308. *Quinamine. Part V.* epi*Quinamine and* epi*Cinchonamine.*

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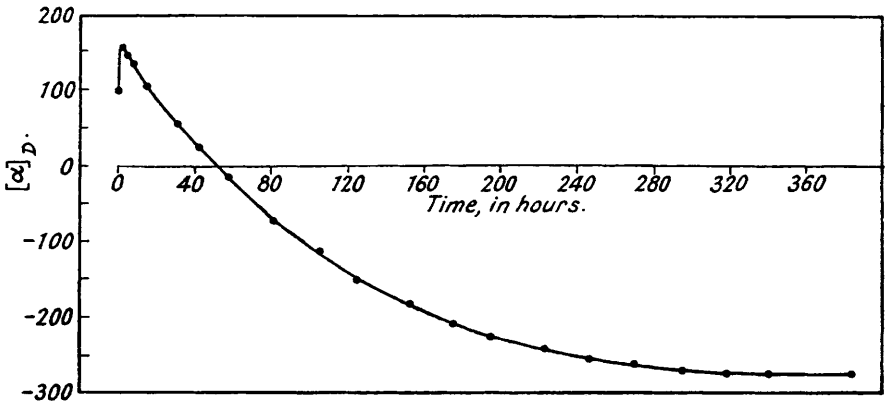
When heated with alcoholic potassium hydroxide, quinamine undergoes rapid epimerisation with formation of about 50% of *epi*quinamine. A slower conversion into *iso*quinamine and *epi-iso*quinamine proceeds simultaneously, so that a true equilibrium is not attained. *epi*Quinamine is probably identical with conquinamine, a minor *Cinchona* alkaloid which is a congener of quinamine. *epi*Quinamine is reduced by lithium aluminium hydride to *epi*-cinchonamine, a stereoisomeride of cinchonamine which has not been isolated from natural sources. Supporting evidence has been obtained for the formulation of the *iso*quinamines as the indoxyl derivatives (V). The structure (VI) for *apo*quinamine is confirmed by reduction of this base to a mixture of cinchonamine and *epi*cinchonamine. It is considered that the epimerisation of quinamine occurs at $C_{(8)}$ in the quinuclidine nucleus.

The conversion of quinamine into *iso*quinamine by heating it with amyl-alcoholic potassium hydroxide was reported in Part III (*J.*, 1949, 735), and it was stated that a second isomer was

probably also formed since, under similar conditions, dihydroquinamine gave rise to two isomeric dihydro*iso*quinamines (provisionally termed -I and -II). A more detailed investigation has now been made of the action of alcoholic alkali on quinamine, and it is found that, in addition to *iso*quinamine, two other isomerides, *epi*quinamine and *iso*quinamine-II, are produced together with some unidentified material. Under the conditions given in Part III for the preparation of *iso*quinamine, all three products are formed and may be isolated by a suitable procedure. *iso*Quinamine is the main product (48%), while *epi*quinamine is obtained in very small amount along with a little unchanged quinamine.

*iso*Quinamine-II is apparently a diastereoisomeride of *iso*quinamine: the ultra-violet absorption spectra of the two substances are very similar (Fig. 3, where the II-isomer is recorded as *epi-iso*quinamine) and both substances are yellow and exhibit the same green fluorescence in alcoholic solution. However, *iso*quinamine-II resembles dihydro*iso*quinamine-II in that the solid crystals show a blue fluorescence in ultra-violet light, in contrast to the bright yellow fluorescence of solid *iso*- and dihydro*iso*-quinamine-I. In harmony with this conclusion *iso*quinamine-II is converted quantitatively into dihydro*iso*quinamine-II on hydrogenation in the presence of palladised charcoal.

FIG. 1.



Change in optical rotation on heating quinamine (75 mg.) with a solution of sodium (50 mg.) in alcohol (12 c.c.) in a sealed tube at 80°.

When quinamine is heated with ethyl-alcoholic potassium hydroxide, there is a rapid increase in the optical rotation of the mixture, and after 2½ hours *epi*quinamine may be isolated in about 40% yield, the remaining quinamine being mostly recovered unchanged. The yield of *epi*quinamine is not increased, but rather decreased, by a longer period of heating, the actual change in optical rotation with time of heating (with alcoholic sodium ethoxide at 80°) being as shown in Fig. 1. The rotation rises rapidly to +156° (corresponding to 53% of *epi*quinamine) and then falls until it reaches a final steady value of −275° after 320 hours. After this prolonged heating, the only isolable products are *iso*quinamine-I ($[\alpha]_D$ −424°) and *iso*quinamine-II ($[\alpha]_D$ −269°), the latter in somewhat the smaller amount. The proportions of these products were not even approximately those which might be inferred from the final value of the optical rotation, so that unidentified by-products must also have been formed.

*epi*Quinamine may be partly reconverted into quinamine by a similar heating with ethyl-alcoholic potassium hydroxide for 2½ hours. The yield of quinamine was 30% and the unchanged *epi*quinamine was recovered. It is apparent therefore, that alcoholic alkali induces a rapid reversible reaction, quinamine $\rightleftarrows$ *epi*quinamine, which does not reach a true equilibrium because of the slow irreversible transformation of one or both compounds into the *iso*quinamines and other substances.

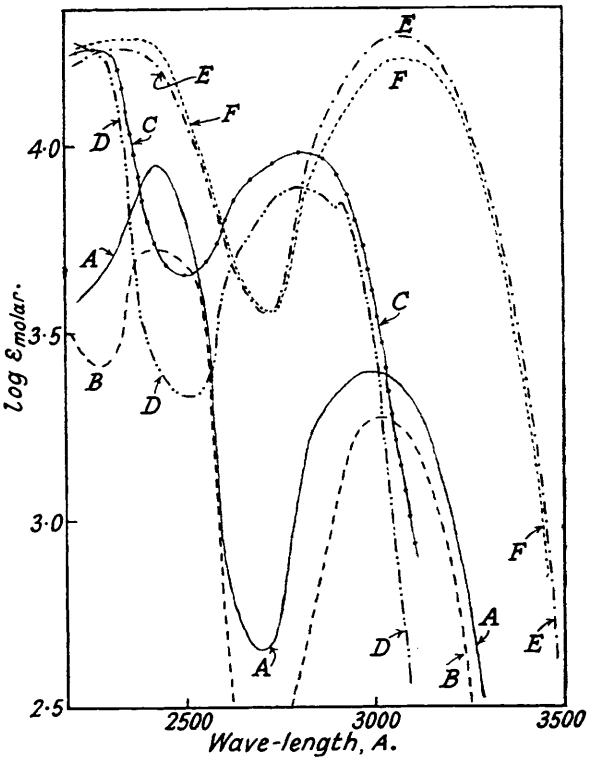
*epi*Quinamine has an ultra-violet absorption spectrum which is very similar to that of quinamine (Fig. 2), while its infra-red absorption spectrum confirms the absence of a carbonyl group. It may be converted into *apo*quinamine and quinamicine by the methods used for quinamine (Part I., *J.*, 1945, 524).

Although confirmation by direct comparison has not been possible, it is almost certain that *epi*quinamine is identical with the alkaloid conquinamine, $C_{19}H_{24}O_2N_2$, m. p. 123°, $[\alpha]_D$ +203°, which accompanies quinamine in small relative amount in *Cinchona* bark and was first isolated

by Hesse (*Ber.*, 1877, **10**, 2158). Conquinamine is reported to form a sparingly soluble nitrate (Oudemann, *Annalen*, 1879, **197**, 48) and possession of the same property by *epi*quinamine provides the basis for its ready separation from quinamine. Unfortunately, although a number of salts of conquinamine have been prepared, no melting points are recorded, and further comparison in this way is not possible. Conquinamine may also be converted into *apo*quinamine and quinamicine (Hesse, *Annalen*, 1881, **209**, 64, 67).

FIG. 2.

Ultra-violet absorption (in alcohol).



(*A*) *Quinamine.*
(*B*) epi*Quinamine.*
(*C*) *Cinchonamine.*
(*D*) epi*Cinchonamine.*
(*E*) apo*Quinamine.*
(*F*) *Acetyl*apo*quinamine.*

Further evidence of the nature of *epi*quinamine is provided by the fact that, like quinamine, it may be reduced by means of lithium aluminium hydride. Goutarel, Janot, Prelog, and Taylor (*Helv. Chim. Acta*, 1950, **33**, 150) have shown that quinamine is reduced by this reagent to cinchonamine, the net result being the loss of one oxygen atom. On repeating this experiment we have obtained the intermediate dihydro-derivative, mixed possibly with some unchanged quinamine, and subsequently dehydrated it to cinchonamine by heat. *epi*Quinamine is reduced in a similar manner to an isomeride of cinchonamine which exhibited a similar ultra-violet absorption spectrum (Fig. 2) and is termed *epi*cinchonamine. It was found in this case that the dihydro-derivative underwent spontaneous dehydration in solution in ether at the ordinary temperature. From these observations it is clear that *epi*quinamine is a diastereoisomeride of quinamine.

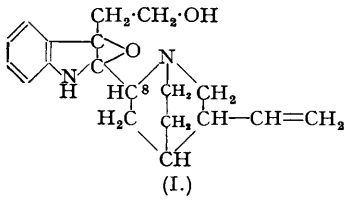
On the basis of the formula (II) proposed by Prelog and his collaborators (*loc. cit.*) for cinchonamine it is clear that stereoisomeric differences must be concerned with the circumstances obtaining in the quinuclidine nucleus, and cannot involve the indole moiety of the molecule. And further, since the isomerism of quinamine and *epi*quinamine persists in cinchonamine and *epi*cinchonamine, we may conclude that the original epimerisation of quinamine occurs in the quinuclidine nucleus. The existence of two *iso*quinamines and dihydro*iso*quinamines is obviously to be attributed to the same cause as that of two quinamines and two cinchonamines.

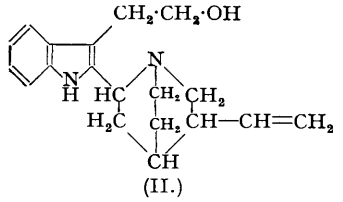
Hence we propose to adopt one system of nomenclature in the three cases and to replace the names *iso*quinamine-II and dihydro*iso*quinamine-II by *epi-iso*quinamine and dihydro*epi-iso*-quinamine, respectively.

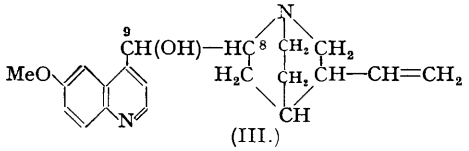
Further evidence for the diastereoisomeric nature of cinchonamine and *epi*cinchonamine has been provided by the formation of both bases when *apo*quinamine was reduced with sodium and alcohol (see below).

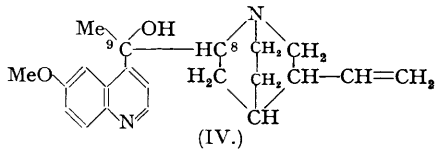
This observation identifies the asymmetric carbon atom concerned in the epimerisation as $C_{(8)}$ in the quinuclidine ring, a deduction in harmony with *a priori* consideration based on our existing knowledge of racemisation phenomena in this group.

The occurrence of the epimerisation has an important bearing on the question of the function of the second oxygen atom in quinamine, for it is found that neither cinchonamine (II) nor the *iso*quinamines are affected by prolonged heating with alcoholic alkali. This precludes the possibility that the racemisation is due simply to the hydrogen atom attached to $C_{(8)}$ being sufficiently labile *per se* to permit of the inversion at that position. Doering, Cortes, and Knox (*J. Amer. Chem. Soc.*, 1947, **69**, 1700) have concluded that the racemisation at $C_{(8)}$ in quinine, cinchonine, and related alkaloids is due to preliminary oxidation of (say) quinine (III) to quininone and enolisation of this to destroy the asymmetry at $C_{(8)}$. This is further substantiated by the finding of Woodward, Wendler, and Brutschy (*ibid.*, 1945, **67**, 1427) that methylquinidine (IV) is unaffected by heating with alcoholic alkali. This base bears the hydroxyl group at $C_{(9)}$ but the potentiality for oxidation and enol formation is precluded by the methyl group.

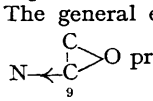
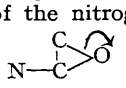
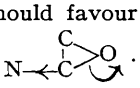
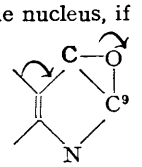

(I.)

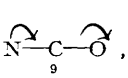

(II.)


(III.)


(IV.)

Without arriving at a definite conclusion from these striking facts as to the validity of Doering's hypothesis in its simplest form, we must at least recognise that racemisation at $C_{(8)}$ will occur if $C_{(9)}$ is $-CO-$ and not if it is $-CMe(OH)-$. This could be attributed to the potentiality for the displacement  in the former case, or some analogous condition of $-CH(OH)-$ which is not possible with $-CMe(OH)-$. It could, for example, be  In any case the essential feature is a positive charge, not necessarily a full one, on $C_{(9)}$. With the ethylene oxide formula for quinamine the same potentiality exists through the displacement  . It must be noted, however, that polarisation of the epoxide group in (I) would not be expected on theoretical grounds to take such a course that $C_{(9)}$ would acquire a positive charge. The general effect of the nitrogen atom should favour the other direction of polarisation.

 promotes  rather than  . An effect of the benzene nucleus, if present at all, should be in the same sense, as shown in the expression 

More plausibly an electromeric displacement,  , may be postulated (and this affords an explanation of the very weak basic strength of the hydroindole-nitrogen atom) but this process does not provide $C_{(9)}$ with a positive charge.

At this stage we are not compelled to invoke a special hypothesis of polarisation, for it may

well be that the inductive effect of N and O combined with the distortion of valency-electronic configuration in the three-membered ring bares the nucleus of $C_{(9)}$, inducing an electric field sufficient to loosen a proton on a neighbouring carbon atom. A decision on these points must await study of appropriate models, which are not available at the present time. The evidence in favour of the formulation of quinamine as an epoxide (I) is all indirect. It may be summarised as follows.*

(*a*) Of the two oxygen atoms, one has aliphatic hydroxy-function and the other must have ether function (absence of CO bond in the infra-red spectrum, absence of *N*-oxide group).

(*b*) This ethereal oxygen is the site of reduction ($LiAlH_4$) and the product is a tertiary alcohol (not an aromatic indole derivative) which easily loses the elements of water with formation of an indole derivative.

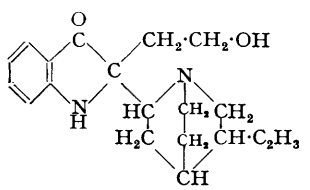
(*c*) There is independent evidence that *iso*quinamine is a 2 : 2-disubstituted indoxyl (cf. Part IV and below), and the rearrangement of (I) required to produce such a substance (V) is of a normal type.

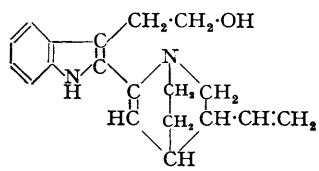
Consideration of (*a*), (*b*), and (*c*) leads to the conclusion that an epoxide constitution provides the best explanation of the findings; (*b*) indicates that the epoxide oxygen is attached to the α- or the β-position of the indole nucleus, and (*c*) indicates that it is attached to both these positions.

The stability of quinamine towards thiourea, potassium selenocyanate, or potassium ethyl xanthate, which react very readily with simple ethylene oxides (Davies *et al.*, *J.*, 1946, 1050; 1949, 278), may be explained as the result of the protective effect of the heavy substituents. All these anionoid reagents must attack a carbon atom of the ring. Cationoid reagents, such as acids, may however attack the more exposed oxygen atom and they do in fact react readily with quinamine.

After the identification of the true 2 : 2-tetramethyleneindoxyl (Plant and Robinson, *Nature* 1950, **165**, 36) a model was available for this type of structure, and the similarity in properties between the *iso*quinamines and this substance was seen to be even more striking than the resemblance to the 4-ketotetrahydroquinolines. Independent evidence now strongly favours the indoxyl constitution for *iso*quinamines and hence the structure (V) in relation to Prelog's suggestions.

(V.)





(VI.)

The *m*-dinitrobenzene test for the group $\begin{matrix}C\\C\end{matrix}\!>\!CH\cdot CO\cdot$ has been improved and found to give a positive reaction with phenyl *iso*propyl ketone, 4-ketotetrahydroquinoline, and hexahydroacridone. It is entirely negative with 2 : 2-tetramethyleneindoxyl and with the *iso*quinamines and dihydro*iso*quinamines.

Furthermore Elderfield and Maggiolo (*J. Amer. Chem. Soc.*, 1949, **71**, 1906) have shown that 4-ketotetrahydroquinolines can be dehydrogenated to 4-hydroxyquinolines by means of palladium catalysts and maleic acid. We have acquainted ourselves with the proper conditions and find that the *iso*quinamines cannot be dehydrogenated in a similar manner.

The structure (V) suggests no plausible mechanism for epimerisation at $C_{(8)}$ and we have been unable to bring about any transformation of *iso*quinamine into *epi-iso*quinamine, or *vice versa*, in the presence of boiling alcoholic sodium ethoxide. It is highly probable that quinamine and *epi*quinamine correspond to *iso*quinamine and *epi-iso*quinamine, although not necessarily respectively. No direct proof of these relations could be obtained because of the rapid equilibrium established between quinamine and *epi*quinamine, much more rapid than the conversion of either into *iso*quinamine.

Fig. 3 shows the ultra-violet absorption spectrum of *iso*quinamine compared with those of

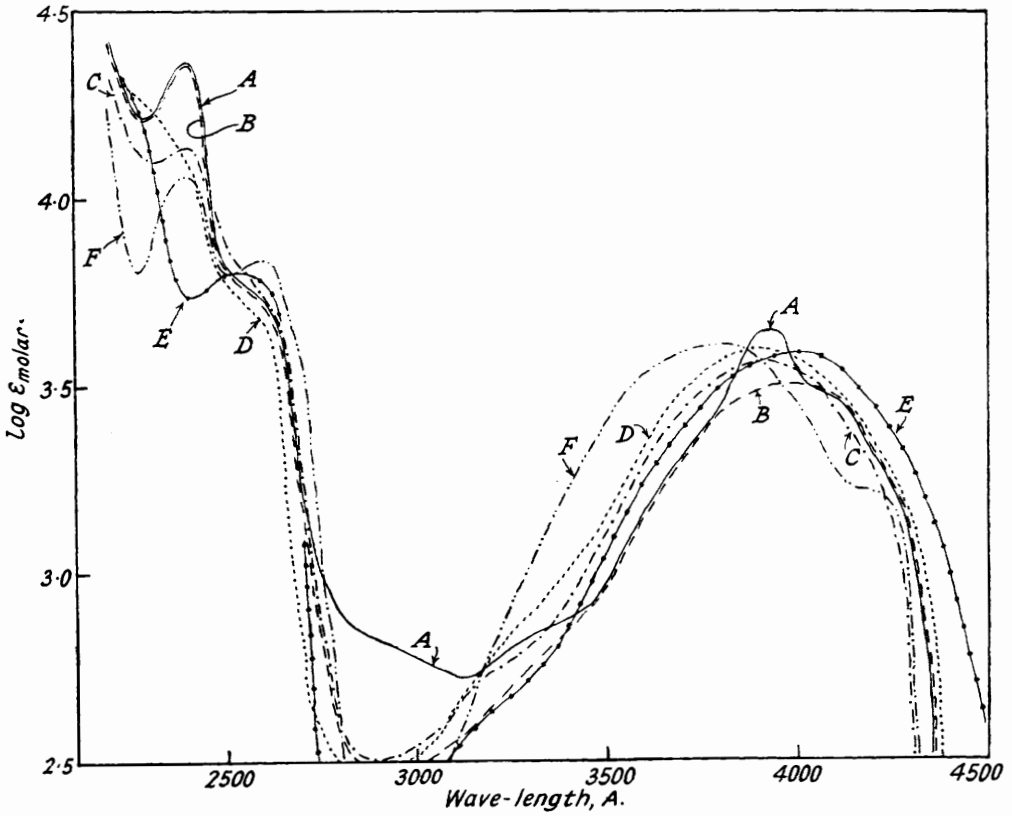
* *Added in Proof.*—Witkop (private communication) has suggested an alternative formulation of quinamine in which the free hydroxyl is in position 3 of the indole nucleus, the oxide ring being 5-membered. This recalls the relation of scopine to oscine, and the new formula appears to us to be preferable to the ethylene oxide structure. The points made in the text are still relevant.

model substances. It can be seen that the results are in harmony with the substituted indoxyl theory but cannot be said to exclude a hydroquinolone hypothesis.

The ultra-violet absorption spectra of *apo*quinamine and acetyl*apo*quinamine are shown in Fig. 2. The indications are that the indole nucleus is present with an additional conjugated centre, and formula (VI) accords with these results. In confirmation it has been found that reduction of *apo*quinamine with sodium and alcohol affords a mixture of cinchonamine and *epi*cinchonamine. The formula (VI) also explains the weak basicity of *apo*quinamine (cf. Hesse, *Ber.*, 1872, **5**, 265) which is exemplified by its extraction from a solution in dilute acetic acid with ether (the purification procedure specified in Part I should therefore be modified). The

FIG. 3.

Ultra-violet absorption (in alcohol).



(*A*) iso*Quinamine*.
(*B*) *Dihydro*iso*quinamine*.
(*C*) epi-iso*Quinamine*.
(*D*) *Dihydro*epi-iso*quinamine*.
(*E*) 2 : 2-*Tetramethyleneindoxyl*.
(*F*) 4-*Ketotetrahydroquinoline*.

constitution of *apo*quinamine is similar to that of *neo*strychnine in that both bases are vinylamine derivatives. Coupling of *neo*strychnine with *p*-nitrobenzenediazonium salts in weakly acid solution causes oxidative fission of the double bond and formation of a *p*-nitrophenylhydrazone :

$$CH{:}CH{\cdot}N- \longrightarrow C{:}N{\cdot}NH{\cdot}C_6H_4{\cdot}NO_2 + OCH{\cdot}N-$$

The product gives at once a light cherry-red colour in alcoholic sodium hydroxide solution.

In the case of *apo*quinamine an orange-coloured amorphous substance was precipitated and this was insoluble in N-hydrochloric acid. Its orange-yellow solution in alcohol became only pale greenish-brown on the addition of sodium hydroxide but this solution developed an intense bluish-red (damson) colour in a few seconds. It is clear that, if the coupling reaction is analogous to that of *neo*strychnine, the last stage is completed by the action of alkali. On acidification, the bluish-red solution became orange-yellow and the bluish-red colour was at once restored by the addition of sodium hydroxide.

Experimental.

Action of Amyl-alcoholic Potassium Hydroxide on Quinamine.—A solution of quinamine (4 g.) and potassium hydroxide (0·72 g.) in amyl alcohol (the technical mixture, chiefly *iso*amyl alcohol) (50 c.c.) was refluxed for 45 minutes, the amyl alcohol removed by steam-distillation, and the residual resin separated and dissolved in a little hot ethyl alcohol. On cooling, bright yellow prisms of *iso*quinamine (1·62 g.), m. p. 203—205°, were obtained and concentration of the filtrate, after the addition of a little water, gave pale yellow clustered needles of (crude) quinamine (0·19 g.), m. p. 165—169°, mixed m. p. 170—174°. After further concentration yellowish-green needles of *iso*quinamine (0·12 g.) separated, having m. p. 201—203° and mixed m. p. 203—204°. The mother-liquors were evaporated *in vacuo* and extracted with benzene, and the washed and dried extract was passed through an alumina column. A rapidly moving band, colourless in ordinary light but showing white fluorescence in ultra-violet light, was collected first and, on evaporation gave a colourless oil which slowly solidified. Recrystallisation from light petroleum afforded material from which quinamine (0·01 g.; hard knobs of needles), m. p. 169—172°, mixed m. p. 171—173°, and epi*quinamine* (0·16 g., large prisms), m. p. 110—113°, were easily separated by hand-picking; the residual solid (0·03 g.) was clearly a mixture of these two components only. Elution of the remaining complex band system with benzene containing 5% of methanol gave the principal components as a yellow band exhibiting chiefly yellow fluorescence in ultra-violet light. However, the band was not homogeneous and both the fore and rear sections showed that a white-fluorescent substance was also present. A second absorption on alumina did not effect a separation, so the solution was evaporated (total solid : 0·82 g., m. p. 145—165°) and the residue recrystallised from benzene with very slow cooling of the solution. In this way, the larger part of the material separated as large, yellowish-green prisms (0·3 g.; m. p. 181—183°) which showed a bluish-white fluorescence in ultra-violet light and were readily separated by hand-picking from smaller, bright yellow prisms of *iso*quinamine (m. p. 195—199°, mixed m. p. 197—201°) which has a bright yellow fluorescence. The yellowish-green prisms were recrystallised from benzene, to give epi-iso*quinamine*, m. p. 182·5—183·5°, $[\alpha]_D^{19}$ −269° ± 5° (*c*, 1·3 in alcohol) (Found : C, 72·5; H, 7·5; N, 9·2. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·7; N, 9·0%). A mixture with quinamine melted at 152—158°. The aqueous layer in the steam-distillation flask from which the original reaction product was centrifuged was concentrated to a small volume and extracted with chloroform, affording a solid consisting almost entirely of *iso*quinamine (0·14 g.), m. p. 199—201°, mixed m. p. 200—202° (total yield of *iso*quinamine, 1·90 g., 48%).

Hydrogenation of epi-iso*Quinamine.*—*epi-iso*Quinamine (50 mg.) and palladised charcoal (15 mg.) were shaken in alcohol with hydrogen at the room temperature and pressure for 3 hours. The filtered and concentrated solution furnished dihydro*epi-iso*quinamine (50 mg.), m. p. 193—196°, mixed m. p. 197—200°.

Action of Ethyl-alcoholic Potassium Hydroxide on Quinamine.—A solution of quinamine (1·0 g.) and potassium hydroxide (0·2 g.) in ethyl alcohol (12 c.c.) was refluxed for 2 hours, the alcohol was removed *in vacuo*, water was added, and the products were extracted with ether. The solid left on evaporation of the extract was triturated with N-nitric acid (5 c.c.) and water (6 c.c.), and the mixture filtered after 2 hours. Basification of the filtrate gave unchanged quinamine (0·56 g.), m. p. 164—168°. The solid nitrate (0·45 g.) crystallised from water in stout prisms (0·38 g.), m. p. 202° (decomp.), which were dissolved in warm 60% alcohol. The solution was neutralised with ammonia and allowed to cool. *epi*Quinamine (0·25 g.) separated as long, prismatic needles, m. p. 119—121°. Recrystallisation from light petroleum gave prisms, m. p. 120—121°, $[\alpha]_D$ +197° (*c*, 2·5 in alcohol) (Found : C, 72·9; H, 8·0; N, 9·0. $C_{19}H_{24}O_2N_2$ requires C, 73·0; H, 7·7; N, 9·0%). Neutralisation of the mother-liquors from the recrystallisation of the crude *epi*quinamine nitrate yielded a further amount (0·03 g.) of nearly pure *epi*quinamine, m. p. 110—112°, so that in subsequent preparations, recrystallisation of the nitrate could be eliminated.

The change in optical rotation of the reaction mixture was followed by heating at 80° a solution of quinamine (75 mg.) and sodium (50 mg.) in absolute alcohol (9·45 g.) in a special sealed tube which functioned also as a polarimeter tube. This was a Pyrex tube, approx. 1 cm. × 10 cm., with optically flat plates sealed on each end, and a side-arm in the middle for filling and sealing. The alcohol used was purified by refluxing it with zinc and sodium hydroxide and distilling it from sodium, and the filling of the tube performed as far as possible under nitrogen in order to minimize colouring of the solution (cf. Doering, Cortes, and Knox, *J. Amer. Chem. Soc., loc. cit.*). With these precautions, the optical rotation could be easily determined even after heating for 380 hours, although the final products were themselves yellow. The results are shown in Fig. 1. After the experiment, the solution was concentrated, a little water added, and the product allowed to crystallise. Clusters of yellow needles were obtained which showed partly yellow and partly white fluorescence in ultra-violet light. Hand-picking gave *iso*quinamine (yellow prisms), m. p. 195—198°, mixed m. p. 197—201°, and *epi-iso*-quinamine (needles), m. p. 156—166°, mixed m. p. 168—178°. The mother-liquors, on further dilution with water, gave *epi-iso*quinamine as a white-fluorescent solid, crystallising from benzene in yellow needles, m. p. and mixed m. p. 182—183°.

Conversion of epi*Quinamine into Quinamine.*—*epi*Quinamine (50 mg.), potassium hydroxide (0·1 g.), and ethyl alcohol (3 c.c.) were refluxed for 2 hours, and the product was converted into the nitrates in the manner described above. *epi*Quinamine nitrate (26 mg.), m. p. 197°, was separated, and neutralisation of the filtrate gave a solid (16 mg.), m. p. 150—156°, which was essentially quinamine. On recrystallisation from aqueous alcohol, it formed glistening needles, m. p. 167—169°, mixed m. p. 169—173°.

Dehydrogenation of 4-Ketotetrahydroquinoline.—Water (2 c.c.) to which 4-ketotetrahydroquinoline (50 mg.) and palladised charcoal (10 mg.; 10% Pd) had been added was refluxed for 14 hours, and then filtered and evaporated. The residue was washed with ether and crystallised from dioxan to give 4-hydroxyquinoline (30 mg.), m. p. and mixed m. p. 195—197°. When the experiment was carried out with the addition of maleic acid as prescribed by Elderfield and Maggiolo (*loc. cit.*) in similar cases the

product separated as clusters of pale yellow needles, m. p. 227°, from hot water, and was apparently formed by combination of two molecules of 4-hydroxyquinoline with one molecule of maleic acid (Found : C, 65·6; H, 4·7; N, 6·9. $C_{22}H_{18}O_6N_2$ requires C, 65·0; H, 4·4; N, 6·9%). This substance was not formed by refluxing a mixture of 4-ketotetrahydroquinoline, maleic acid, and water without a catalyst. The maleic acid was transformed into fumaric acid.

Conversion of epi*Quinamine into* apo*Quinamine.*—*epi*Quinamine (50 mg.) was heated with an excess of acetyl chloride in refluxing benzene for 4 hours, the solvent evaporated, and the residue dissolved in a little alcohol and refluxed for 1 hour with potassium hydroxide (0·2 g.) in aqueous alcohol. The alcohol was removed *in vacuo* and the product, isolated by means of ether, taken up in dilute acetic acid, and the solution clarified centrifugally. Addition of an aqueous solution of potassium iodide (0·15 g.) precipitated an oil which slowly solidified. After 2 hours at 0°, crude *apo*quinamine hydriodide (60 mg.), m. p. 180—185°, mixed m. p. 186—190°, was collected. Neutralisation of a warm, aqueous-alcoholic solution of the hydriodide gave white prisms of *apo*quinamine, m. p. 110—111°, mixed m. p. 110—112°.

Conversion of epi*Quinamine into Quinamicine.*—A solution of *epi*quinamine (50 mg.) in 10% acetic acid (0·5 c.c.) was refluxed for 48 hours and the base precipitated with ammonia. The gum was washed by decantation, taken up in dilute acetic acid, and mixed with alcoholic picric acid. The picrate, which formed, crystallised from water in very small yellow needles, m. p. and mixed m. p. 195—196° (decomp.).

Reduction of Quinamine with Lithium Aluminium Hydride.—A solution of lithium aluminium hydride (0·04 g.) in ether (2 c.c.) was gradually added to one of quinamine (0·1 g. in 10 c.c.), and the mixture was refluxed for 15 minutes. Water was added to decompose the excess of hydride, and the washed and dried ethereal solution was evaporated at room temperature to give a colourles amorphous solid. The composition of this substance, and its subsequent conversion by heat into cinchonamine, indicated that it was the *dihydro*-derivative, formed by the reductive fission of the epoxide ring, mixed possibly with some unchanged quinamine. When heated it began to soften at 60°, then gradually melted with evolution of gas, partly resolidified at about 100°, and slowly melted again as the temperature rose to 150° (Found, in material dried *in vacuo* at the ordinary temperature : C, 72·4; H, 9·0. $C_{19}H_{26}O_2N_2$ requires C, 72·5; H, 8·3%). Dehydration of this compound by heating it at 12 mm. for 1 hour at 150°, and finally for 10 minutes at 190°, followed by crystallisation from benzene–light petroleum, yielded cinchonamine, identified by m. p. and mixed m. p. 184° with an authentic specimen.

epi*Cinchonamine.*—Reduction of *epi*quinamine with lithium aluminium hydride, under precisely the conditions described above for the reduction of quinamine, yielded a colourless solid, very similar in composition and behaviour on heating to the product that was obtained from quinamine (Found, in material dried *in vacuo* at the ordinary temperature : C, 72·2; H, 8·4; N, 8·2. $C_{19}H_{26}O_2N_2$ requires C, 72·5; H, 8·3; N, 8·9%). Considerable difficulty was being experienced in attempts to obtain from this amorphous substance either cinchonamine, or an isomer thereof, by high-temperature dehydration when a chance observation led to the discovery that dehydration could occur spontaneously at the ordinary temperature. It was noticed that some crystals had separated from a concentrated ethereal solution of the reduction product, which had been kept for about an hour at room temperature. These proved to consist of the isomer of cinchonamine which we have designated epi*cinchonamine*. The following procedure was then adopted for its preparation : A solution of lithium aluminium hydride (0·7 g.) in ether (28 c.c.) was gradually added to one of *epi*quinamine (1·43 g. in 36 c.c.), and the solution was refluxed for 3 hours. The excess of hydride was decomposed by the cautious addition of water, and the ethereal solution was washed, dried, and concentrated to a volume of approx. 10 c.c. When the solution was kept, crystals of pure *epi*cinchonamine separated in the form of long prisms (0·36 g.), m. p. 168°, $[\alpha]_D$ +48° (*c*, 2·0 in alcohol) (Found : C, 76·9; H, 8·1; N, 9·2. $C_{19}H_{24}ON_2$ requires C, 77·0; H, 8·1; N, 9·5%). By submitting the mother-liquor from the crystallisation to further treatment with lithium aluminium hydride an additional small amount (0·12 g.) of pure *epi*cinchonamine was obtained.

*epi*Cinchonamine closely resembles cinchonamine in crystalline form and solubility in the common solvents. It is readily soluble in alcohol, chloroform, or benzene, less so in ether, very sparingly so in light petroleum, and it is almost insoluble in water. Like cinchonamine it forms a very sparingly soluble *nitrate*, which separates as oily droplets, soon becoming crystalline, on adding an aqueous solution of potassium nitrate to one of the hydrochloride. The salt, recrystallised from hot water, in which it is moderately readily soluble, has m. p. 197° (Found: C, 63·5; H, 7·0. $C_{19}H_{24}ON_2,HNO_3$ requires C, 63·5; H, 7·0%). The behaviour of *epi*cinchonamine towards Ehrlich's reagent is the same as that of cinchonamine. No coloration is given in the cold, but on heating a red colour develops, which is intensified to purple by the addition of a trace of sodium nitrite. When *epi*cinchonamine is treated with a methyl-alcoholic solution of vanillin, with the addition of concentrated hydrochloric acid, a rose colour develops at once in the cold and slowly intensifies to a reddish purple. When the solution is heated, the colour is almost discharged, changing to a faint yellow, which turns to red on the addition of a trace of sodium nitrite. Cinchonamine, when treated in the same way under exactly comparable conditions, behaves differently. On mixing the reagents no colour is given in the cold, but on heating a faint rose colour develops which intensifies to red on the addition of a trace of nitrite.

Attempts to Epimerise Cinchonamine.—No change in the optical rotation of a solution of cinchonamine (0·1 g.) in ethyl alcohol (14 c.c.) containing potassium hydroxide (0·02 g.) was observed after heating in a sealed tube at 70° for 12 hours. Heating with more concentrated alkali at a higher temperature and for a longer period similarly had no effect; there was no change in rotation when a solution of the alkaloid (0·05 g.) in amyl alcohol (5 c.c.) containing potassium hydroxide (0·1 g.) was heated for 2 days at 120°.

Reduction of apo*Quinamine.*—A refluxing solution of *apo*quinamine (0·2 g.) in dry ethyl alcohol (10 c.c.) was treated with small pieces of sodium (0·5 g.). When all the sodium had dissolved, water (10 c.c.) was added and the alcohol removed *in vacuo*. The product separated first as an emulsion but crystallised before all the alcohol had been removed; after some time at 0°, white needles (0·2 g.), m. p. 134—138°, were collected. An earlier experiment had shown that, although cinchonamine was easily isolated by reason of its sparing solubility, the second product was very difficult to obtain pure (separation by means of the nitrates being unsuccessful because of the insolubility of *epi*cinchonamine

nitrate). The material was therefore subjected to fractional crystallisation from ether. The first crop was pure cinchonamine [47 mg.; m. p. 180—181°; $[\alpha]_D$ +123° (18·7 mg. in 1·04 c.c. of alcohol); mixed m. p. 182—183°; nitrate, m. p. and mixed m. p. 227° (decomp.)], but the subsequent fractionation did not effect a consistent separation of the two components, both of which are sparingly soluble in ether. One crystallisation, however, gave a mixture (14 mg.) from which *epi*cinchonamine in the form of massive prisms {6 mg.; m. p. 165—168°; mixed m. p. 166—168°; $[\alpha]_D$ +51° (5·5 mg. in 0·33 c.c. of alcohol)} was readily separable by hand. The following data permit the calculation of the approximate isolated yields of the two products as cinchonamine 47% and *epi*cinchonamine 26%. The fractions obtained by successive concentrations of the ethereal solution of the total product were : 47 mg., m. p. 180—181°; 81 mg., m. p. 147—155°; 5 mg., m. p. 181·5—182°; and 20 mg., m. p. 157—165° (this last being shown by mixed melting points to consist largely of *epi*cinchonamine). Melting points of synthetic mixtures with the stated percentages of cinchonamine were as follows : 80%, 165—175°; 50%, 143—158°; 35%, 143—152°; 29%, 145—157°.

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