H_{26}O_2N_2,2H_2SO_4$ requires C, 60·1; H, 7·25; N, 7·4%). No satisfactory sulphur values could be obtained. The acid oxalate crystallises from aqueous alcohol in faintly pink needles, m. p. 207° after sintering at 180°. The dihydrobromide crystallises from water in tiny, brittle, anhydrous needles, m. p. 248° (decomp.) after darkening from about 210° onwards, $[\alpha]_D^{15°}$ — 134·5°, — 137·9° (water). *Nitrosodihydroniquine* was prepared by cooling in ice a solution of dihydroniquine hydrochloride (0·5 g.) in dilute hydrochloric acid (20 c.c.) and adding a large excess of a concentrated solution of sodium nitrite. An oil formed, which crystallised on standing (0·49 g.). This nitroso-nitrate, which crystallised from alcohol in circular sheaves of fine colourless needles and was very sparingly soluble in water, was dissolved in alcohol and treated with aqueous sodium hydroxide; the solution was evaporated to low bulk and extracted with ether. The aqueous liquor gave the reactions of nitrate but not of nitrite, showing that dihydroniquine, like niquine, gives with nitrous acid the nitroso-nitrate and not the nitroso-nitrite or hydrochloride (compare Skraup). The ethereal extract deposited on concentration transparent, anhydrous, almost colourless, irregular plates, m. p. 131° (Found: C, 66·4; H, 7·5; N, 12·0. $C_{19}H_{25}O_3N_3$ requires C, 66·4; H, 7·3; N, 12·2%).

N-*Methyldihydroniquine*.—A warm, two-phase mixture of a solution of dihydroniquine (26 g.) in ether (600 c.c.) and 10% sodium carbonate solution (105 c.c.) was shaken for 2 hours with methyl sulphate (11 g.). The golden-brown ethereal layer was washed with alkalised water and refluxed with charcoal; it then furnished a crystalline residue (19 g.), which was recrystallised from acetone (35 c.c.)–petroleum (b. p. 60—80°; 100 c.c.). This *base* (17·5 g.) separated from acetone in silky, colourless needles, m. p. 121°, $[\alpha]_D^{15°}$ — 227·3° (0·1N-hydrochloric acid) or — 169·9° (alcohol) (Found: loss at 95° in a vacuum, 4·9. Found for the base so dried: C, 73·0; H, 8·6; N, 8·3; OMe, 9·8; NMe, 8·2. $C_{20}H_{28}O_2N_2,H_2O$ requires H_2O, 5·2%. $C_{20}H_{28}O_2N_2$ requires C, 73·15; H, 8·6; N, 8·5; OMe, 9·45; NMe, 8·8%). The *tartrate* crystallised from acetone in felted needles, m. p. 134—136°, $[\alpha]_D^{17°}$ — 113·1° (water) (Found: loss at 90° in a vacuum, 3·4. Found for the salt so dried: C, 65·2; H, 7·8; N, 6·9. $2C_{20}H_{28}O_2N_2,C_4H_6O_6,1·5H_2O$ requires H_2O, 3·2%. $2C_{20}H_{28}O_2N_2,C_4H_6O_6$ requires C, 65·5; H, 7·75; N, 6·9%). The methiodide crystallised from acetone in tiny, fawn-coloured, granular masses of needles, m. p. 216—218° (decomp.).

Epimerisation of Dihydroniquine by Boiling Dilute Acetic Acid.—Dihydroniquine hydrochloride (5 g.) was refluxed with 10% acetic acid (55 c.c.) for 24 hours. The basic product (4·4 g.), discharged to ether by sodium hydroxide solution, was an optically inactive, brown oil,

which gave no reaction for cinchonatoxins with the sodium nitroprusside reagent of Bachstez and Caro (*loc. cit.*); it contained dihydroniquidine and *epi*-C_9-dihydroniquidine (see Part VI). The former was isolated as crude acid oxalate by converting the total product into that salt and crystallising it from water as far as possible. The uncrystallisable mother-liquors, containing about two-thirds of the original material, were then worked up for base and converted into acid hydrobromide in aqueous solution. Crude *epi*-C_9-dihydroniquidine sesquihydrobromide (see Part VI) separated, and after recovery of as much as would crystallise, there was left about one-third of the original material, and this would not crystallise as oxalate, hydrobromide, hydrochloride, or tartrate.

Dihydroniquidine from Epimerisation of Dihydroniquine.—From the crops of dihydroniquidine acid oxalate obtained above, the base was recovered and crystallised several times from ether and from acetone. It had m. p. and mixed m. p. 166—168°, $[\alpha]_D^{17°}$ + 230·2° (0·1N-hydrochloric acid), and $[\alpha]_D^{20°}$ + 124·8° (alcohol). [The corresponding figures given in Part VI for this substance as obtained from quinidine *via* niquidine were m. p. 165°, $[\alpha]_D^{18°}$ + 231·6° (0·1N-sulphuric acid), and $[\alpha]_D^{18°}$ + 126·8° (c = 1 in alcohol)] (Found: C, 72·25; H, 8·2; N, 8·9; OMe, 9·6. Calc. for $C_{19}H_{26}O_2N_2$: C, 72·6; H, 8·3; N, 8·9; OMe, 9·9%). The *hydrochloride* has m. p. 238° and $[\alpha]_D^{22°}$ + 206·3° (0·1N-hydrochloric acid) (Found: loss at 115° in a vacuum, 7·0. Found for the substance so dried: C, 64·65; H, 7·85; N, 7·7; Cl, 10·0; OMe, 8·5. $C_{19}H_{26}O_2N_2$,HCl,1·5H_2O requires H_2O, 7·15%. $C_{19}H_{26}O_2N_2$,HCl requires C, 65·0; H, 7·8; N, 8·0; Cl, 10·1; OMe, 8·8%). The acid oxalate crystallises from water or alcohol in tiny apricot-coloured needles, m. p. 189—191° after sintering at 165°. It is fairly readily soluble in water.

epi-C_9-*Dihydroniquidine from Epimerisation of Dihydroniquine.*—The crude substance, obtained above as sesquihydrobromide, was repeatedly recrystallised from water. The identity of the *epi*-C_9-dihydroniquidine so obtained with that prepared by the epimerisation of dihydroniquidine and described in Part VI, is apparent from the following table.

epi-C_9-*Dihydroniquidine.*

Derivative.	From dihydroniquine; or found (analytical figures).	From dihydroniquidine; quoted from Part VI, or calc. (analytical figures).
Base:	Oil:	Glass:
	$[\alpha]_D^{17°}$ −132° (0·1N-sulphuric acid)	$[\alpha]_D^{18°}$ −140·8° (0·1N-sulphuric acid)
Sesquihydrobromide	Felted needles from water, m. p. 241° (decomp.) with previous darkening, mixed m. p. 237°	Silky needles from 50% alcohol; B_2,3HBr,H_2O, m. p. 240°
	$[\alpha]_D^{18°}$ −106·0° (0·1N-sulphuric acid)	$[\alpha]_D^{18°}$ −102·8° (0·1N-sulphuric acid)
	Loss at 110° in a vacuum, 2·0%	Calc. for $(C_{19}H_{26}O_2N_2)_2$,3HBr,H_2O: H_2O, 2·1%
	C, 51·7; H, 6·4; N, 6·5; Br, 27·45; OMe, 7·15%	Calc. for $(C_{19}H_{26}O_2N_2)_2$,3HBr: C, 52·4; H, 6·4; N, 6·4; Br, 27·5; OMe, 7·1%
Sesquinitrate	Rosettes of needles from aqueous alcohol, m. p. 205° (decomp.), mixed m. p. 201°	Clusters of needles from alcohol, B_2,3HNO_3,2H_2O, m. p. 196° (decomp.). [On taking the m. p. of this specimen, 203° (decomp.) is now recorded]
	$[\alpha]_D^{17°}$ −113° (0·1N-sulphuric acid)	$[\alpha]_D^{18°}$ −110·3° (0·1N-sulphuric acid)
	Loss at 120° in a vacuum, 4·3%	Calc. for $(C_{19}H_{26}O_2N_2)_2$,3HNO_3,2H_2O: H_2O, 4·5%
	C, 55·7; H, 6·8; N, 11·6%	Calc. for $(C_{19}H_{26}O_2N_2)_2$,3HNO_3: C, 55·8; H, 6·7; N, 12·0%

Oxidation of Dihydroniquine with Hydrogen Peroxide.—Dihydroniquine (7·1 g.) was heated on a steam-bath with hydrogen peroxide ("90/100 volume"; 35·5 c.c.) for 2 hours. The product consisted of a dark crystalline paste containing much tar under a paler liquor. The latter was decanted, and the tarry paste boiled with water (35 c.c.) for 1 minute. After cooling, the supernatant liquor was decanted into the original one, and this process was repeated. The combined aqueous liquors were treated with sodium hydroxide until they were just alkaline to phenolphthalein, and were then boiled with traces of platinum-black until no further effervescence occurred and they no longer turned potassium iodide–starch paper blue. The vapours were alkaline to litmus. The solution was then nearly neutralised with dilute sulphuric acid, concentrated, and acidified and the crystalline quininic acid (2·43 g.) precipitated was removed (see below). The filtrate was repeatedly extracted with ether; the extracts in the course of concentration deposited a further amount of crude quininic acid (0·23 g.) and finally furnished an oil (2·61 g.); this was dissolved in water, and the solution filtered and evaporated to dry-

ness again (2·52 g.). This crude acid was refluxed for 20 minutes with thionyl chloride (20 c.c.), the mixture evaporated to dryness, and the residue dissolved in benzene and treated with a solution of aniline (3·5 g.) in benzene. The crystalline dianilide of β-propylglutaric acid (2·2 g.) was recrystallised from alcohol, 0·8 g. being obtained, m. p. and mixed m. p. 212—214° (the specimen used for admixture was that stated in Part VII to have m. p. 219°). The crude quininic acid (above) (2·43 g.) was boiled out with alcohol, and the filtrate allowed to crystallise. The crop (1·62 g.) showed m. p. 282°, which, for a mixture with authentic quininic acid (m. p. 296°), rose to 293°.

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