275. *Modified Cinchona Alkaloids. Part VII. The Constitution of Niquidine.*

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In Part VI (this vol., p. 240) a formula (II) was suggested for the two geometrical isomerides, niquidine and *iso*niquidine, formed in the dehalogenation of halogenodihydroquinidines (I; X = Hal.) by silver nitrate. Further evidence for this formula is now provided by a study of the oxidation products of " niquidine " (the mixture of the two geometrical isomerides) and dihydroniquidine (II; $CH_3 \cdot CH{:}CH \cdot \rightarrow CH_2 \cdot CH_2 \cdot CH_2 \cdot$). On oxidation with potassium permanganate " niquidine " yields acetaldehyde and two acids, $C_{17}H_{20}O_4N_2$ and $C_{17}H_{14}O_4N_2$. The latter may be represented by (IV), and the former by (IV) with the pyridyl ring reduced to piperidyl. Vigorous oxidation of dihydroniquidine with hydrogen peroxide leads to scission of the molecule at the secondary carbinol group, with the formation of quininic acid and its amine oxide, and from the 4-propylpiperidine ring, β-propylglutaric acid (III) and ammonia. A similar decomposition ensues when dihydroquinidine (I; X = H) is oxidised by hydrogen peroxide, the products in this instance being quininic acid and its amine oxide, with *ω-ethylmethanetriacetic acid* [*β-(α'-carboxypropyl)glutaric acid*] (V) and ammonia as the degradation products of the quinuclidine nucleus of the alkaloid.

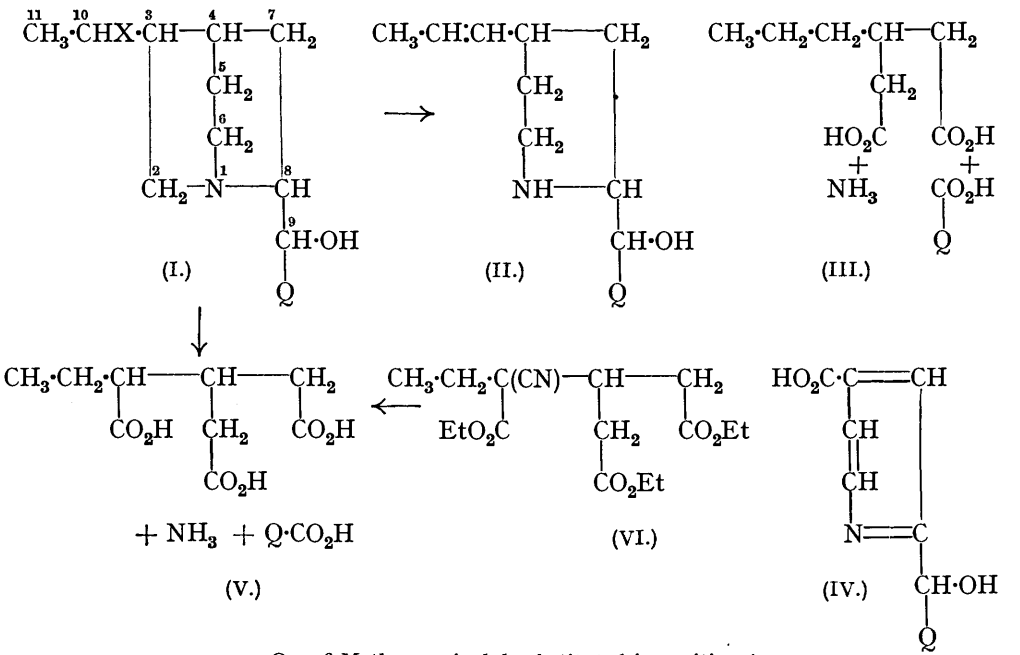
Domanski and Suszko (*Bull. Acad. Polonaise*, 1935, *A*, 457) oxidised " niquidine " with hydrogen peroxide, but were only able to isolate quininic acid from the products of the reaction. The present authors, using the same reagent on dihydroniquidine (II; $\cdot CH{:}CH \cdot \rightarrow \cdot CH_2 \cdot CH_2 \cdot$), which as shown in Part VI (*loc. cit.*) is formed by the hydrogenation of " niquidine " or either of its pair of isomeric components, niquidine and *iso*niquidine, obtained quininic acid and its *amine oxide*, together with ammonia and β-propylglutaric acid (III). The latter was identified by direct comparison of the acid, and of its *diamide*, anilide, and *dianilide*, with β-propylglutaric acid, prepared by the method of Day and Thorpe (J., 1920, **117**, 1471), and the corresponding derivatives. Wolffenstein (*Ber.*, 1892, **25**, 2777) found that piperidine on oxidation with hydrogen peroxide yielded ammonia and glutaric acid, and the formation of β-propylglutaric acid from

dihydroniquidine clearly indicates the presence in this alkaloid of a 4-propylpiperidine nucleus.

When " niquidine " is oxidised with ice-cold potassium permanganate solution there is formed acetaldehyde, identified as the dimedon derivative and the *p*-nitrophenylhydrazone. There can be little doubt, therefore, that the 4-propylpiperidine ring in dihydroniquidine arises from a 4-propenylpiperidine nucleus in niquidine and *iso*niquidine as required by formula (II), already suggested by the authors (*loc. cit.*) for these isomerides.

The other products of the oxidation of " niquidine " by potassium permanganate were isolated with difficulty and obtained only in minute quantity, but were eventually separated into two *acids*, $C_{17}H_{14}O_4N_2$ (substance E) and $C_{17}H_{20}O_4N_2$ (substance F). The former acid contains one methoxyl and one carboxyl group. Having regard to these characteristics and to its source and mode of formation, it is suggested that it is represented by formula (IV) and that it arises from the $C_{17}H_{20}O_4N_2$ acid by the conversion of a piperidine into a pyridine ring during oxidation.

Since hydrogen peroxide yielded such well-defined results with dihydroniquidine, it was tried with several other bases consisting of, or containing, saturated heterocyclic nuclei, *viz.*, α-pipecoline, tropine, and dihydroquinidine (I; X = H). α-Pipecoline yielded succinic and acetic acids (*cf.* Wolffenstein, *Ber.*, 1893, , 2991); tropine gave tropinone and succinic acid, with ammonia and formic acid, the last two resulting no doubt from the methylimino-group of the alkaloid: all these substances have been obtained previously from these sources, or are to be expected, but dihydroquinidine furnished more interesting products, *viz.*, quininic acid and its amine oxide and a new tribasic acid, *ω-ethylmethanetri-*



Q = 6-Methoxyquinolyl substituted in position 4.

acetic acid (V). The constitution assigned to the last was confirmed by its synthesis by appropriate change of starting materials, in the modified Michael method used by Kohler and Reid (*J. Amer. Chem. Soc.*, 1925, **47**, 2803) for the preparation of the lower homologue, methanetriacetic acid. Ethyl glutaconate was condensed with ethyl α-cyanobutyrate, and the resulting cyano-ester (VI) hydrolysed with constant-boiling hydrochloric acid to the required acid (V), which is identical with the acid formed by oxidation of dihydroquinidine, with the exception that the oxidation product shows a small optical rotation of − 1·3°, and so far it has not proved possible to deracemise the synthetic acid. It is of

interest that the next lower homologue of the acid now described, *viz.*, ω-methylmethanetriacetic acid, was obtained by Skraup (*Monatsh.*, 1900, **21**, 879) as a degradation product of quinine, by the fusion of dimethylcincholoiponic acid with potassium hydroxide and, was synthesised by that author and more recently by Ingold and Perren (J., 1921, **119**, 1588).

The action of hydrogen peroxide on a number of cinchona alkaloids, under milder conditions than those used by the present authors, was investigated by Speyer and Becker (*Ber.*, 1922, **55**, 1321), who prepared in this way amine oxides of the intact alkaloids in which the oxygen atom was assumed to be attached to the nitrogen atom of the quinuclidine ring. These alkaloidal amine oxides differ from quininic acid amine oxide in liberating iodine from potassium iodide and in undergoing reduction to the alkaloid on treatment with sulphurous acid. The latter is without action on quininic acid amine oxide, which can, however, be reduced to quininic acid by hydrogenation in presence of palladised barium sulphate. Quinine amine oxide is not deoxygenated on catalytic hydrogenation, but is converted into dihydroquinine amine oxide.

In the preliminary investigation of methods for the preparation of niquidine (*loc. cit.*), a search was made for intermediate products between bromodihydroquinidine and "niquidine," which might indicate the mechanism by which the $-CH_2-$ group at position 2 (I) is eliminated as formaldehyde, but none could be isolated. No record of a similar elimination of a cyclic methylene group has been found in the literature, but it is noteworthy that this reaction appears to be a reversal of a process, originally due to Pictet and Spengler (*Ber.*, 1911, **44**, 2030), by which condensation with formaldehyde, or methylal, has been employed to complete the formation of a heterocyclic ring in the synthesis of alkaloids, *e.g.*, in the conversion of 1-homopiperonyl-6 : 7-dimethoxytetrahydro*iso*quinoline to tetrahydro-*ψ-epi*berberine (Buck and Perkin, J., 1924, **125**, 1677) and in the preparation of numerous derivatives of *nor*harman, beginning with the synthesis of *nor*harman itself from tryptophan and formaldehyde by Kermack, Perkin, and Robinson (J., 1921, **119**, 1604).

Experimental.

As explained in Part VI (*loc. cit.*), it is convenient to use "niquidine," the mixture of the two geometrical isomerides, niquidine and *iso*niquidine, for degradation experiments such as those now described.

Oxidation of "Niquidine" by Potassium Permanganate.—The base (5 g.; $[\alpha]_D$ − 234°) was dissolved in dilute sulphuric acid (10%, 53·5 c.c.), the solution cooled in melting ice, and potassium permanganate solution (4·05 g. in 140 c.c.) added drop by drop with constant stirring. Oxidation slackened after the addition of about 100 c.c. of the reagent, and the mixture had an odour of acetaldehyde. The filtrate from the manganese dioxide was steam-distilled. One half of the distillate was mixed with a little sodium chloride and an alcoholic solution of dimedon. The crystalline product, which separated in a few minutes, had m. p. 140° undepressed on admixture with the dimedon derivative of acetaldehyde. To the other half of the distillate a solution of *p*-nitrophenylhydrazine in 2N-sulphuric acid was added; the precipitate formed was collected, and after crystallisation from dilute alcohol (50%) had m. p. 128°, which remained unchanged on admixture with acetaldehyde-*p*-nitrophenylhydrazone.

The manganese dioxide precipitate was dried in a vacuous desiccator and exhausted with boiling alcohol, yielding extract A (0·8 g.). It was then extracted with hot water and the filtrate added to the original liquor left after the removal of acetaldehyde. The combined liquors were neutralised, concentrated to about 50 c.c., made acid to Congo-red paper, and extracted continuously with ether (extract B, 0·1 g.). The liquid was then made alkaline and again extracted continuously with ether (extract C, 2·3 g.). It was finally neutralised, taken to dryness, and the residue boiled with alcohol, yielding extract D, 0·4 g. Extract A on solution in a little dilute alcohol (70%) deposited a yellow substance, E, m. p. >300°. The filtrate from this was mixed with extracts B, C, and D, from which no crystalline product could be obtained, and the mixture re-oxidised in dilute sulphuric acid (1%) with potassium permanganate solution (4 g. in 100 c.c.) at room temperature. The alcoholic extract (A_1 corresponding to A above) of the dried manganese dioxide precipitate yielded a little more of substance E. The combined oxidation liquors, assembled as before, were neutralised, concentrated to low bulk, acidified with hydrochloric acid, and after cooling, filtered from crystalline matter, which was identified as

quininic acid. It formed slender needles, from 50% alcohol and showed no depression of m. p. 290° (decomp.) on admixture with quininic acid (Found, for substance dried at 120° in a vacuum: C, 64·9; H, 4·65; N, 6·7; OMe, 15·2. Calc. for $C_{11}H_9O_3N$: C, 65·0; H, 4·5; N, 6·9; OMe, 15·3%).

The filtrate was worked up as before, yielding extracts B_1, C_1, and D_1. From B_1 a little more quininic acid was obtained, but as the others yielded no crystalline material they were united, dissolved in dilute sodium hydroxide solution, and the hot solution treated with charcoal, filtered, acidified, and extracted with ether, which removed a little more quininic acid. The filtrate was then neutralised, taken to dryness, and extracted with alcohol. The residue left on removal of the solvent was dissolved in a mixture of alcohol and acetone and this, on long standing, deposited crystals. The sticky crop so obtained was purified by concentration of a filtered solution in boiling water, yielding substance F.

Substance E. This yellow *product*, after crystallisation from dilute hydrochloric acid (5%), formed needles, m. p. >300° (Found: loss in a vacuum at 120°, 19·9. Found, in substance so dried: C, 65·7; H, 4·1; N, 8·6; OMe, 9·9. $C_{17}H_{14}O_4N_2$ requires C, 65·8; H, 4·55; N, 9·0; OMe, 10%). The *methyl* ester after crystallisation twice from methyl alcohol had m. p. 168° (Found: C, 67·1; H, 4·5; N, 8·5; OMe, 19·1. $C_{18}H_{16}O_4N_2$ requires C, 66·7; H, 5·0; N, 8·6; OMe, 19·1%).

Substance F. This forms long, prismatic, colourless crystals, m. p. 247° (air-dry; decomp.) (Found: loss at 110° in a vacuum, 5·2. Found, for *substance* so dried: C, 64·2; H, 6·5; N, 9·0; OMe, 9·3; CMe, 0·4. $C_{17}H_{20}O_4N_2$ requires C, 64·5; H, 6·4; N, 8·9; OMe, 9·8; CMe, nil%). Like substance E, it was obtained in too small quantity for detailed investigation, but its formation, composition and properties suggest that it is substance E with the pyridyl ring (as in IV) reduced to piperidyl.

Oxidation of Dihydroniquidine by Hydrogen Peroxide.—Dihydroniquidine (10 g.) and hydrogen peroxide solution (100-vol., 50 c.c.) were heated on a boiling water-bath under a reflux condenser during 2 hours, with frequent agitation. After cooling, the aqueous liquor was decanted from the viscous oil formed, the latter dissolved in hot alcohol, and the crystalline matter (G) which separated was collected. The filtrate from this was evaporated to dryness, and the residue boiled with two portions (50 c.c.) of water, the aqueous extract being added to the original decanted, aqueous liquor and the whole made alkaline and boiled (ammonia evolved) for a few minutes to decompose unused peroxide. The liquor was then neutralised, concentrated to about 50 c.c., made acid to Congo-red paper, and extracted with ether. The residue left on evaporation of the ether was dissolved in water, the solution treated with charcoal, filtered from a small amount of tar, and taken to dryness under reduced pressure to yield the acid residue, H.

Examination of Residue G. Quininic Acid Amine Oxide.—This residue was partly soluble in dilute acid, and from the solution quininic acid was recovered and identified as described already (above). The portion insoluble in dilute acid crystallised from boiling alcohol in anhydrous needles, m. p. 268° (decomp.). It is sparingly soluble in water, alcohol or dilute acid, readily soluble in sodium carbonate solution, and is acid to litmus (Found, for *substance* dried at 110° in a vacuum: C, 60·1; H, 4·5; N, 6·7; MeO, 13·7. $C_{11}H_9O_4N$ requires C, 60·3; H, 4·1; N, 6·4; MeO, 14·2%). It yields an ethyl ester crystallising in silky, yellow needles, m. p. 141°, and on hydrogenation in sodium hydroxide solution (0·23 g. in 1·2 c.c. of N-NaOH) in presence of palladised barium sulphate, it absorbed 24·2 c.c. of hydrogen (Calc.: 23·5 c.c.), yielding quininic acid, m. p. 288° (decomp.). These properties indicated that the substance was *quininic acid amine oxide*, and this was confirmed by comparison with the amine oxide prepared in the following manner. Quininic acid (1 g.) was dissolved in N-sodium hydroxide solution (5 c.c.) and hydrogen peroxide solution (100-vol., 10 c.c.) added, followed by sodium hydroxide solution (10%) drop by drop until the liquid was faintly alkaline to litmus. This mixture was then heated on a boiling water-bath for 4 hours, made acid to Congo-red paper with dilute sulphuric acid, and the crystalline precipitate collected, digested with dilute sulphuric acid (10%), and the insoluble matter collected and crystallised from boiling alcohol, from which it separated in needles, m. p. 272° (decomp.), showing no depression of m. p. below 268° on admixture with the dihydroniquidine oxidation product.

Examination of Residue H. β-Propylglutaric Acid.—As this acid residue could not be induced to crystallise, it was treated with thionyl chloride, and the resulting crude acid chloride slowly stirred into well-cooled, concentrated ammonia solution. The *diamide* so formed, after recrystallisation, had m. p. 195° (Found, for substance dried at 105° in a vacuum: C, 55·95; H, 9·4; N, 15·9. $C_8H_{16}O_2N_2$ requires C, 55·8; H, 9·35; N, 16·3%). A further supply of acid residue H was converted *via* the crude acid chloride into the *dianilide*, which after recrystallis-

ation from alcohol had m. p. 219° (Found, for substance dried at 100° in a vacuum: C, 74·0; H, 7·7; N, 8·7. $C_{20}H_{24}O_2N_2$ requires C, 74·0; H, 7·5; N, 8·6%). On hydrolysis by boiling with concentrated hydrochloric acid, the dianilide yielded the free acid, which crystallised from dilute hydrochloric acid (10%) in hexagonal prisms, m. p. 50° (Found, for substance dried at atmospheric temperature in a vacuum over sulphuric acid: C, 55·3; H, 7·95. Calc. for $C_8H_{14}O_4$: C, 55·1; H, 8·1%).

These results indicated that the chief component of acid residue H was β-propylglutaric acid, and the authors are greatly indebted to Professor Kon for the opportunity of confirming this identification by comparison with a specimen of Day and Thorpe's original preparation. As the diamide and dianilide of this acid had not been prepared previously, a supply of the acid was made by Day and Thorpe's process (*loc. cit.*). The synthetic acid had m. p. 50° and yielded a diamide, m. p. 195°, and dianilide, m. p. 219°, none of which showed any depression of m. p. on admixture with the corresponding acid, diamide, and dianilide described above. The natural and the synthetic acid also both yielded the monoanilide, m. p. 128°, described by Day and Thorpe.

Oxidation of Other Bases with Hydrogen Peroxide.—In the oxidation of dihydroniquidine by hydrogen peroxide as described above, a more concentrated reagent and a higher temperature were employed than those adopted by Wolffenstein (*loc. cit.*) for the oxidation of piperidine and α-pipecoline. The authors found in oxidising bases soluble in water, such as pipecoline, tropine, and sparteine, that the reaction was too vigorous under the conditions found convenient in the case of dihydroniquidine, but that it could be moderated by using a salt instead of the base itself. The products formed in these oxidations have been enumerated already (p. 1295) and as they were all isolated by well-known methods, no further description need be given.

Oxidation of Dihydroquinidine with Hydrogen Peroxide.—The reaction was carried out as described for dihydroniquidine (p. 1297) and the product worked up in the same manner. The viscous oil formed, again yielded a mixture of quininic acid and its amine oxide, and the filtrate from this after removal of the alcohol used as solvent was re-oxidised and worked up as before. The combined aqueous extracts thus obtained were made alkaline, boiled (ammonia evolved) to remove excess of peroxide, acidified, and extracted with ether. The residue from this extract after the removal of some acetic acid under reduced pressure and of some tar by solution in a little water, was dried in a vacuum and converted *via* the crude acid chloride into the *trianilide*, which is sparingly soluble in most organic solvents but was eventually recrystallised from a mixture of methyl alcohol and ethyl acetate in minute anhydrous prisms, m. p. 280° (decomp.) (Found, for substance dried at 100° in a vacuum: C, 72·85; H, 6·4; N, 9·5. $C_{27}H_{29}O_3N_3$ requires C, 73·1; H, 6·6; N, 9·5%). The trianilide on boiling with hydrochloric acid (20%) until dissolved (15 hours) yielded by extraction with ether the free acid, which crystallised from hydrochloric acid (20%) in prisms, m. p. 120°, $[\alpha]_D$ − 1·3° (c = 1·006 in water) (Found, for substance dried at 100° in a vacuum: C, 49·5; H, 6·3. $C_9H_{14}O_6$ requires C, 49·5; H, 6·5%). In the hope of securing an increased yield of this acid from the crude acid residue, the latter was converted into methyl esters. Of this, a fraction, b. p. 85—200°/1 mm., was hydrolysed, the regenerated acids being extracted with ether, converted into the acid chlorides, and the latter treated with aniline. The product isolated on this occasion was a *dianilide*, which crystallised from alcohol in anhydrous needles, m. p. 222° (Found, for substance dried at 120° in a vacuum: C, 68·5; H, 6·4; N, 7·7. $C_{21}H_{24}O_4N_2$ requires C, 68·45; H, 6·6; N, 7·6%). On hydrolysis by boiling with hydrochloric acid it yielded the same acid, m. p. 120°.

As it seemed likely from its composition and mode of formation that this $C_9H_{14}O_6$ acid might be ω-ethylmethanetriacetic acid (V), the latter was synthesised by the method used by Kohler and Reid (*loc. cit.*) for the lower homologue, methanetriacetic acid. Ethyl α-cyanobutyrate, prepared by Hessler's method (*J. Amer. Chem. Soc.*, 1913, **35**, 990) and thoroughly dried, was mixed with ethyl glutaconate, also well dried, in alcoholic solution, and the mixture boiled under reflux condenser for 12 hours, care being taken to keep it just alkaline by addition of a little sodium ethoxide solution (1·8 g. of sodium in dry alcohol, 25 c.c.) to start with, and at intervals of about 2 hours afterwards. The reaction mixture was neutralised with acetic acid and distilled, the fraction, b. p. 180—200°/3 mm., being collected as the crude cyano-ester (VI) (yield 50%), which on hydrolysis by boiling with concentrated hydrochloric acid for several hours and subsequent extraction with ether yielded a viscous, oily acid (yield 25%), which crystallised from hydrochloric acid in anhydrous prisms, m. p. 123—124° (Found, for acid dried in a vacuum at 100°: C, 49·1; H, 6·4. $C_9H_{14}O_6$ requires C, 49·5; H, 6·5%). Mixed m. p. determinations confirmed the identity of the synthetic and the natural acid and of their dianilides. This oxidation product of dihydroquinidine must therefore be *ω-ethylmethanetriacetic acid* (V).

The acid yields crystalline salts with strychnine and cinchonine, but as might be expected with a substance showing such a small specific rotation, the results of attempted deracemisation of the synthetic acid by the use of these salts were uncertain, and so far no derivative of higher rotation has been found, which would serve as a satisfactory indicator of successful deracemisation.

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