

and deposited the hydroxyazo dye almost quantitatively. Redissolved in hot 50% alcohol with the aid of ammonia and re-acidified with hydrochloric acid it formed a purple powder which appeared under the microscope as rosets of brown platelets. It is practically insoluble in neutral solvents and does not melt when heated to 290°.

Analyses. Calc. for $C_{16}H_{13}O_5N_3S \cdot H_2O$: H_2O , 4.77. Found: H_2O , 5.51. Calc. for $C_{16}H_{13}O_5N_3S$: N, 11.68. Found: N, 11.78.

5,8-Dihydroxy-6-methoxyquinoline.—When 5 g. of diamino-methoxyquinoline were boiled for 3 hours in 1:1 hydrochloric acid and then chilled, red-brown crystals of the dihydroxy hydrochloride slowly separated. This salt was washed with the acid, dissolved in water, and treated with an excess of sodium acetate. On rubbing, 3 g. of the base quickly separated as yellow microscopic prisms which became purple on exposure. It was recrystallized from about 40 parts of alcohol and then from toluene, forming lustrous yellow leaflets and needles melting at 195–197° with slight preliminary softening and darkening. It is sparingly soluble in the cold in methyl and ethyl alcohols and in acetone, but more readily soluble if the solvent is warmed. It dissolves in dil. acids with the formation of a brown-orange colored solution and in conc. sulfuric acid with an orange-yellow color. The solution in alkali is brown and the shade deepens on standing, while an alcoholic solution gives an olive color with ferric chloride.

Analyses. Calc. for $C_{10}H_9O_3N$: C, 62.80; H, 4.71; N, 7.33. Found: C, 62.90; H, 4.72; N, 7.81.

Action of Acids on 5,8-Diaminoquinoline.—Two and a half g. of diaminoquinoline were boiled 3 hours with 1:1 hydrochloric acid, a portion of the hydrochloride remaining undissolved throughout. From the collected salt almost all of the base was recovered unchanged. When the mother liquor was rendered alkaline, it showed the presence of a trace of hydroxy compound by the deposition of green flocks, but the odor of ammonia was scarcely detectable on boiling.

Summary

Like the amino groups in the amino azo dyes derived from 5-amino-dihydroquinine and 5-amino-6-methoxyquinoline, those in the 5,8-diamino-compounds obtained from the dyes by reduction are easily replaceable by hydroxyl. A number of the intermediate and end products of this transformation are described.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

SYNTHESES IN THE CINCHONA SERIES. VIII. THE HYDROGENATION OF DIHYDROCINCHONINE, CINCHONINE AND DIHYDROQUININE¹

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The hydrogenation of the cinchona alkaloids has been studied by many workers in the past. Since the attempts of others by different methods had yielded substances of indefinite character, Konek von Norwall,² and Lippmann and Fleissner³ applied the Ladenburg method of reduction

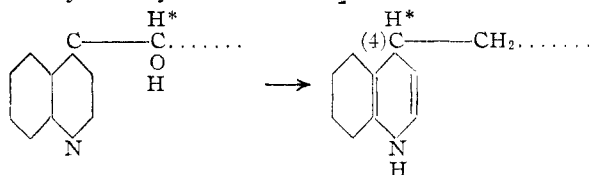
¹ Presented at the Annual Meeting of the American Chemical Society, New York, September, 1921.

² von Norwall, *Monatsh.*, **16**, 630 (1895).

³ Lippmann and Fleissner, *ibid.*, **16**, 321 (1895); *Ber.*, **28**, 1637 (1895); **29**, 801 (1896).

with sodium and alcohol with the idea of reducing the quinoline portion of the substance. Lippmann and Fleissner obtained from quinine a strongly basic, thick oil or resin which gave the color reactions of a tetrahydroquinoline derivative but from which no crystalline compounds were obtained, with the exception of a chloroplatinate. Konek von Norwall reduced cinchonine with sodium and ethyl alcohol to an amorphous non-crystallizable substance which he believed to be a dihydrocinchonine. He subsequently substituted amyl alcohol as the solvent and then obtained a product which, although amorphous as the free base, was readily converted by nitrous acid into a crystalline salt which he described as the nitrite of a nitrosotetrahydrocinchonine. Quinine, quinidine and cinchonidine were then found to yield similar products.

In 1901 Tafel⁴ noted that by the use of his electrolytic reduction method on the cinchona alkaloids 4 hydrogen atoms were absorbed, the product, however, being non-crystalline. More recently Freund and Bredenberg⁵ repeated Tafel's work and obtained from cinchonine a compound in 40% yield in which one hydrogen molecule entered the quinoline nucleus, with simultaneous reduction of the secondary alcoholic group by the other. This substance was identified as a Q-dihydro-desoxycinchonine or Q-dihydrocinchonane.⁶ A by-product of the reaction was an oily non-crystalline substance possessing the same composition and which these workers considered to be an isomer and designated as isodihydro-desoxycinchonine. With the reduction of the secondary hydroxyl group to hydrogen, the asymmetry of the carbon⁷ atom



connecting the quinoline and the quinuclidine nuclei is destroyed, while the addition of the two hydrogen atoms to the quinoline nucleus creates a new asymmetric carbon at Position 4 which would explain the production of two isomeric bases. On reduction of the crystalline base with sodium and amyl alcohol an oily tetrahydro-desoxycinchonine (tetrahydrocinchonane) was obtained which yielded on hydrogenation with palladium and hydrogen an oily hexahydrocinchonane, both bases forming crystalline salts.

A year later Skita and Brunner⁷ succeeded in reducing the cinchona alkaloids with a large excess of platinum black and hydrogen under pressure

⁴ Tafel, *Ber.*, **34**, 3299 (1901).

⁵ Freund and Bredenberg, *Ann.*, **407**, 43 (1915).

⁶ For the meaning of the suffix *-ane*, cf. *THIS JOURNAL*, **42**, 1489 (1920).

⁷ Skita and Brunner, *Ber.*, **49**, 1597 (1916).

to high-melting crystalline hexahydro alkaloids and finally to the do-decahydro compounds. In the case of the hexahydro alkaloids, however, they make no mention of the occurrence of isomers resulting from the new asymmetry of carbon (4).

In connection with our synthetic studies in the cinchona group we were led to seek for a less costly and cumbersome method for their reduction than that devised by Skita and Brunner. Because of the rather indefinite results of Konek von Norwall and Lippmann and Fleissner, it occurred to us that, by using the dihydro alkaloids as starting material, sodium and amyl alcohol should yield products the same as those described by Skita and Brunner. To our surprise, however, dihydrocinchonine yielded an oil which was found to be a mixture of different bases. On converting this mixture into the dihydrochlorides in absolute alcoholic solution, it was found possible by fractional crystallization to isolate three different salts. The least soluble of these was obtained in about 25% yield and proved to be the dihydrochloride of a hexahydrocinchonane⁸ which yielded a crystalline base melting at 106-7°. The most soluble salt proved also to be the dihydrochloride of a hexahydrocinchonane and was obtained in about equal amount. This salt likewise yielded a

⁸ After this communication had been sent to the editor, papers by G. Giemsa and J. Halberkann [*Ber.*, **54**, 1167, 1189 (1921)] appeared in which these authors criticize our use of the ending "ane" as a simplification of the term "desoxy" alkaloids on the ground that such a name should just as properly belong to the "still hypothetical reduction products of hydroquinene" and consequently necessitate the confusing use of prefixes α -, β -, etc. These authors apparently have failed to realize that if Rabe's views on the stereochemical relationships of the cinchona alkaloids are correct (and they are supported by excellent evidence) the reduction of hydroquinene should yield a mixture of what we have called dihydroquinane (dihydro-desoxyquinine) and dihydroquinidane (dihydro-desoxyquinidane), a third substance being impossible. In spite of their objections to this terminology, they have applied it to their own apparently isomeric substances, designating as hydrocupreane and hydroquinane the substances prepared by them by diazotization of the 5-amino alkaloids. They justify this on the ground that their substances are produced by a method so gentle as to make unlikely the occurrence of optical isomerization in the reduction of the secondary alcoholic group to CH_2 , whereas the reaction involving the use of phosphorus pentachloride for the preparation of the desoxy alkaloids over the chloro compounds is more apt to affect the steric relationship of these to the parent alkaloids.

These statements are incompatible with Rabe's views, and unless Giemsa and Halberkann's "hydrocupreane" had undergone optical or other intramolecular rearrangement it should have been identical with our dihydrocupreane. Since it has been shown to be different it must be concluded that their substances, the products of a little understood reaction, are the result of some such rearrangement.

Finally, the possibility of any isomerization with phosphorus pentachloride seems most remote since the direct reduction of dihydrocinchonine with sodium or zinc as described in this paper yields the same α - and β -hexahydrocinchonanes as those obtained by reduction of dihydrocinchonane which was prepared over the chloro compound. We see no reason, therefore, for discontinuing the use of the terminology which we have begun.

crystalline base melting at 106–106.5°. We have designated the former base α - and the latter as β -hexahydrocinchonane. These substances are unquestionably epimers, both being formed when carbon atom (4) of the quinoline ring becomes asymmetric, just as was assumed by Freund and Bredenberg in the electrolytic reduction of cinchonine. That these substances are tetrahydroquinoline derivatives was shown by the fact that they form stable dihydrochlorides, nitrosamines, N-acyl derivatives and phenylazo dyes, the last of which was obtained in crystalline form only in the case of the α -compound. They also give the characteristic color reactions of tetrahydroquinoline with ferric chloride.

It appeared rather surprising that the reduction of the secondary alcoholic group of cinchonine to the CH_2 group should have occurred here as well as in the electrolytic reduction. To prove the correctness of the findings, however, dihydrocinchonine was converted through the chloro compound into dihydrocinchonane, which was in turn reduced with sodium and amyl alcohol; α - and β -hexahydrocinchonane were obtained exclusively. One of these isomers must therefore be the hexahydro-desoxycinchonine described by Freund and Bredenberg but not obtained by them in crystalline form.⁹

The third substance obtained by fractionation of the hydrochlorides was isolated finally as a dihydrobromide. Its elementary composition corresponds to that of a hexahydrocinchonine. Unfortunately, the base could not be obtained crystalline and could not, therefore, be compared with the product of Skita and Brunner. We are, however, of the opinion that our substance is different from theirs. From our experience and that of Freund and Bredenberg, it is rather strange that Skita and Brunner did not observe the formation of epimeric isomers in the reduction of the alkaloids by their method. Our third substance also gives all of the reactions of a tetrahydroquinoline. Under the conditions employed it would seem, therefore, that the alcoholic group does not suffer reduction in all of the alkaloid used.

To ascertain whether other reducing agents would yield the same compounds, dihydrocinchonine was reduced with zinc and hydrochloric acid; this process yielded an oily base from which an appreciable amount of α -hexahydrocinchonane was isolated by means of the hydrochloride. Since the yield of this product was much poorer than that obtained by the sodium method, the reaction unquestionably proceeded partly in a different sense.

⁹ Since a tetrahydrocinchonane (tetrahydro-desoxycinchonine) which they also describe was found by them to possess $[\alpha]_D$ 64.6°, this substance must therefore be isomeric with the tetrahydrocinchonane prepared by us by the reduction of cinchonine and which is described further on. This base gave $[\alpha]_D$ 209.0°. Accordingly, our β -base should belong to the series of compounds which these workers obtained from their crystalline dihydrocinchonane and should therefore be the same as their amorphous hexahydro-desoxycinchonine. Unfortunately, they did not describe its rotation.

It was then of interest to repeat the experiments of Konek von Norwall with cinchonine itself. Here, also, a viscous sirup was obtained which was likewise found to be a mixture. By conversion into the hydrochloride a crystalline fraction was obtained with little difficulty which yielded a crystalline base melting at 116.5–117.5° and with practically the same rotation given by α -hexahydrocinchonane. This base proved to be α -tetrahydrocinchonane, since on reduction with palladium and hydrogen it yielded the α -hexahydro base. From the mother liquor of the above salt it was found difficult to isolate any other products of the reduction. A clue to their nature was found, however, by reducing the residue with palladium and hydrogen, a process which could reduce only the vinyl side-chain. From the resulting mixture the hydrochlorides of α - and β -hexahydrocinchonane and hexahydrocinchonine dihydrobromide were readily isolated, showing that the original reduction mixture contained besides α -tetrahydrocinchonane, β -tetrahydrocinchonane and tetrahydrocinchonine. The so-called nitroso-tetrahydrocinchonine nitrite described by Konek von Norwall was therefore probably a mixture and not solely, if at all, a derivative of tetrahydrocinchonine.

Finally dihydroquinine was also reduced by this method, but curiously enough the only substance which could be isolated in pure crystalline form and in fair yield was the dihydrochloride of hexahydroquinine. The nature of this salt was established by the preparation of a nitroso and monobenzoyl derivative and the usual color reactions. The base unfortunately could not be obtained in crystalline form.

Experimental Part

A. Reduction of Dihydrocinchonine (Cinchotine)

100 g. of dihydrocinchonine were dissolved in 2 kg. of boiling dry amyl alcohol and reduced at the boiling temperature with 150 g. of sodium. The reaction required in all from 4 to 6 hours. When the practically colorless solution was treated with water and the amyl alcohol removed with steam, a resinous residue remained which was extracted with ether. Concentration of the dried ethereal solution left an amber colored oil which was dissolved in 1 liter of absolute alcohol. A solution of hydrochloric acid in absolute alcohol was added until the reaction became acid to congo red. A copious crop of microscopic needles gradually separated and was collected and washed with cold, acidulated absolute alcohol, forming a faintly bluish-purple mass which weighed 50 g. when dry. Recrystallization from 3 parts of boiling water gave a crop of almost flat, minute, colorless needles which, after they had been washed with ice water and dried, weighed 16 g. and proved to be practically pure α -hexahydrocinchonane dihydrochloride. The aqueous mother liquor, concentrated to 75 cc., gradually deposited a second crop of crystals, which, on recrystallization from a small volume of water, yielded 7 g. of the characteristic flat needles of the salt of the α -compound. The mother liquors treated in a similar manner finally gave an additional 5 g., or 28 g. in all.

When the aqueous mother liquor from the last fraction was concentrated to about 50 cc. and treated with an equal volume of 40% hydrobromic acid a hydrobromide crystallized rapidly. Under the microscope, it was found to consist mainly of 6-sided elongated plates and prisms of the salt of hexahydrocinchonine, mixed with small, com-

compact prisms of the hydrobromide of β -hexahydrocinchonane, which was easily removed by recrystallization. The yield of the mixed salt was 17 g.

The original alcoholic mother liquor from which the first crude fraction had been obtained was concentrated *in vacuo* to a sirup and dissolved in about 150 cc. of absolute alcohol. On standing in the refrigerator the solution, which had deepened considerably in color, slowly deposited a hard, compact crust of pyramided rhombs which were filtered off after 3 or 4 days and washed with cold absolute alcohol. This fraction weighed 32 g. and consisted mainly of β -hexahydrocinchonane dihydrochloride. The mother liquor from this fraction, concentrated to small bulk and allowed to stand in the refrigerator for several weeks, gave a further slow deposit of crystals, but this fraction was obviously a mixture, and the amount too small to make its study profitable.

α -Hexahydrocinchonane.—When the hydrochloride of the α -base first described was dissolved in water and treated with an excess of alkali, a colorless gum was obtained which was easily extracted with ether. The dried extract, on concentration, left an almost colorless sirup which crystallized on standing. When this material was dissolved in sufficient hot ligroin and seeded after it cooled, the base separated as a hard crust of rhombic plates and flat prisms. After repeated recrystallization from ligroin and finally from a small volume of alcohol, and cooling to 0° , the base melted sharply at $106\text{--}107^\circ$ (corr.). Although colorless at first the α -base rapidly turns amber colored on the surface when exposed to sunlight; but when kept in brown glass containers it remains colorless. It is readily soluble in organic solvents, except ligroin which, however, dissolves it appreciably. The base yields stable di-acid salts, solutions of which give an olive-green color with ferric chloride and an emerald-green color with permanganate. It couples slowly with diazotized sulfanilic acid to form a red solution of the salt of the azo dye. $[\alpha]_D^{25}$ is $212\text{--}217^\circ$ in absolute alcohol, $c=1.123$ (g. of substance per 100 cc. of solvent).

Analyses. Calc. for $C_{15}H_{25}N_2$: C, 80.23; H, 9.86; N, 9.86. Found: C, 80.10; H, 9.63; N, 10.05.

THE DIHYDROCHLORIDE.—This salt is readily purified by recrystallization from water; it forms characteristic long, flat, colorless, glistening needles which darken slightly but do not melt when heated to 285° . It is fairly soluble in water, especially on warming, and very difficultly so in cold absolute alcohol, although the hot solvent dissolves it more readily. Hydrochloric acid or sodium chloride salts it out of a not too dilute aqueous solution. Strong hydrobromic acid likewise precipitates the dihydrobromide as long, flat needles which resemble the hydrochloride. The aqueous solution of the salt is acid to litmus, but not to congo red. $[\alpha]_D^{24}$ is 69.2° in water; $c=1.026$.

Analyses. Calc. for $C_{15}H_{25}N_2 \cdot 2HCl$: C, 63.83; H, 8.41; N, 7.84; Cl, 19.85. Found: C, 63.60; H, 8.23; N, 8.04; Cl, 19.75.

N-Nitroso- α -hexahydrocinchonane Hydrochloride.—A conc. aqueous solution of the dihydrochloride was treated with a slight excess of a conc. solution of sodium nitrite, yielding a yellow gum which crystallized rapidly when it was rubbed. Since purification of the hydrochloride by simple recrystallization was made difficult because of contamination with the sparingly soluble nitrite of the nitroso compound, the collected salt was dissolved in water and the nitroso base precipitated with alkali and extracted with ether. The washed ether was shaken with a slight excess of dil. hydrochloric acid and the hydrochloride was isolated from the resulting solution by concentration *in vacuo*. Recrystallized from a small volume of water containing a little hydrochloric acid, the hydrochloride separates as flat, lustrous, cream colored needles which melt and effervesce at $203\text{--}205^\circ$. It is easily soluble in alcohol, quite readily in water, and much less so in dilute hydrochloric acid or salt solution. It gives the Liebermann reaction. $[\alpha]_D^{27}$ is $+68.0^\circ$ in water; $c=1.000$. Alkali precipitates the base as a gum which is easily soluble in ether and could not be made to crystallize.

Analyses. Calc. for $C_{19}H_{27}ON_3 \cdot HCl$: N, 12.00; Cl, 10.14. Found: N, 12.15; Cl, 10.13.

N-Acetyl- α -hexahydrocinchonane Hydrochloride.—Two g. of the α -base were dissolved in 10 cc. of benzene, treated with 1 cc. of acetic anhydride and boiled for several minutes, until the benzene boiled away. A small volume of absolute alcohol was added and then alcoholic hydrochloric acid until the solution was acid to congo red. On the addition of several volumes of dry ether the hydrochloride gradually crystallized. Reprecipitated with ether from a concentrated alcoholic solution, the salt formed colorless microscopic leaflets which melted at $235-237^\circ$ with slight preliminary softening. It dissolves easily in water or alcohol and very sparingly in acetone. Contrary to the unacylated base, it no longer couples with diazo compounds and gives no color with ferric chloride or permanganate. $[\alpha]_D^{27}$ is $+37.0^\circ$ in water; $c=1.000$. Alkali precipitates the base as a gum which dissolves easily in ether, but could not make it crystallize.

Analyses. Calc. for $C_{21}H_{31}ON_3 \cdot HCl$: N, 7.73; Cl, 9.78. Found: N, 7.65; Cl, 9.56.

N-Benzoyl- α -hexahydrocinchonane Hydrochloride.—One and a half g. of the α -base dissolved in 25 cc. of dry acetone were treated with 1 cc. of benzoyl chloride. The solution warmed slightly and deposited a trace of a precipitate. The filtrate was concentrated to a small volume, acidified with alcoholic hydrochloric acid, and then treated with dry ether to incipient turbidity. The crystallization which ensued on rubbing the vessel was aided by the occasional addition of more ether. Recrystallized from methyl ethyl ketone, the salt separated slowly as colorless microscopic platelets which sinter at about 175° and slowly melt at $215-220^\circ$. The salt is easily soluble in water or alcohol. $[\alpha]_D^{27} = +13.0^\circ$ in water; $c=0.384$. The free base was obtained from the salt as a colorless gum which could not be made to crystallize.

Analyses. Calc. for $C_{26}H_{32}ON_3 \cdot HCl$: N, 6.59; Cl, 8.35. Found: N, 6.78; Cl, 8.29.

6-Phenylazo- α -hexahydrocinchonane.—Half a gram of aniline dissolved in 15 cc. of *N* hydrochloric acid was diazotized with 5 cc. of *N* sodium nitrite and added to a chilled solution of 1.9 g. of the α -dihydrochloride in 25 cc. of water. Fifteen cc. of 20% sodium acetate were then added, causing the separation of a reddish-orange gum, presumably mostly a diazo-amino compound. An equal volume of alcohol was added and, when solution was complete, this was followed by sufficient strong hydrobromic acid to form a deep purple-red solution which deepened in color on standing. After the solution had stood for 24 hours at room temperature, the removal of the alcohol *in vacuo* caused the separation of a deep red tar which changed when rubbed with water to a purple mass of microscopic needles. The separation was aided by the addition of sodium bromide. The collected salt was dissolved in warm 50% alcohol and made alkaline with sodium hydroxide, which caused the purple-red solution to change to a brown-orange color and deposit the dye base as lustrous orange colored leaflets. The yield was 0.7 g. Recrystallized from 85% alcohol it forms rosetts of thin, rounded platelets which melt at $153-156^\circ$. The dye is very readily soluble in benzene and in chloroform and easily in the other solvents except ligroin. It dissolves in dil. acids with a deep red color, purplish-pink in thin layers, while the solution in conc. sulfuric acid shows a deep brown-red hue which appears light olive-green in thin layers.

Analysis. Calc. for $C_{25}H_{32}N_4$: N, 14.43; Found: N, 14.65.

β -Hexahydrocinchonane.—The free base was obtained from the pure hydrochloride described below as a colorless oil which crystallized on standing. Recrystallized from ligroin, it forms lustrous rhombic plates which, after a final recrystallization from alcohol with the aid of a freezing mixture, melt at $106-106.5^\circ$, or at about the same point as the α -base. However, a mixture of both bases melts $15-20^\circ$ lower. Contrary to the action of the α -base, the β -compound remains colorless on exposure to sunlight. Its salts give

the same color reactions as those of the α -base with ferric chloride, with permanganate, and with diazotized sulfanilic acid. It is readily soluble in organic solvents with the exception of ligroin. $[\alpha]_D^{25}$ is 18.15° in absolute alcohol; $c=0.992$.

Analyses. Calc. for $C_{19}H_{28}N_2$: C, 80.23; H, 9.86; N, 9.86. Found: C, 79.90; H, 10.02; N, 9.77.

THE DIHYDROCHLORIDE.—The crude salt (32 g.) previously described as the second fraction (p. 1084) was readily purified by recrystallization from water. It separates slowly as a hard crust of rhombs and pyramidal prisms which occasionally measured 5 mm. in diameter and contain 1 molecule of water of crystallization. When heated rapidly to 230° and then slowly, the salt melts at $237\text{--}240^\circ$ to a liquid filled with bubbles. It is readily soluble in water, appreciably so in alcohol, and insoluble in acetone or in ether. The aqueous solution reacts acid to litmus, but neutral to congo red. $[\alpha]_D^{26}$ is 84.0° in water; $c=1.000$.

Analyses. Calc. for $C_{19}H_{28}N_2 \cdot 2HCl \cdot H_2O$: H_2O , 4.80. Found: 4.54. Calc. for $C_{19}H_{28}N_2 \cdot 2HCl$: N, 7.84; Cl, 19.85. Found: N, 8.07; Cl, 19.68.

Nitroso- β -hexahydrocinchonane and its Hydrochloride.—As in the case of the α -salt, the β -hydrochloride yielded the hydrochloride of the nitroso compound, which was purified by recrystallization from water with the addition of hydrochloric acid. The base obtained from the salt formed an amber colored oil which crystallized on standing. When allowed to separate slowly from ligroin, it forms long, prismatic, cream colored needles which melt at $92.5\text{--}93.5^\circ$ (corr.). It is readily soluble in organic solvents and gives the Liebermann reaction. $[\alpha]_D^{29}$ is 107.0° in absolute alcohol; $c=1.000$.

Analysis. Calc. for $C_{19}H_{27}ON_3$: N, 13.41. Found: N, 13.76.

The salt isolated above forms glistening, cream colored leaflets which contain 1 molecule of water of crystallization and melt with effervescence at $209\text{--}211^\circ$. It is sparingly soluble in cold water, more readily in alcohol and very sparingly in acetone. $[\alpha]_D^{29}$ is 68.4° in water; $c=0.746$.

Analyses. Calc. for $C_{19}H_{27}ON_3 \cdot HCl \cdot H_2O$: H_2O , 4.90. Found: 4.87. Calc. for $C_{19}H_{27}ON_3 \cdot HCl$: N, 12.00; Cl, 10.14. Found: N, 12.36; Cl, 10.28.

N-Benzoyl- β -hexahydrocinchonane Hydrochloride.—One and a half g. of the β -base dissolved in 25 cc. of dry acetone were treated with 1 cc. of benzoyl chloride. After 15 minutes the clear solution was treated with dry ether and rubbed until the salt crystallized. Recrystallized from methyl ethyl ketone, it forms aggregates of colorless needles which melt at $232\text{--}234^\circ$ and are easily soluble in water. $[\alpha]_D^{27}$ is 95.0° in water; $c=1.000$.

Analyses. Calc. for $C_{26}H_{32}ON_2 \cdot HCl$: N, 6.59; Cl, 8.35. Found: N, 6.86; Cl, 8.47.

Hexahydrocinchonine Dihydrobromide.—This salt was obtained as previously described (p. 1084) by the addition of hydrobromic acid to the aqueous mother liquors from the α -dihydrochloride. The crude hydrobromide (17 g.) was recrystallized repeatedly from small volumes of water until the optical rotation became constant. It then formed characteristic long, lustrous, faintly violet, hexagonal plates and prisms which sinter and darken slightly, but do not melt below 290° . The salt is quite readily soluble in water and very sparingly in alcohol. $[\alpha]_D^{27}$ is 50.0° in water; $c=1.000$. It gives the same color reactions with ferric chloride, with permanganate and with diazotized sulfanilic acid as the salts of the α - and β -bases. Its aqueous solution reacts acid to litmus, but neutral to congo red, and yields a nitrosamine with sodium nitrite. Alkali precipitates the free base as a gum which, so far, has failed to crystallize.

Analyses. Calc. for $C_{19}H_{28}ON_2 \cdot 2HBr$: C, 49.35; H, 6.55; N, 6.06; Br, 34.63. Found: C, 49.65; H, 6.51; N, 6.34; Br, 34.72.

Reduction of Dihydrocinchonine with Zinc and Hydrochloric Acid.—Twenty g. of dihydrocinchonine were dissolved in 400 cc. of 1:1 hydrochloric acid, and the solution was boiled and treated gradually with 40 g. of granulated zinc (30 mesh). When the zinc was dissolved, water was added to redissolve the pasty double salt which separated as the mixture cooled, and then an excess of ammonia was added. The dried ether extract was concentrated and yielded a yellow oil which was dissolved in 100 cc. of absolute alcohol and treated with dry hydrogen chloride until acid to congo red. When seeded with α -hexahydrocinchonane dihydrochloride, rapid crystallization occurred which was completed in the refrigerator. The dried salt weighed 3 g., or much less in proportion to the yield obtained by the sodium reduction. It proved identical with the salt of the α -base previously isolated. In all probability the β -base is to be found in the mother liquors from the α -hydrochloride, but the poor yield and its solubility rendered its isolation difficult.

B. Reduction of Dihydrocinchonane

Eighteen g. of dihydrocinchonane hydrochloride (see below) were converted into the base and the dried ether extract concentrated to a sirup. This was dissolved in 320 g. of amyl alcohol and reduced with 24 g. of sodium. After removal of the amyl alcohol, the ether extract yielded a colorless oil which was dissolved in 160 cc. of absolute alcohol and made acid to congo red by dry hydrogen chloride. Thus 10.5 g. of a salt corresponding to that of α -hexahydrocinchonane was obtained. On conversion of this into the free base, an oil was obtained which crystallized readily when seeded with α -hexahydrocinchonane. Recrystallized from ligroin, it formed rhombic plates and prisms which melted at 106–107° (corr.). When mixed with the previously described α -base no change in melting point occurred. $[\alpha]_D^{26}$ is 213.0° in absolute alcohol; $c = 1.000$.

Analysis. Calc. for $C_{19}H_{23}N_2$: N, 9.86. Found: N, 9.98.

When the mother liquor of the α -hydrochloride was concentrated, 6 g. of stout prisms characteristic of the β -dihydrochloride were obtained. The base liberated from this salt melted at 106–106.5° (corr.). No change in melting point was observed when it was mixed with the β -hexahydrocinchonane previously described. $[\alpha]_D^{26}$ is 18.7° in absolute alcohol; $c = 1.016$.

Analysis. Calc. for $C_{19}H_{23}N_2$: N, 9.86. Found: N, 9.94.

From the mother liquors from the above salts none of the characteristic hexagonal plates of the dihydrobromide of hexahydrocinchonine could be separated.

The dihydrocinchonane used above was obtained as follows.

Chloro-dihydrocinchonine and its Hydrochloride.—Sixty-nine g. of dry dihydrocinchonine dihydrochloride were suspended in dry chloroform and poured in a thin stream, with cooling, into a suspension of 115 g. of phosphorous pentachloride in the same solvent. After the mixture had been warmed to 40–50° for several days, it was decomposed with ice and water, and the base liberated from the aqueous extract with alkali and extracted with ether. The oily residue was dissolved in absolute alcohol and neutralized with alcoholic hydrochloric acid. This caused the *hydrochloride* to separate as aggregates of microscopic needles. The mother liquor yielded an additional amount on addition of dry ether, or 43 g. in all. When recrystallized from 85% alcohol it forms radiating aggregates of microscopic needles and narrow leaflets which turn olive colored when heated and melt slowly at 227–228°. It is difficultly soluble in cold water and alcohol, but readily on boiling. $[\alpha]_D^{23}$ is 48.8° in water; $c = 1.107$.

Analyses. Calc. for $C_{19}H_{23}N_2Cl.HCl$: N, 7.98; Cl, 10.09. Found: N, 8.09; Cl, 10.04.

On treating the aqueous solution of the salt with sodium carbonate, an oil formed which crystallized when it was seeded with crystals obtained from a preliminary ethereal

extract. Dissolved in acetone and treated with water to incipient turbidity the hydrate of the base separated slowly as rhombs which contained 1.5 molecules of water of crystallization. It softens above 55° and is completely melted to a turbid liquid at 70° . Dried in a desiccator, the hydrate lost its crystalline structure. It is easily soluble in organic solvents. $[\alpha]_D^{24}$ is 36.4° in absolute alcohol; $c = 1.001$.

Analyses. Calc. for $C_{19}H_{23}N_2Cl \cdot 1.5H_2O$: H_2O , 7.91; N, 8.20. Found: H_2O , 7.83; N, 8.32.

Dihydrocinchonane and its Hydrochloride.—Thirty-six g. of chlorodihydrocinchonine hydrochloride were reduced as in the case of dihydroquinane.¹⁰ The base was obtained at first as an oil which was dissolved in absolute alcohol and treated with dry hydrogen chloride until it was neutral to moist litmus, the salt separating rapidly as glistening platelets. These were washed with a little absolute alcohol and then with dry acetone, until all the yellow color due to picric acid had been removed. Yield, 22 g. When crystallized from absolute alcohol the hydrochloride forms narrow, glistening plates and prisms which turn yellow and melt slowly at 197 – 199° to a liquid containing bubbles. It is quite soluble in absolute alcohol, very readily in dry methyl alcohol and chloroform, and difficultly in acetone. $[\alpha]_D^{25}$ is 69.3° in water; $c = 1.068$.

Analyses. Calc. for $C_{19}H_{24}N_2 \cdot HCl$: N, 8.85; Cl, 11.19. Found: N, 9.04; Cl, 11.38.

On treating a solution of the salt in 50% alcohol with an excess of sodium carbonate and diluting with water, the hydrate of the base crystallized slowly. When dissolved in acetone and treated with water to incipient turbidity, the hydrate separated as rhombs, hexagonal prisms and diamond-shaped platelets which retained 2 molecules of water of crystallization after they had been dried to constant weight in air saturated with water vapor. It is easily soluble in organic solvents and melts at 59.5 – 60° (corr.). When it is dried in a desiccator or in dry air it loses its crystalline character. $[\alpha]_D^{30}$ is 113.8° in absolute alcohol; $c = 1.014$.

Analyses. Calc. for $C_{19}H_{24}N_2 \cdot 2H_2O$: H_2O , 11.39; C, 72.10; H, 8.16; N, 8.86. Found: H_2O , 11.17; C, 72.42; H, 8.16; N, 9.17.

C. Reduction of Cinchonine

Fifty g. of cinchonine, which had been purified by recrystallization of the sulfate and then of the base from 50% alcohol, were reduced in 1 kg. of amyl alcohol with 75 g. of sodium. On concentration, the ethereal extract yielded an amber colored oil which was dissolved in 150 cc. of absolute alcohol and made acid to congo red by the addition of dry hydrogen chloride. On standing in the refrigerator, the almost colorless solution became deep red-brown and deposited colorless needles which were collected and washed with cold absolute alcohol. The yield was 12.5 g.

α -Tetrahydrocinchonane.—On converting the above salt as usual into the base an oil was obtained which partially crystallized on standing. When the mixture was dissolved in hot ligroin, cooled, and seeded, a gradual deposition of the base occurred. A second recrystallization from ligroin yielded stout cream colored prisms which melted at 116.5 – 117.5° (corr.) and were readily soluble in organic solvents, except ligroin. $[\alpha]_D^{31}$ is 209.0° in absolute alcohol, $c = 1.000$, a value practically the same as the specific rotation of α -hexahydrocinchonane. The solution of its hydrochloride gives the same color reactions as the latter with ferric chloride, permanganate and diazotized sulfanilic acid.

Analyses. Calc. for $C_{19}H_{26}N_2$: C, 80.80; H, 9.29; N, 9.93. Found: C, 81.25; H, 9.24; N, 9.90.

To establish its relationship to α -hexahydrocinchonane, the tetrahydro compound

¹⁰ THIS JOURNAL, 42, 1492 (1920).

was reduced in dil. acetic acid with palladium black and hydrogen. α -Hexahydrocinchonane was isolated from the resulting solution.

Since the products contained in the mother liquor from the crude α -tetrahydrocinchonane dihydrochloride proved too soluble for separation, a clue to the nature of the main products of the reduction was obtained by reduction with palladium and hydrogen. The mother liquor was accordingly concentrated to remove alcohol and the residue dissolved in 200 cc. of water, a solution of 0.1 g. of palladium chloride added and the mixture reduced with hydrogen. When absorption was complete, the filtrate was concentrated to dryness *in vacuo*, redissolved in absolute alcohol, concentrated again, and the process repeated to remove all water. On dissolving the residue in 200 cc. of absolute alcohol it crystallized rapidly, and yielded 10 g. of hydrochloride which on fractional recrystallization from water gave 3 g. of the characteristic crystals of α -hexahydrocinchonane dihydrochloride. This would indicate that the original separation of the hydrochloride of α -tetrahydrocinchonane from the other products of the reduction of cinchonine had been incomplete.

On treatment with hydrobromic acid the aqueous mother liquor from the α -dihydrochloride yielded the 6-sided platelets of hexahydrocinchonine dihydrobromide.

The alcoholic mother liquor from the above hydrochlorides gave, on concentration, a copious crystallization of β -hexahydrocinchonane dihydrochloride.

D. Reduction of Dihydroquinine

Sixty g. of dihydroquinine, recrystallized from toluene,¹¹ were reduced as in previous cases with sodium in amyl alcohol. After removal of the latter, an oily base was obtained by extraction with ether. This was dissolved in 200 cc. of absolute alcohol, cooled, and made acid to congo red by passing dry hydrogen chloride through it. A small test portion of the solution was partially precipitated with ether. The gummy precipitate was dissolved in a little absolute alcohol and then ether was added cautiously, causing crystallization to occur gradually. When the main solution was seeded and kept at room temperature (gelatinization occurred in the refrigerator), a copious separation of hair-like needles and denser crystals occurred. After washing with a little absolute alcohol the salt weighed 29 g. The mother liquors from this salt, treated with ether and allowed to stand, yielded a small quantity of fibrous needles which appeared to be the salt of a different base. The quantity of this substance at our disposal and pressure of other work prevented the completion of the study of this fraction and other substances contained in the mother liquors.

Hexahydroquinine Dihydrochloride.—To recrystallize the above first fraction it was dissolved in the minimum amount of boiling methyl alcohol, cooled, and treated with dry ether. The crystals thus formed were recrystallized until the optical rotation had become constant, yielding about 15 g. of optically pure salt. It formed practically colorless rhombic plates which melted at 271–273° with gas evolution and preliminary softening. Although readily soluble in ordinary boiling methyl and ethyl alcohols, the salt is rather sparingly soluble in the dry solvents and almost insoluble in dry acetone and chloroform. It dissolves easily in water, and the solution gives with ferric chloride an emerald-green color which changes to an orange color on long standing. $[\alpha]_D^{25}$ is -36.5° in water; $c = 1.067$. Sodium bromide salts out the *dihydrobromide* as lustrous plates. Attempts to obtain the free base in crystalline form were unsuccessful.

Analyses. Calc. for $C_{20}H_{28}O_2N_2 \cdot 2HCl$: C, 59.52; H, 8.00; N, 6.95; Cl, 17.59. Found: C, 59.68; H, 7.92; N, 7.10; Cl, 17.60.

¹¹ In an experiment in which a less pure product was used considerable charring occurred.

N-Nitroso-hexahydroquinine Hydrochloride.—A solution of the salt in 3 parts of water and a few drops of acetic acid was treated in the cold with a slight excess of sodium nitrite. The hydrochloride soon crystallized as radiating masses of delicate needles which changed on standing to glistening, pale yellow rhombs and prisms which were recrystallized twice from water containing a little hydrochloric acid. It turns lemon-yellow when heated, melts at 212–213° with decomposition, and is fairly soluble in water and alcohol, especially on boiling. It gives the Liebermann reaction and its aqueous solution is not changed at once by permanganate or ferric chloride. $[\alpha]_D^{31}$ is -85.1° in water; $c = 1.034$.

Analyses. Calc. for $C_{20}H_{29}O_3N_3 \cdot HCl$: N, 10.62; Cl, 8.96. Found: N, 10.76; Cl, 8.92.

N-Benzoyl-hexahydroquinine.—The dried sirupy base from 4.1 g. of hexahydroquinine dihydrochloride was treated with 15 cc. of benzoyl chloride and heated on the water-bath for 1 hour, after which benzene was added and the solution treated with very dilute hydrochloric acid and ice. A gum separated which gradually dissolved when the mixture was shaken and ether was added to facilitate the process. The aqueous layer was then covered with ether, treated with ice and a slight excess of alkali, and quickly shaken out. The dried ethereal extract left a viscous oil which crystallized after several days. Dissolved in hot ligroin, then cooled and seeded, the base formed lustrous platelets which were purified by solution in a little benzene and addition of ligroin. It melts at 160–160.5° with slight preliminary softening and is soluble in the usual solvents, except ligroin. It does not give a color with ferric chloride. $[\alpha]_D^{26}$ is -115.2° in absolute alcohol; $c = 1.088$.

Analyses. Calc. for $C_{27}H_{34}O_3N_2$: C, 74.61; H, 7.89; N, 6.45. Found: C, 74.81; H, 8.12; N, 6.69.

Summary

Reduction of dihydrocinchonine with sodium and amyl alcohol yielded a mixture of hexahydrocinchonine and two epimeric hexahydrocinchonanes in the last of which the alcoholic group, as well as the quinoline ring, had suffered reduction. These two bases were also obtained by reduction of dihydrocinchonane. The relationships of these compounds to those obtained by reduction with zinc, and by the reduction of cinchonine were worked out, and necessary intermediates and derivatives described. Dihydroquinine was also reduced, yielding mainly a hexahydroquinine.