49. *Modified Cinchona Alkaloids. Part VI. Niquidine.*

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Owing to the difficulty of accounting for the loss of one atom of carbon in the formation of niquine from quinine, and of its analogue, niquidine, from quinidine, there has been a tendency to regard these two substances as isomerides of quinine, $C_{20}H_{24}O_2N_2$, although combustion results require the formula $C_{19}H_{24}O_2N_2$. It is now shown that one carbon atom is eliminated as formaldehyde in the conversion of quinidine into niquidine and that the latter is a mixture of two geometrical isomerides, $C_{19}H_{24}O_2N_2$, which have been fully examined and for which a new constitutional formula is suggested.

In Part IV (J., 1937, 592) the characters and constitution of the isomerides and other transformation products formed by the action of sulphuric acid (60%) on quinine and quinidine were discussed. The same isomerides are formed when the halogenodihydro-derivatives of these two alkaloids are dehalogenated, but they may then be accompanied, or largely replaced, by products of a different type, *viz.*, niquine from quinine and niquidine from quinidine. Niquine was first prepared by Skraup (*Ber.*, 1892, **25**, 2909; *Monatsh.*, 1893, **14**, 428), who assigned to it the formula $C_{19}H_{24}O_2N_2$, which differs from that of quinine by one atom of carbon. It has been repeatedly examined since then and though Skraup stated that a volatile reducing substance, probably formaldehyde, was formed in the reaction, later workers, *e.g.*, Rosenmund and Kittler (*Arch. Pharm.*, 1924, **262**, 18) and Reyman and Suszko (*Bull. Acad. Polonaise, A*, 1935, 360; cf. Suszko, *ibid.*, 1925, 129), in spite of the evidence of combustion results, have accepted the view that niquine is an isomeride of quinine, $C_{20}H_{24}O_2N_2$, mainly because of the difficulty of accounting for the loss of a carbon atom in the simple reactions by which it is formed. The same difficulty occurs with the quinidine analogue, niquidine, for which Domanski and Suszko (*ibid.*, 1935, 457) obtained combustion results agreeing with $C_{19}H_{24}O_2N_2$, though they regard their niquidine as probably stereoisomeric with niquine, for which Reyman and Suszko (*loc. cit.*) adopted the formula $C_{20}H_{24}O_2N_2$. The formula $C_{20}H_{26}O_2N_2$ was proposed by Léger (*Bull. Soc. chim.*, 1920, **27**, 58; *Ann. Chim.*, 1920, **14**, 183) for niquine on the ground of its similarity to the α- and β-cinchonhydrines, similarly obtainable from cinchonine, and which he represented as structural isomerides of dihydrocinchonine, $C_{19}H_{24}ON_2$, having the constitution (I, Q = quinolyl). On this basis niquine, and therefore also niquidine, is represented by (I, Q = 6-methoxyquinolyl), the only constitutional formula so far suggested for this substance.

In the present paper the preparation of niquidine by the dehalogenation of bromo- or iodo-dihydroquinidines is dealt with and an account is given of an investigation of this substance, the results of which differ considerably from those recorded by Domanski and Suszko (*loc. cit.*). In particular it has been found that the niquidine of these authors is a mixture of two isomerides. It is convenient to refer to this mixture as " niquidine," the name *niquidine*, without quotation marks, being retained for one of the isomerides, the other being called iso*niquidine*.

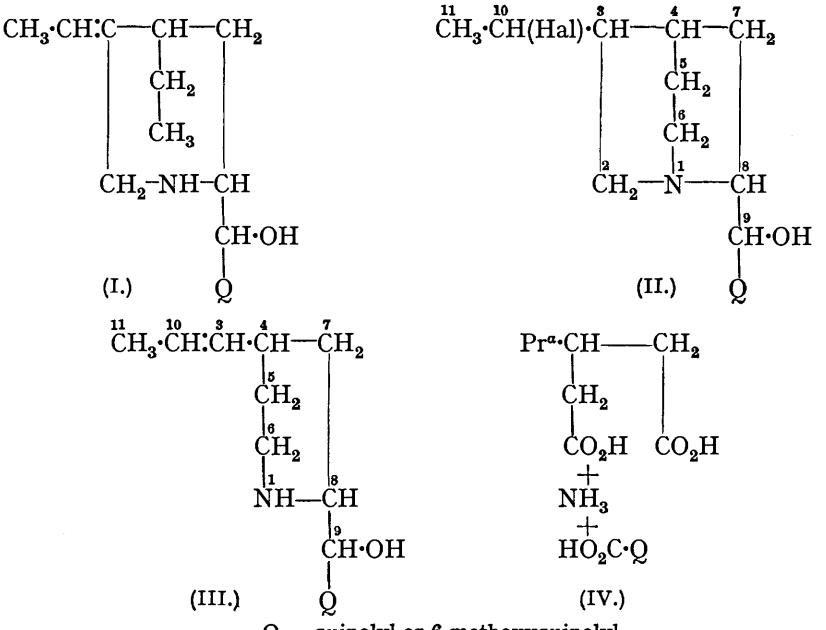
When the elements of a molecule of halogen acid are added to one of the cinchona alkaloids, it has been assumed generally that a centre of asymmetry is developed at C_{10} (II) and the resulting halogenodihydro-base occurs in two stereoisomeric forms, which may be distinguished as α- for the form of higher rotation and α'- for the other (Part III; Goodson, J., 1935, 1094). For the production of " niquidine " it has been necessary to prepare bromo- and iodo-dihydroquinidines in quantity, as primary materials, and in the course of this work α-iododihydroquinidine has been isolated in pure condition, as well as α- and *α'-bromodihydroquinidines*, though for the preparation of " niquidine " it is not necessary to separate the two forms.

After numerous experiments to determine which method gave the best yield of niquidine, the results of which are summarised in the experimental section, dehalogenation of the bromodihydroquinidines by silver nitrate was finally selected. This process gives yields of 50—70% of the theoretical, which are about 10 times as large as those obtained by

Domanski and Suszko (*loc. cit.*), who used potassium hydroxide in alcohol as a dehalogenating agent. In all cases the formation of " niquidine " is accompanied by the production of formaldehyde.

The " niquidine " so obtained, on recrystallisation as the dihydrobromide, separated into niquidine and *iso*niquidine, both represented by the formula $C_{19}H_{24}O_2N_2$. This composition makes it necessary to modify the Léger formula (I). The data already on record regarding niquidine are that it contains (*a*) one imino- and one hydroxyl group, as indicated by the formation of a nitroso-, a monoacetyl and a diacetyl derivative, (*b*) one ethylenic linkage, since it yields a dibromide, (*c*) the 6-methoxyquinoline nucleus of quinidine, as it furnishes quininic acid on oxidation by hydrogen peroxide (Domanski and Suszko, *loc. cit.*). All these points have been confirmed and further facts added in the present investigation. Niquidine and *iso*niquidine absorb one molecular proportion of hydrogen, forming the same *dihydroniquidine*, indicating that they are geometrical isomerides. On oxidation with a cold solution of potassium permanganate niquidine yields quininic acid and acetaldehyde. The latter implies the presence of a $CH_3{\cdot}CH{:}C{:}$ group and this is confirmed by Kuhn–Roth determinations, which give good results for one :CMe group in niquidine and *iso*niquidine, but low results for dihydroniquidine, which the authors have found to be the case generally for reduced cinchona bases in which the group $:C{:}CH{\cdot}CH_3$ has been converted into $:CH{\cdot}CH_2{\cdot}CH_3$ as in the reduction of β-*iso*quinine to dihydroquinine (Part IV, *loc. cit.*).

Domanski and Suszko found that niquidine on prolonged ebullition in dilute acetic acid underwent the Pasteur reaction and was converted into a quinatoxine (quinicine). The authors were unable to confirm this observation with niquidine, but found it more convenient to investigate the reaction with dihydroniquidine. The product was strongly lævorotatory, gave no derivatives with reagents for carbonyl groups, was fluorescent in acid solution, and yielded readily crystallisable salts, differing in all these and other respects from a typical quinatoxine. As the marked lævorotation of the substance suggested epimerisation at C_9, the series of reactions used in the conversion of quinidine into dihydroniquidine was applied to *epi*-C_9-quinidine. The resulting *epi*-C_9-dihydroniquidine was compared with the product described above, and found to be identical with it.



Q = quinolyl or 6-methoxyquinolyl.

This formation of *epi*-C_9-dihydroniquidine from quinidine implies the following changes at certain centres of asymmetry.

	Direction of rotation at				
	C_3.	C_4.	C_8.	C_9.	C_{10}.
Quinidine	+	−	+	+	nil
Bromodihydroquinidines	+	−	+	+	+ and −
Dihydroniquidine	nil	−	+	+	nil
epi-C_9-Dihydroniquidine	nil	−	+	−	nil

The fact that the nitrogen atom in niquidine is secondary indicates that, in the formation of this substance from quinidine, scission in the quinuclidine complex (II) must occur at the tertiary nitrogen linkage with C_2, C_6 or C_8, most probably C_2, a $-CH_2-$ group being eliminated as formaldehyde and hydrogen being added to the adjoining nitrogen and carbon atoms. On the assumption that it is the methylene group at position 2 which is eliminated, formula (III) represents niquidine and *iso*niquidine and, with the change of $CH_3{\cdot}CH{:}CH{\cdot} \longrightarrow CH_3{\cdot}CH_2{\cdot}CH_2{\cdot}$, dihydroniquidine. This formula accounts for the carbon atom lost in the conversion of quinidine into niquidine, and for all the reactions characteristic of the latter referred to above; it explains the existence of two niquidines as geometrical isomerides and their conversion into the same dihydroniquidine on hydrogenation. Niquidine and dihydroniquidine are now being examined by degradative methods with a view to confirming this formula. Oxidation in various ways has given promising results, which are not yet quite ready for publication, but it may be mentioned now that it has been clearly established that, alongside quininic acid and ammonia, β-propylglutaric acid (IV) is one of the oxidation products of dihydroniquidine, a fact which constitutes the first definite piece of evidence as to the nuclear structure of the " second half " of this type of substance, and which quite clearly supports formula (III) for niquidine and *iso*niquidine, and also for niquine, since the last is undoubtedly stereoisomeric with niquidine.

These considerably modified cinchona alkaloids are of some biological interest, as it has been found that, whereas in the natural cinchona alkaloids the lævorotatory bases are more efficient drugs, as tested in avian malaria, than the dextrorotatory forms the reverse is the case with the niquines and niquidines, niquidine itself having an activity of about the same order as dihydroquinine and being the most active dextrorotatory cinchona alkaloid so far found (Buttle, Henry, Solomon, Trevan, and Gibbs, *Biochem. J.*, 1938, **32**, 47).

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 name of the solvent used is given in parentheses.

Iododihydroquinidines.—Dry quinidine (25 g.), purified as already described (Part II, J., 1935, 969), was dissolved in hydriodic acid (*d* 1·94, 100 c.c.) previously decolorised by shaking with washed, red phosphorus. The solution was warmed at 70° for 2 minutes and set aside in the dark for 48 hours. The deposited iododihydroquinidine dihydriodide, m. p. 240° (decomp.), was collected, washed with dilute hydriodic acid and finally with water, and dried in a vacuous desiccator. Further crops of less pure material (m. p. 180—230°) were obtained by diluting the mother-liquors with water. The dihydriodide is sparingly soluble in water and dilute acids and the base is sparingly soluble in ether, so that recovery of the latter can only be effected in small quantities at a time. No separation into two components was observed during recrystallisation of the base or its salts and the product is assumed to consist of α-iododihydroquinidine, as the specific rotation is of about the value expected for that form. A second form probably occurs in the secondary crops and in the mother-liquors, but it has not been possible to isolate it because, on recrystallisation, decomposition ensues with loss of iodine. The crude base recovered from these sources differs from the α-form in giving a much larger yield of " niquidine " on dehalogenation with potassium hydroxide in alcohol.

α-Iododihydroquinidine crystallises from alcohol in prisms, m. p. 202° (decomp.), $[\alpha]_D^{18°}$ + 259° (N/10-hydrochloric acid) (Found: I, 27·5. Calc. for $C_{20}H_{25}O_2N_2I$: I, 28·1%). Schubert and Skraup (*Monatsh.*, 1891, **12**, 667) give m. p. 218—220° for the base and m. p. 230° for the dihydriodide, and Lippmann and Fleissner (*ibid.*, 1892, **13**, 432) give m. p. 205—206° for the base and m. p. 217° for the hydriodide. No other constants appear to have been recorded for the base or its salts. The *dihydrochloride* crystallises from water in long needles, m. p. 202° (decomp.), $[\alpha]_D^{18°}$ + 224·4° (N/10-hydrochloric acid) (Found: loss at 100° in a vacuum, 15·9.

$C_{20}H_{25}O_2N_2I,2HCl,5\frac{1}{2}H_2O$ requires H_2O, 15·9%). The dinitrate forms long, anhydrous prisms, m. p. 192° (decomp.), $[\alpha]_D^{18°}$ + 203·4° (N/10-hydrochloric acid). The *acid sulphate* separates from solution in boiling water in laminæ, m. p. 172° (decomp.), $[\alpha]_D^{18°}$ + 212·3° (N/10-hydrochloric acid) (Found: loss at 110° in a vacuum, 11·4. $C_{20}H_{25}O_2N_2I,H_2SO_4,4H_2O$ requires H_2O, 11·6%).

Bromodihydroquinidines.—Dry quinidine base (100 g.) was dissolved in hydrobromic acid (*d* 1·7, 300 c.c.) below 50°, and the solution kept at 40—50° for 50 hours. It was then cooled and partially neutralised with sodium hydroxide solution (50%). A large crop of bromodihydroquinidine dihydrobromide separated. A second crop was obtained by further partial neutralisation, and a third by addition of alkali until the filtrate was just acid to Congo-red paper. The remaining base was recovered by pouring the filtrate into excess of sodium hydroxide solution. This fractional precipitation effected a considerable separation of the α- and α′-forms: fraction 1 consisted almost wholly of α-bromodihydroquinidine dihydrobromide and fractions 2 and 3 of the dihydrobromide of the α′-form. Fraction 1 was purified by conversion into and recrystallisation as the dihydrochloride.

α-Bromodihydroquinidine crystallises from ether in anhydrous prisms, darkens at 195° and melts and decomposes at 235°, $[\alpha]_D^{18°}$ + 271·2° (N/10-hydrochloric acid) (Found: Br, 19·8. $C_{20}H_{25}O_2N_2Br$ requires Br, 19·7%). The dihydrochloride crystallises from water and has m. p. 217° (decomp.); it cannot be dried even at 100° in a vacuum without some decomposition, which also ensues on repeated crystallisation from water, as the final crops are low in bromine and the mother-liquors gradually acquire an odour of formaldehyde. The nitrate separates from dilute alcohol in anhydrous needles, m. p. 215° (decomp.), $[\alpha]_D^{18°}$ + 233·7° (N/10-hydrochloric acid). The *acid sulphate* forms needles from 50% alcohol and has m. p. 180°, $[\alpha]_D^{18°}$ + 217·2° (N/10-hydrochloric acid) (Found: loss on drying at 120° in a vacuum, 12·8. $C_{20}H_{25}O_2N_2Br,H_2SO_4,4H_2O$ requires H_2O, 12·5%).

The pure base (6 g.), dissolved in alcohol (150 c.c.) and N-sodium hydroxide (15 c.c.), was shaken with hydrogen in presence of palladised calcium carbonate (6 g.). When about half the calculated amount of gas had been taken up, the rate of absorption became slow and further catalyst (5 g.) was added. The total hydrogen absorption at *N.T.P.* was 347 c.c. (calc. for 1 mol. of hydrogen, 332 c.c.). The base recovered was recrystallised successively as base, dihydrobromide, and base. The final crop from alcohol had m. p. 170°, $[\alpha]_D$ + 298° (N/10-sulphuric acid) and showed no depression of m. p. on admixture with dihydroquinidine. No " niquidine " could be isolated from the mother-liquors.

α′-Bromodihydroquinidine. The base (10 g.) recovered from fractions 2 and 3 of the crude dihydrobromide was purified through the hydrochloride; the regenerated *base* crystallised from ether in needles, m. p. 210° (decomp.), $[\alpha]_D^{18°}$ + 231·7° (N/10-hydrochloric acid) (Found: loss in a vacuum at 110°, 12·4. Found in base so dried: C, 59·0; H, 6·25; N, 6·7; OMe, 7·4; Br, 19·8. $C_{20}H_{25}O_2N_2Br,3H_2O$ requires H_2O, 11·8%. $C_{20}H_{25}O_2N_2Br$ requires C, 59·2; H, 6·2; N, 6·9; OMe, 7·65; Br, 19·7%).

The *nitrate* crystallises from water in anhydrous plates, m. p. 225° (decomp.) (Found for salt dried at 110° in a vacuum: C, 51·3; H, 5·6; N, 8·4. $C_{20}H_{25}O_2N_2Br,HNO_3$ requires C, 51·3; H, 5·6; N, 9·0%).

The hydrochloride forms small prismatic crystals from 50% alcohol, m. p. 238° (decomp.), $[\alpha]_D^{18°}$ + 213·8° (N/10-hydrochloric acid).

The *dihydrobromide* separates from dilute (10%) hydrobromic acid in long needles, m. p. 235° (decomp.), $[\alpha]_D^{18°}$ + 166° (water) (Found: loss on drying at 105° in a vacuum, 10·5. $C_{20}H_{25}O_2N_2Br,2HBr,3H_2O$ requires H_2O, 10·4%).

The *sulphate* crystallises from 70% alcohol in needles, m. p. 207°, $[\alpha]_D^{18°}$ + 206·1° (N/10-hydrochloric acid) [Found: loss in a vacuum at 120°, 5·2. $(C_{20}H_{25}O_2N_2Br)_2,H_2SO_4,3H_2O$ requires H_2O, 5·6%].

As hydrogenation could not be effected in acid solution in presence of palladised barium sulphate, or platinic oxide catalyst, the α′-bromo-base (5 g.) was dissolved in alcohol (100 c.c.) and N-sodium hydroxide solution (12·5 c.c.), and the mixture shaken with palladised calcium carbonate in an atmosphere of hydrogen, the catalyst being renewed from time to time until absorption of hydrogen ceased. The alkaloidal product, recovered in the usual way and dissolved in boiling alcohol, yielded a crop of dihydroquinidine, identified by a mixed m. p. determination, m. p. 171°, with an authentic specimen. The mother-liquor from this crop on treatment with oxalic acid yielded an acid oxalate, m. p. 205°, of a base, m. p. 160°, $[\alpha]_D$ + 278·5° (N/10-sulphuric acid), agreeing in characters with crude " niquidine " and, like the latter, on hydrogenation in presence of palladised barium sulphate, yielding dihydroniquidine, m. p.

165°, $[\alpha]_D$ + 230·7° (N/10-sulphuric acid), identified by a mixed m. p. determination with an authentic specimen (see p. 245). The mother-liquor from the " niquidine " acid oxalate was reworked to base, which on treatment with an aqueous solution of tartaric acid yielded a crop of a hydrogen tartrate, from which *γ-iso*quinidine was isolated as the dinitrate, m. p. 213° (decomp.), $[\alpha]_D$ + 53·3° (water), which showed no depression of m. p. on admixture with an authentic specimen.

The results of a separate experiment, in the absence of hydrogen, showed that the production of niquidine and *γ-iso*quinidine in this operation was due to the action of the alkali on the α′-bromodihydroquinidine, which is much more easily dehalogenated than the α-isomeride. The niquidine formed is not hydrogenated in presence of palladised calcium carbonate, but is converted into dihydroniquidine in presence of palladised barium sulphate.

Preparation and Separation of Niquidines.—A systematic study has not been made of the conditions which determine the production of " niquidine " rather than quinidine isomerides in the dehalogenation process, but many experiments have been made with a view to improving the yield of " niquidine " and the results are of some interest apart from this particular purpose. With potassium hydroxide in alcohol, the products were α- and *γ-iso*quinidines, *apo*quinidine methyl ether and, exceptionally, β-*iso*quinidine with small quantities of " niquidine," 4% in the case of chlorodihydroquinidine, 7—8% with bromodihydroquinidine, and 10% with iododihydroquinidine. With boiling alcohol, iododihydroquinidine base was converted into a mixture of iododihydroquinidine hydriodide and niquidine with a small amount of *iso*niquidine, a reaction corresponding with that already recorded by Reyman and Suszko (*loc. cit.*) for iododihydroquinine, boiled with benzene. With silver nitrate in alcohol, the bromodihydroquinidines yielded some α-*iso*quinidine but chiefly " niquidine." The α-form gave *iso*niquidine (46%) and niquidine (8%), and the α′-isomeride yielded niquidine (63%) and *iso*niquidine (10%). With iododihydroquinidine, the same reagent furnished *iso*niquidine (56%) and niquidine (24%). All these results refer to the action of the specified reagent on the halogenated dihydro-base and the production of " niquidine " is invariably accompanied by the liberation of formaldehyde.

When salts were used, the results were different except when potassium hydroxide in alcohol was the dehalogenating reagent. α′-Bromodihydroquinidine dihydrobromide with silver nitrate in alcohol, in quantity more than sufficient to precipitate all the bromine as silver bromide, gave *γ-iso*quinidine (68%). Iododihydroquinidine dihydriodide with the same reagent produced *apo*quinidine methyl ether (20%) but no " niquidine."

The method finally adopted was as follows: Dry crude bromodihydroquinidine (1 g.) was dissolved in 80% alcohol (20 c.c.), silver nitrate (0·5 g.) in water (1 c.c.) added, the mixture, after being boiled for 30 minutes, diluted with water and made acid, the excess of silver removed by precipitation with sodium chloride, and the filtrate evaporated in a vacuum to remove alcohol. The distillate had a strong odour of formaldehyde and the latter was definitely identified by conversion into the dimedon compound, m. p. 188°, mixed m. p. 188°. The aqueous residue was then made alkaline, and the base extracted with ether and converted into the readily crystallisable acid oxalate, m. p. 205°. The base recovered from this salt, on conversion into the dihydrobromide and recrystallisation of the latter from water, deposited first *iso*niquidine dihydrobromide. Niquidine was recovered from the mother-liquors as base and purified by conversion into and recrystallisation of the hydrobromide.

Niquidine. The *base* recovered from the pure hydrobromide crystallises from moist ether in stellate groups of needles, m. p. 172°, $[\alpha]_D^{18°}$ + 301·5° (N/10-sulphuric acid) or + 186° (c = 1; alcohol) (Found: C, 73·2; H, 7·7; N, 9·0; OMe, 9·9; CMe, 8·0. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·75; N, 9·0; OMe, 9·9; CMe, 8·65%). The base not being sufficiently soluble in solvents suitable for Zerewitinoff determinations, replaceable hydrogen could not be determined. The hydrobromide forms anhydrous, prismatic crystals, m. p. 217°, $[\alpha]_D^{18°}$ + 240·2° (N/10-sulphuric acid), and is very sparingly soluble in water. The *dihydrobromide* crystallises from water in large prisms, m. p. 230° (decomp.), $[\alpha]_D^{18°}$ + 198·7° (water) (Found: loss at 120° in a vacuum, 6·9. $C_{19}H_{24}O_2N_2,2HBr,2H_2O$ requires H_2O, 7·05%). The acid oxalate forms minute needles, m. p. 215°. On hydrogenation as described later for *iso*niquidine, niquidine yields dihydroniquidine, m. p. 165°, $[\alpha]_D^{18°}$ + 229·1° (N/10-sulphuric acid), identical with that obtained by the hydrogenation of *iso*niquidine.

iso*Niquidine.* The *base* recovered from the purified dihydrobromide crystallises from acetone in rectangular prisms, m. p. 163°, $[\alpha]_D^{18°}$ + 222·0° (N/10-sulphuric acid) or + 122° (c = 1; alcohol) (Found for base dried in a vacuum at 110°: C, 73·1; H, 7·8; N, 9·1; OMe, 10·1; CMe, 8·2. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·75; N, 9·0; OMe, 9·9; CMe, 8·65%). The

dihydrobromide forms pale yellow, anhydrous prisms, m. p. 265° (decomp.), $[\alpha]_D^{18°}$ + 146·8° (water). The acid oxalate forms minute anhydrous needles, m. p. 223°, from alcohol.

Dihydroniquidine.—This substance is formed by the hydrogenation of either niquidine or *iso*niquidine. The latter (0·46 g.), dissolved in dilute sulphuric acid and shaken in hydrogen in presence of palladised barium sulphate (0·1 g.), absorbed 32·9 c.c. (Calc. for H_2, 33·1 c.c.). For hydrogenation of larger quantities (10 g. or more) Adams's platinic oxide proved a speedier catalyst for the reaction. *Dihydroniquidine* crystallises from moist ether or acetone (1 g. in 40 c.c.) in slender, anhydrous needles, m. p. 165°, $[\alpha]_D^{18°}$ + 231·6° (N/10-sulphuric acid) or + 126·8° (c = 1·0 alcohol) (Found for base dried at 110° in a vacuum: C, 72·8; H, 8·4; N, 9·1; OMe, 9·7; CMe, 2·9 to 7·0%. $C_{19}H_{26}O_2N_2$ requires C, 72·6; H, 8·3; N, 8·9; OMe, 9·9; CMe, 8·6%). Zerewitinoff determinations for replaceable hydrogen (RH) gave with anisole as solvent (1) at atmospheric temperature 4·68 (calc. for HO, 5·4%) and (2) additional at 130°, 4·05 (calc. for NH, 4·7%). These results are regarded as due to reaction with the hydroxyl group alone in anisole at atmospheric temperature, and reaction with the imino-group in anisole at 130°.

The dihydrobromide crystallises from water in anhydrous needles, m. p. 245° (decomp.), $[\alpha]_D^{18°}$ + 152·9° (water). The *sulphate* forms needles from 80% alcohol and has m. p. 180°, $[\alpha]_D^{18°}$ + 200·4° (N/10-sulphuric acid) [Found: loss on drying at 110° in a vacuum, 4·7. $(C_{19}H_{26}O_2N_2)_2,H_2SO_4,2H_2O$ requires H_2O, 4·7%]. The acid sulphate forms rosettes of silky needles, m. p. 182° (decomp.), $[\alpha]_D^{18°}$ + 177·2° (water). During the recrystallisation of the base or any of its salts no indication was obtained of the existence of more than one form. This is accounted for by formula (III) now proposed for niquidine, whereas the Léger formula (I) requires the production of two dihydroniquidines, since C_3 would become a centre of asymmetry on hydrogenation.

Dihydroniquidine base (1 g.) was dissolved in water (30 c.c.) containing concentrated hydrochloric acid (10 c.c.), and the solution immersed in ice and salt. Sodium nitrite (3·5 g.) in water (10 c.c.) was then added drop by drop with constant agitation, and the mixture left in the refrigerator overnight. The crop of nitrosodihydroniquidine salt was worked up for base and the *nitrosodihydroniquidine* recrystallised from benzene. It formed minute, anhydrous needles, m. p. 170° (Found for base dried at 100° in a vacuum: C, 66·2; H, 7·4; N, 12·0; OMe, 8·5. $C_{19}H_{25}O_3N_3$ requires C, 66·4; H, 7·3; N, 12·2; OMe, 9·0%).

N-*Methyldihydroniquidine* prepared by a usual *N*-alkylation method (yield, 12·5%) crystallised from methyl alcohol in anhydrous rectangular plates, m. p. 212°, $[\alpha]_D^{18°}$ + 234° (N/10-sulphuric acid) (Found for base dried at 120° in a vacuum: C, 73·15; H, 8·6; N, 8·5; OMe, 9·4; NMe, 8·7. $C_{20}H_{28}O_2N_2$ requires C, 73·1; H, 8·6; N, 8·5; OMe, 9·4; NMe, 8·8%). *Dihydroniquidine phenylthiocarbamide* obtained by direct interaction of the components in a little benzene, can be crystallised from the same solvent and has m. p. 112° (Found: S, 7·0. $C_{26}H_{31}O_2N_3S$ requires S, 7·1%).

Conversion of Dihydroniquidine into epi-C_9-*Dihydroniquidine.*—Dihydroniquidine base (10 g.) was dissolved in acetic acid (12·5 g.) and water (125 c.c.), the solution boiled for 20 hours, and the altered base isolated by addition of ammonia and extraction with ether. It was neutralised with hydrobromic acid, the crop removed, and the residues acidified to dihydrobromide, yielding a further crop, which, like the first, proved to consist mainly of a sesquihydrobromide of a new base with some unchanged dihydroniquidine as hydrobromide. These were separated by crystallising the recovered base from acetone to eliminate the less soluble dihydroniquidine. The mother-liquors were freed from acetone, and the residue dissolved in alcohol and made just acid to Congo-red paper with hydrobromic acid. The *sesquihydrobromide* of the new base crystallised at once and was recrystallised from 50% alcohol. It formed silky needles, m. p. 240° (decomp.), $[\alpha]_D^{18°}$ − 102·8° (N/10-sulphuric acid) [Found: loss at 110° in a vacuum, 1·9. $(C_{19}H_{26}O_2N_2)_2,3HBr,H_2O$ requires H_2O, 2·1%. Found for substance so dried: C, 52·4; H, 6·5; N, 6·5; Br, 27·2; OMe, 7·1. $(C_{19}H_{26}O_2N_2)_2,3HBr$ requires C, 52·4; H, 6·4; N, 6·4; Br, 27·5; OMe, 7·1%]. The base recovered from the sesquihydrobromide was a hard glassy solid, $[\alpha]_D^{18°}$ −140·8° (N/10-sulphuric acid) or − 33·3° (c = 1; alcohol), which has not yet been crystallised. It behaves like dihydroniquidine in Zerewitinoff determinations, yielding with anisole as solvent RH 6·25 (calc. for HO, 5·4%) at atmospheric temperature, and additional RH 4·6 (calc. for NH, 4·8%) on warming to 130°. The *sesquinitrate* separates from alcohol in clusters of small needles, m. p. 196° (decomp.), $[\alpha]_D^{18°}$ − 110·3° (N/10-sulphuric acid) [Found: loss at 100° in a vacuum, 4·6. $(C_{19}H_{26}O_2N_2)_2,3HNO_3,2H_2O$ requires $2H_2O$, 4·5%. Found for salt so dried: C, 55·8; H, 6·7; N, 11·9; OMe, 7·3. $(C_{19}H_{26}O_2N_2)_2,3HNO_3$ requires C, 55·8; H, 6·7; N, 12·0; OMe, 7·6%].

Solutions of the base in sulphuric acid or nitric acid show a marked blue fluorescence, and a solution in dilute sulphuric acid is not hydrogenated in presence of palladium catalyst.

This substance had not the properties of the " niquinotoxine " which might be expected to be produced in this reaction and its high lævorotation suggested that it might be the unknown *epi*-C_9-dihydroniquidine. The latter was prepared from *epi*-C_9-quinidine, by the series of reactions used in the conversion of quinidine into dihydroniquidine, the intervening products being *iododihydro*-epi-C_9-*quinidine*, prisms from ether, m. p. 150—155° (decomp.) (Found: I, 27·7. $C_{19}H_{25}O_2N_2I$ requires I, 28·1%), and *epi*-C_9-niquidine (probably a mixture of the two isomerides), the latter being hydrogenated to the required *epi*-C_9-dihydroniquidine, which, when dissolved in alcohol and the solution made just acid to Congo-red, deposited a sesquihydrobromide, silky needles, m. p. 240° (decomp.), $[\alpha]_D^{18°}$ — 102·2° (N/10-sulphuric acid), identical with the sesquihydrobromide of the transformation product from dihydroniquidine.

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