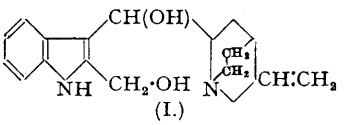
## 156. *Quinamine. Part III.* iso*Quinamine.*

By K. S. Kirby.

An isomeric compound, iso*quinamine*, is produced when quinamine is heated with amyl-alcoholic potash. It is yellow and crystalline and a number of derivatives and reactions are described.

The alkaloid quinamine, $C_{19}H_{24}O_2N_2$, which occurs in Cinchona barks, produces 2 : 3-dimethylindole on degradation and a constitution (I) has been suggested (Henry, Kirby, and Shaw, *J.*, 1945, 524; Kirby, *ibid.*, p. 528). It is of interest that cinchonamine, $C_{19}H_{24}ON_2$, isolated from *Remijia purdieana* has been shown to give colour reactions which indicate the presence of an indole nucleus (Raymond-Hamet, *Compt. rend.*, 1941, **212**, 135) and similar reactions are given by aricine, $C_{23}H_{26}O_4N_2$, from *Cinchona pelletierana* (Raymond-Hamet, *ibid.*, 1945, **221**, 307).



(I.)

When quinamine is heated with amyl-alcoholic potash at least two isomeric substances are formed. One of these, iso*quinamine*, is strongly lævorotatory and crystallises as yellow prisms which dissolve in acids or in ethanol with a green fluorescence. *iso*Quinamine, like quinamine, forms a *monohydrochloride* and a *monomethochloride*, and on hydrogenation with palladium one molecule of hydrogen is absorbed and *dihydro*iso*quinamine* is produced, which has the same

colour as the original compound. This can also be prepared by refluxing an amyl-alcoholic solution of dihydroquinamine with potassium hydroxide.

When *iso*quinamine is heated with acetic anhydride the elements of water are lost and the amorphous product, anhydro*iso*quinamine, forms a crystalline *picrate* and a *hydrogen* and a *neutral sulphate*. The same compound results when *iso*quinamine is treated with benzoyl chloride or heated with *cyclo*hexanone and aluminium phenoxide in xylene in the manner of the Oppenauer oxidation. A deep red solution is produced when anhydro*iso*quinamine is added to aqueous sodium hydroxide. Dihydro*iso*quinamine is also converted into an anhydro-derivative by reaction with acetic anhydride.

*iso*Quinamine forms a resinous nitroso-derivative which gives a crystalline acetyl compound but is best identified as its p-*nitrobenzoyl* derivative. When boiled with 10% acetic acid, *iso*quinamine is recovered unchanged, whereas quinamine produces a ketonic " toxin " by this reaction.

2 : 3-Dimethylindole is isolated as the picrate when *iso*quinamine is heated with zinc dust, and on heating either *iso*quinamine or its dihydro-derivative at 230—240° in a current of nitrogen, acetaldehyde is obtained (identified as its dimedone compound). Quinamine gives formaldehyde under similar conditions. The production of 1 mole of acetic acid by a Kuhn–Roth estimation on *iso*quinamine is further evidence of a $CH_3 \cdot C \cdot$ grouping which is absent in quinamine. Since dihydro*iso*quinamine produces rather more than one mole of acetic acid by a Kuhn–Roth oxidation, the vinyl side chain is probably present in *iso*quinamine. Rabe, Irschick, Müller, Nielsen, Kolbe, von Riegen, and Hochstätter (*Annalen*, 1932, **492**, 242) found that by heating cinchonine, cinchonidine, quinine, or quinidine with amyl-alcoholic potash the vinyl groups were unaffected although rearrangement to the *epi*-bases took place.

The nature of the rearrangement from quinamine to *iso*quinamine is not immediately obvious although it is significant that *apo*quinamine is recovered mainly unchanged on boiling with amyl-alcoholic potash.

When dihydroquinamine is heated with amyl-alcoholic potash a second *compound*, isomeric with *iso*quinamine, is also formed and crystallises as pale yellow needles from *iso*propanol. It may be a diastereoisomeride of *iso*quinamine but it has not yet been investigated.

## Experimental.

iso*Quinamine*.—Potassium hydroxide (0·37 g.) was dissolved in amyl alcohol (25 ml.), and quinamine (2 g.) added. The solution was boiled gently for 45 minutes and then poured into water (100 ml.). The amyl alcohol was removed by distillation in steam and the water was decanted from the brown resin, which was dissolved in ethanol. iso*Quinamine* crystallised as yellow prisms and was recrystallised from ethanol (0·6 g.), m. p. 211—213°, $[\alpha]_D$ −424° (*c*, 0·761 in 0·1N-$H_2SO_4$) [Found: C, 72·75; H, 7·85; N, 9·05; $CH_3(C)\cdot$, 4·85. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·75; N, 8·97; $CH_3(C)\cdot$, 4·81%]. It is almost insoluble in ether, benzene, and light petroleum.

*Dihydro*iso*quinamine*.—*iso*Quinamine (1 g.) was dissolved in ethanol (40 ml.), palladium–barium sulphate (0·4 g.) added, and the mixture shaken in an atmosphere of hydrogen: 74·6 ml. were absorbed (1 $\equiv$ requires 71·6 ml.). The catalyst was filtered off, and the product crystallised, by concentration of the solvent, as yellow prisms, m. p. 202—204° [Found: C, 72·4; H, 8·3; N, 8·9; $CH_3(C)\cdot$, 5·3. $C_{19}H_{26}O_2N_2$ requires C, 72·5; H, 8·3; N, 8·9; $CH_3(C)\cdot$, 4·78%]. *Dihydro*iso*quinamine* was also obtained when dihydroquinamine was heated in amyl alcohol with potassium hydroxide in the manner described for *iso*quinamine above; the m. p. was not lowered on admixture with the dihydro*iso*quinamine prepared by the first method.

A second *compound* could be separated from dihydro*iso*quinamine by its easy solubility in chloroform. Recrystallised from *iso*propanol, it separated as pale yellow needles, m. p. 204° [Found: C, 72·3; H, 8·6; N, 8·9; $CH_3(C)\cdot$, 5·68. $C_{19}H_{26}O_2N_2$ requires C, 72·5; H, 8·3; N, 8·9; $CH_3(C)\cdot$, 4·78%].

iso*Quinamine Hydrochloride*.—This *salt* was obtained when *iso*quinamine was dissolved in 1 or 2 equivs. of 10% hydrochloric acid, the water removed in a desiccator, and the crystalline mass recrystallised from ethanol–ether. It formed pale yellow plates, m. p. 227—228° (Found: C, 65·4; H, 7·3; N, 8·3; Cl, 10·0. $C_{19}H_{24}O_2N_2$,HCl requires C, 65·4; H, 7·2; N, 8·0; Cl, 10·2%).

iso*Quinamine Methochloride*.—*iso*Quinamine (1 g.) was dissolved in acetone, methyl iodide (2 ml.) added, and the solution left overnight. The solvent was then evaporated, and the methiodide crystallised from ethanol–ethyl acetate as pale yellow needles, m. p. 165—166°. This methiodide (0·6 g.) was dissolved in methanol, and silver chloride (1·0 g.) added. The mixture was shaken, filtered, and the *methochloride* crystallised as pale yellow needles by addition of ether; m. p. 145—147, $[\alpha]_D$ −16·8° (*c*, 0·893 in methanol). The solution had a bluish fluorescence (Found: C, 60·7; H, 7·85; N, 7·3; Cl, 9·1; NMe, 7·7. $C_{19}H_{24}O_2N_2$,$CH_3Cl$,$2H_2O$ requires C, 60·2; H, 7·8; N, 7·0; Cl, 8·9; NMe, 7·3%).

*Nitroso*iso*quinamine*.—*iso*Quinamine (1 g.) was dissolved in 10% acetic acid (10 ml.), sodium nitrite (1·0 g.) in water (3·0 ml.) added, and the solution kept overnight. The fluorescence had disappeared, and after the solution had been made alkaline with sodium carbonate, the yellow precipitate was extracted with chloroform, and the extract was dried ($Na_2SO_4$), filtered, and evaporated, leaving a yellow resin (1·1 g.). This resin (0·25 g.) was dissolved in benzene (5 ml.) and pyridine (1 ml.), and *p*-nitrobenzoyl chloride (0·25 g.) was added, and after standing for 3 hours at room temperature the solution was heated for 20 minutes on the water-bath. 10% Sodium carbonate was added, the resin

extracted with chloroform, the extract dried ($Na_2SO_4$), and the solvent evaporated. Addition of ethanol produced yellow needles of the p-*nitrobenzoyl* derivative, which were recrystallised from the same solvent; m. p. 155—156° (Found: C, 63·7; H, 5·6; N, 11·2. $C_{26}H_{26}O_6N_4$ requires C, 63·7; H, 5·35; N, 11·4%).

*Anhydroisoquinamine.*—*iso*Quinamine (2 g.) was heated with acetic anhydride (7 ml.) and 4 drops of pyridine on the steam-bath for 4 hours. Water was then added, the solution made alkaline with sodium carbonate, and the product extracted with butanol, to which a bright green fluorescence was imparted. The solvent was evaporated under reduced pressure, 20% sulphuric acid (5 ml.) added, and the *hydrogen sulphate* crystallised as yellow needles. Recrystallisation was effected from water containing a little sulphuric acid; m. p. 246—247°, $[\alpha]_D$ +128·3° (*c*, 0·967 in water) (Found: C, 58·3; H, 6·3; N, 7·4; S, 8·1. $C_{19}H_{22}ON_2,H_2SO_4$ requires C, 58·2; H, 6·2; N, 7·1; S, 8·2%).

When 10% sodium carbonate was added to a solution of this sulphate in water, the neutral *sulphate* crystallised immediately as yellow plates, m. p. 302—304° (decomp.). It was recrystallised from water [Found, for air-dried material: C, 56·2; H, 7·5. $(C_{19}H_{22}ON_2)_2,H_2SO_4,7H_2O$ requires C, 56·1; H, 7·45%. Found, for material dried at 105°/12 mm.: C, 65·4; H, 6·9; N, 7·9. $(C_{19}H_{22}ON_2)_2,H_2SO_4,0{\cdot}5H_2O$ requires C, 65·6; H, 6·8; N, 8·05%].

The *picrate* was prepared by addition of an ethanolic solution of picric acid to a solution of the original base in ethanol. It separated as yellow needles which were almost insoluble in ethanol and were recrystallised from acetone; m. p. 232—234°, $[\alpha]_D$ +77·6° (*c*, 0·49 in acetone) (Found: C, 57·15; H, 4·9; N, 13·2. $C_{19}H_{22}ON_2,C_6H_3O_7N_3$ requires C, 57·35; H, 4·8; N, 13·4%).

Anhydro*iso*quinamine was also isolated as the hydrogen sulphate (i) when *iso*quinamine (0·6 g.) was heated with benzoyl chloride (2 ml.), chloroform (2 ml.) and one drop of pyridine, and (ii) after *iso*quinamine (2 g.) was heated with dry xylene (50 ml.), dry *cyclo*hexanone (50 ml.), and aluminium phenoxide (10 g.) at 150° for 50 hours.

Dihydroanhydro*iso*quinamine was prepared from dihydro*iso*quinamine and acetic anhydride in the same manner as above. The hydrogen sulphate separated as yellow rods, m. p. 236—238°, and the neutral *sulphate* as yellow plates, m. p. 315—317° [Found: C, 56·05; H, 7·65. $(C_{19}H_{24}ON_2)_2,H_2SO_4,7H_2O$ requires C, 56·0; H, 7·7%].

*Action of Dilute Acetic Acid on* iso*Quinamine.*—*iso*Quinamine (1 g.) was heated with 10% acetic acid (10 ml.) and water (1 ml.) for 50 hours at 100°. The solution was made alkaline with sodium carbonate, and the precipitate (0·9 g.) crystallised from ethanol. The crystals melted at 208° and the m. p. was not lowered on admixture with *iso*quinamine.

*Amyl-alcoholic Potash and* apo*Quinamine.*—*apo*Quinamine (2 g.) was dissolved in amyl alcohol (25 ml.), potassium hydroxide (0·37 g.) added, and the solution boiled for 1 hour. The amyl alcohol was removed by distillation in steam, and the brown resin taken up in ether. After drying, filtration, and evaporation of the solvent, the residue was crystallised from benzene–light petroleum. 1·4 G. were obtained, m. p. 114°, not lowered on admixture with *apo*quinamine.

*Zinc-dust Distillation.*—*iso*Quinamine (4 g.) was mixed with zinc dust (60 g.) and an equal bulk of pumice, and the mixture heated at 350° in a current of hydrogen for 1·5 hours. The distillate was distilled in steam and the steam-volatile products were extracted with ether. The ethereal solution was washed several times with 10% sulphuric acid, then with 10% sodium carbonate, and after drying, filtration, and evaporation of the solvent, a yellow oil was obtained (0·27 g.). This was dissolved in benzene–light petroleum (1 : 1) and poured through a column of alumina, which was then washed with 50 ml. of the same mixture. The filtrate was collected, the solvents evaporated, and the residue (0·2 g.) treated with picric acid (0·3 g.) in benzene. The deep red solution was concentrated, and a crystalline mass separated. Recrystallisation from benzene produced brown-red needles, m. p. 153°, not lowered on admixture with 2 : 3-dimethylindole picrate.

*Action of Heat on* iso*Quinamine.*—*iso*Quinamine (5 g.) was heated in a stream of nitrogen at 230—240° for 2 hours, and the gases passed through a solution of dimedone (0·2 g.) in water (50 ml.). The precipitate, which formed slowly, was allowed to stand overnight and then filtered off (30 mg.). It was recrystallised from ethanol–water; m. p. 139°, not lowered on admixture with a synthetic specimen of acetaldehyde–dimedone compound (Found: C, 70·3; H, 8·7. Calc. for $C_{18}H_{26}O_4$: C, 70·6; H, 8·55%).

When dihydro*iso*quinamine (5 g.) was treated in the same manner 35 mg. of acetaldehyde–dimedon precipitate were formed.

The author thanks Dr. T. A. Henry and Mr. T. M. Sharp, M.Sc.Tech., for their interest, and Mr. A. Bennett for the microanalyses.

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LONDON, N.W. 1. [*Received, August 24th,* 1948.]