134. *Quinamine. Part II. Constitution.*

By K. S. Kirby.

Quinamine, a minor cinchona alkaloid, has been shown to contain an indole nucleus in place of the quinoline nucleus characteristic of all the other cinchona alkaloids of known constitution. A probable structural formula (I) for the alkaloid is proposed.

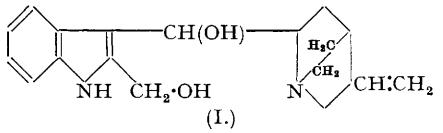
Quinamine has been shown to differ from all other cinchona alkaloids of known constitution in that the quinuclidine nucleus survives chromic acid oxidation whereas no recognisable fragment of the second nucleus has been isolated (Part I; preceding paper). This nucleus is revealed, *e.g.*, in the case of quinine by the formation of 6-methoxyquinoline-4-carboxylic acid (Skraup, *Monatsh.*, 1881, **2**, 587).

Oxidation of quinamine with nitric acid gave picric acid and a *compound*, $C_9H_4O_7N_4$, in quantity too small for further investigation (see below). The picric acid could be derived from either a tetrahydroquinoline or an indole nucleus. The former seemed the more probable, as the other cinchona alkaloids are quinoline derivatives, and consequently attempts were made to dehydrogenate the alkaloid with nitrous fumes. In cold alcoholic solution the gases were rapidly absorbed with the formation of a *nitroquinamine* and a *nitronitrosoquinamine*. Dihydroquinamine under the same conditions gave rise to a *dinitrodihydroquinamine* and a *nitronitrosodihydroquinamine*. When the reaction was carried out with quinamine in dilute nitric acid solution, and the product heated with concentrated nitric acid, a tetranitronitrosodihydroquinamine nitrate (characterised as *chloride*) was formed. The latter compound is very stable and may be recrystallised from concentrated nitric acid, and the nitroso-group survives boiling with dilute hydrochloric acid. Two of the nitro-groups in this compound are probably attached to the vinyl double bond, as the substance dissolves in sodium hydroxide solution to form a deep red liquid the colour of which fades on standing.

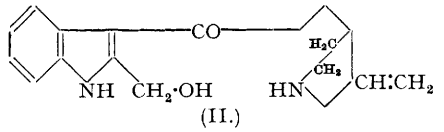
Indications of the presence of an indole were obtained by colour reactions; with vanillin or piperonal and alcoholic hydrochloric acid quinamine gives an immediate rose-red coloration, and with Ehrlich's reagent a purple colour. A pyrrole pine-shaving reaction is given by the vapours evolved on heating quinamine with zinc dust. Similar indole colour reactions are given by dihydroquinamine, but *apo*quinamine gives purple colours with vanillin or Ehrlich's reagent only on warming. *apo*Quinamine also gives a positive pine-shaving reaction on heating with zinc dust.

Definite evidence of the presence of an indole nucleus in quinamine was provided by heating the base with zinc dust at 320°. From the non-basic fraction of the steam distillate 2 : 3-dimethylindole was isolated as the picrate, identical (mixed m. p.) with a synthetic specimen prepared by Fischer's method (*Annalen*, 1886, **226**,

129). Since quinamine, $C_{19}H_{24}O_2N_2$, has 19 carbon atoms, and vinylquinuclidinecarboxylic acid (Part I, *loc. cit.*) and dimethylindole each have 10 carbon atoms, one, obviously that present in the carboxyl group of the acid, must form a connecting link between the indole and the quinuclidine portion of the molecule. On phytochemical grounds the link is most probably in the 3-position of the indole nucleus, since most of the indole alkaloids of known structure can be regarded as derivatives of tryptamine.



(I.)

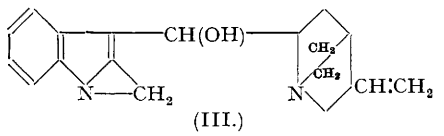


(II.)

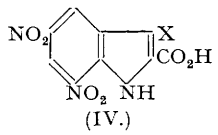
As quinamine is neither phenolic nor ketonic and forms an *N*-nitroso-derivative, the two oxygen atoms must be present in carbinol groups attached to the 2- and the 3-position of the indole nucleus, giving structure (I) for quinamine. The presence of a secondary alcoholic group in the 3-position accords with the formation of a ketonic quinatoxin, quinamicine (II), by the action of dilute acetic acid on quinamine (Part I, *loc. cit.*). Evidence for the presence of a primary carbinol group in position 2 is furnished by the evolution of formaldehyde (identified as its dimedon derivative) on heating either quinamine or dihydroquinamine above its melting point. A similar decomposition has been recorded by Fischer and Nenitzescu (*Annalen*, 1925, **443**, 119), who obtained formaldehyde by heating 3-carbethoxy-5-hydroxymethyl-2 : 4-dimethylpyrrole at 130°. The small amount of methyl iodide formed when quinamine is subjected to the Herzig–Meyer process for determination of methylimino-groups (Part I, *loc. cit.*) is probably due to this decomposition.

When quinamine is treated with acetic anhydride the elements of water are lost and acetyl*apo*quinamine is formed. Since *N*-nitrosoquinamine on treatment with acetic anhydride is acetylated but does not lose water, the hydrogen attached to the indole nitrogen atom must be involved in the reaction, and *apo*quinamine would then have structure (III). Tetrahydro*apo*quinamine presumably results through saturation of the vinyl group and opening of the 3-membered ring.

In view of the constitution derived for quinamine, a tentative formula (IV; X = NO) for the compound $C_9H_4O_7N_4$ (see above), obtained by nitric acid oxidation, may be suggested. This formula seems probable,



(III.)



(IV.)

as trinitrostrychol, which Tafel (*Annalen*, 1898, **301**, 336) obtained in the nitric acid degradation of strychnine, has been formulated by Menon and Robinson (J., 1931, 773) as (IV; X = NO_2).

Indole alkaloids have been isolated from a number of botanically unrelated plants (cf. Witkop, *Die Chemie*, 1943, **56**, 265), but quinamine is the first recorded instance of such an alkaloid found in *Cinchona*. Yohimbine, another indole alkaloid, occurs in *Pausinystalia Yohimba* which is included in the same botanical tribe, *viz.*, *Cinchoneæ*, as *Cinchona*. It has been suggested by Robinson (J., 1917, **111**, 876) that the quinoline ring in quinine may have been formed in the plant from quinic acid; it seems likely, however, that the source of the indole nucleus in quinamine is tryptophan. If the 3-membered ring, postulated above for *apo*quinamine, were to be opened by rupture of the C–N bond in the pyrrole nucleus a quinoline would result, a change which could form a hypothetical connection between quinamine and the other cinchona alkaloids of known constitution.

Experimental.

Nitric Acid Oxidation.—Quinamine (8 g.) in nitric acid (8 c.c., 10%) was cooled and treated slowly with nitric acid (100 c.c., *d* 1·42). The solution became bright green, changing quickly to dark brown; it was then heated for 48 hours on a water-bath, poured into a large volume of water, partly neutralised with ammonia, and extracted continuously in turn with ether and ethyl acetate. The ethereal extract on evaporation yielded picric acid, and the ethyl acetate a yellow resin containing some crystalline solid. Crystallisation from alcohol, followed by three crystallisations from water, gave yellow needles, m. p. 303—306° (decomp., corr.) (Found: C, 38·9; H, 1·4; N, 19·6. $C_9H_4O_7N_4$ requires C, 38·6; H, 1·4; N, 20·0%).

Nitro- and Nitronitroso-quinamine.—Nitrous fumes (from nitric acid and arsenious oxide) were passed for an hour through a suspension of quinamine (2 g.) in ethanol (5 c.c.). The solution turned through green to brown, and was poured into water (100 c.c.), made alkaline with sodium carbonate, and extracted with ether. The solvent on evaporation furnished a solid residue, which on crystallisation from ethanol gave a mixture of a fine powder (m. p. ~250°) and well-formed crystals (m. p. ~185°) which were easily separated mechanically. Each fraction was dissolved in benzene and poured through a column of alumina. In each case the yellow benzene filtrate on evaporation gave a solid which formed yellow rods from ethanol, m. p. 185° (corr.), and proved to be a *nitronitrosoquinamine* [Found: C, 59·45; H, 5·7; N, 14·0. $C_{19}H_{22}O_2N_2(NO)(NO_2)$ requires C, 59·05; H, 5·7; N, 14·5%]. The compound gave a positive Liebermann reaction. The alumina on elution with benzene–methanol (20 : 1) yielded a *nitroquinamine*, pale yellow needles, from methanol, m. p. 284—288° (corr.), $[\alpha]_D$ + 79·1° (*c* 0·826 in N/10-H_2SO_4) [Found: C, 63·8; H, 6·5; N, 11·4. $C_{19}H_{23}O_2N_2(NO_2)$ requires C, 63·8; H, 6·5; N, 11·75%]. Both these compounds are insoluble in 50% potassium hydroxide solution.

Tetranitronitrosodihydroquinamine.—Nitrous fumes were passed for 1½ hours through a cooled solution of quinamine (5 g.) in 10% nitric acid (40 c.c.). A yellow resin separated: after the addition of a further quantity of 10% nitric acid (10 c.c.) and nitric acid (40 c.c., *d* 1·42), the solution was heated for an hour on the water-bath, cooled, and poured into water (500 c.c.). The precipitate which formed (3·5 g.) was crystallised by dissolution in warm concentrated nitric acid and gradual addition of 10% nitric acid, whereupon it separated in fine yellow needles decomposing explosively

at 210—212°. This is presumably the nitrate; it was converted into the *hydrochloride* by boiling with 10% hydrochloric acid, from which it separates in yellow needles, m. p. 227° (decomp., corr.) [Found: C, 41·3; H, 3·9; N, 16·5; Cl, 6·2. $C_{19}H_{21}O_2N_2(NO_2)_4(NO)$,HCl requires C, 40·8; H, 4·0; N, 17·5; Cl, 6·3%]. Tetranitronitrosodihydroquinamine is soluble in 10% KOH to a red solution the colour of which fades on standing.

Nitronitroso- and *Dinitro-dihydroquinamine.*—Dihydroquinamine (1·0 g.), treated in ethanolic suspension with nitrous fumes in the manner described above for quinamine, yielded to ethyl acetate extraction a mixture of crystalline compounds which were separated by extraction with a small quantity of acetone. The acetone-insoluble fraction (0·4 g.) separated from ethanol in yellow rods, m. p. 228—230° after darkening at 194°, and consisted of a *nitronitroso-dihydroquinamine* [Found: C, 58·8; H, 6·1; N, 14·0. $C_{19}H_{24}O_2N_2(NO_2)(NO)$ requires C, 58·75; H, 6·2; N, 14·4%]. The acetone-soluble fraction crystallised from ethanol in yellowish-brown needles, m. p. 146—148° (corr.), and has the composition of a *dinitrodihydroquinamine* [Found: C, 56·55; H, 6·15; N, 13·9. $C_{19}H_{24}O_2N_2(NO_2)_2$ requires C, 56·45; H, 6·0; N, 13·9%].

Zinc dust distillation. Quinamine (4 g.) was mixed with zinc dust (30 g.) and an equal bulk of powdered pumice and heated in a metal-bath at 320° for 3 hours in current of hydrogen; the distillate was dissolved in ether, the ether evaporated, and the residue, after being acidified (litmus) with dilute sulphuric acid, was distilled with steam. The bulky steam-distillate was extracted with ether, the solvent removed, and the semicrystalline residue (0·3 g.) purified by solution in petroleum (b. p. 40—60°) and passage through a column of alumina. The residue obtained on evaporation of the petroleum was treated with a benzene solution of picric acid (0·5 g.), whereupon a picrate separated in reddish-brown needles, m. p. 157—159°, giving no depression on admixture with synthetic 2 : 3-dimethylindole (Found: C, 51·0; H, 3·7; N, 15·3. Calc. for $C_{10}H_{11}N,C_6H_3O_7N_3$: C, 51·3; H, 3·8; N, 15·0%).

Liberation of Formaldehyde from Quinamine.—Quinamine (6 g.) was heated at 210° for 1½ hours in a current of nitrogen, and the gases passed through a solution of dimedon (0·2 g.) in water (50 c.c.). The precipitate which formed (25 mg.) was collected and recrystallised from methanol; m. p. 189°, not depressed on admixture with an authentic specimen (Found: C, 69·8; H, 8·45. Calc. for $C_{17}H_{24}O_4$: C, 69·8; H, 8·3%). Dihydroquinamine (5 g.) under the same conditions gave 24 mg. of formaldehyde dimedon derivative, m. p. 189°.

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