102. *Conversion of Hydroquinidine into Hydrocinchonine and of Cupreine into Cinchonidine.*

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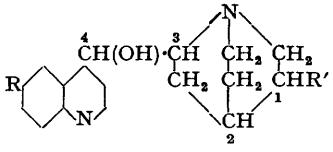
The aim of this investigation was the removal of the methoxyl groups from the methoxylated cinchona alkaloids by a mild method which would leave the stereochemical structure intact. This has been accomplished for dihydroquinidine and cupreine by an application of the Bucherer reaction. The former base yields dihydrocinchonine and the latter cinchonidine. The classification of the eight main cinchona alkaloids on a stereochemical basis by King and Palmer (*J.*, 1922, **121**, 2580) is supported.

KING and PALMER (*loc. cit.*) proposed a classification of the natural cinchona alkaloids depending on the optical contribution of the four asymmetric centres present to the observed rotation. On this system the main cinchona alkaloids and their dihydro-derivatives (I)



(I.)

were classified as follows :

Alkaloid.	Optical sign of— C1 with C2.	C3.	C4.
Cinchonine (R = H; R′ = CH:CH_2) and Dihydrocinchonine	+	+	+
Cinchonidine (R = H; R′ = CH:CH_2) and Dihydrocinchonidine	+	−	−
Quinine (R = OMe; R′ = CH:CH_2) and Dihydroquinine	+	−	−
Quinidine (R = OMe; R′ = CH:CH_2) and Dihydroquinidine	+	+	+

This classification was accepted by Rabe (*Annalen*, 1932, **492**, 242) with a greater wealth of experimental results. Henry, Solomon, and Gibbs (*J.*, 1937, 592) and Solomon (*J.*, 1938, 6) have expanded the classification by furnishing experimental evidence which enabled them to suggest signs for the optical contribution of each of the carbon atoms C1 and C2, a subject also dealt with more recently by Prelog and Zalan (*Helv. Chim. Acta*, 1944, **27**, 535). Emde (*ibid.*, 1932, **15**, 557), however, questioned the above classification and preferred to regard the spatial arrangement around C1, C2, and C3 as identical in all the natural bases, the isomerism between cinchonine and cinchonidine, for instance, being solely dependent on the different spatial arrangement around C4.

On either system quinine and dihydroquinine should be the methoxylated derivatives of cinchonidine and dihydrocinchonidine respectively, and quinidine and dihydroquinidine should be the methoxylated derivatives of cinchonine and dihydrocinchonine respectively. Apart from the regularities in the rotations on which this classification is based there is no experimental evidence in support of this view. The present communication furnishes a proof of these relationships.

For the replacement of the methoxyl group of the methoxylated cinchona alkaloids by hydrogen, the process used by O. Fischer (*Chem. Soc. Abstr.*, 1901, i, 405) for conversion of harmine *via* harmol into aminoharman by heating harmol at 250° with zinc chloride and ammonia seemed too drastic. In recent years considerable success has attended the application of the Bucherer reaction to hydroxyquinolines. Thus Woroshtzow and Kogan (*Ber.*, 1932, **65**, 142) were able to convert 6- and 8-hydroxyquinolines in good yield into the corresponding aminoquinolines by ammonium sulphite solution at 150°. Renfrew, Carlson, and Cretcher (*J. Amer. Chem. Soc.*, 1943, **65**, 2309) have also converted apocupreine (an isomeride of demethylated quinine) into derivatives of aminoapocinchonidine in a workable yield at 160°. Finally C. F. Boehringer and Soehne (D.R.P. 720,160) have patented the preparation of 6-aminodihydrocinchonine and 6-aminodihydrocinchonidine by allowing hydrocupreidine or hydrocupreine respectively to react with ammonium sulphite in presence of aqueous ammonia and water-soluble organic solvents at an elevated temperature.

A number of trial experiments along the lines of this patent were carried out on hydrocupreidine (demethylation product of hydroquinidine) and it was found that it could be converted into an aromatic amino-derivative by dissolving in ethylene glycol and heating to 150° with ammonium sulphite solution. The amino-compound was not very stable and did not crystallise as base or as a salt with the acids so far tried. It formed a soluble salt with sulphuric acid which could be diazotised and which on treatment with hypophosphorous acid by Mai's method (*Ber.*, 1902, **35**, 162) gave a workable yield of crystalline dihydrocinchonine identical in the melting point of the base and the dihydrobromide and in the optical rotation with an authentic specimen of natural dihydrocinchonine.

Through the generosity of Mr. Bernard F. Howard, Managing Director of Howards & Sons, Ilford, I was presented with a small specimen of cupreine first isolated by Howard and Hodgkin (*J.*, 1882, **41**, 16) from Cuprea bark. Cupreine on methylation gives quinine and thus is a phenolic alkaloid with a vinyl side-chain. It was of interest to apply the Bucherer reaction to this base under similar conditions. It readily gave an amino-base, soluble in dilute sulphuric acid, which could be diazotised and reduced by Mai's method to cincho-

nidine, identified as base and dihydrobromide by comparison with an authentic specimen of natural cinchonidine and its dihydrobromide.

It follows from these results that quinine and quinidine and their dihydro-derivatives are the methoxy derivatives respectively of cinchonidine and cinchonine and their dihydro-derivatives, a result consistent with the original classification of King and Palmer.

Experimental.

Conversion of Hydroquinidine into Hydrocinchonine.—Hydrocupreidine (1 g.) prepared by demethylation of pure hydroquinidine by the method of Heidelberger and Jacobs (*J. Amer. Chem. Soc.*, 1919, **41**, 817) was dissolved in ethylene glycol (2 c.c.) by warming, and the solution cooled. Aqueous ammonia (7·5 c.c., 20%) was then added followed by ammonium bisulphite solution (7·5 c.c.) prepared by passing excess of sulphur dioxide into cold aqueous ammonia (20%). The mixture was heated in a sealed Pyrex tube at 150° for 7·5 hours. The contents of 6 such tubes were filtered, the main bulk of the amorphous amino-base being insoluble. The filtrate was made strongly alkaline by addition of 50% sodium hydroxide solution and extracted three times with chloroform. The amorphous solid which had been filtered off was ground in a mortar and treated with the combined chloroform extracts in the presence of 2N-sodium hydroxide. Two clear solutions usually resulted, the upper dark coloured aqueous alkaline solution containing some unchanged hydrocupreidine. The chloroform was separated and the alkaline solution extracted several times with chloroform to remove all non-phenolic base. The combined chloroform extracts were washed with a little 2N-sodium hydroxide and finally with water and then distilled, the last small volume of chloroform being removed under reduced pressure. The residue of crude 6-aminodihydrocinchonine (2·22 g.) was dissolved in N-sulphuric acid (21·4 c.c.; 3 equiv.), cooled to 0°, and diazotised by addition of a solution of sodium nitrite (0·52 g.) in water (5 c.c.). The clear solution was then run fairly rapidly into hypophosphorous acid (50 c.c., 30%) previously cooled to 0° and kept at 0° for 24 hours. There was no noticeable evolution of nitrogen. The solution was treated with 2N-ammonia (125 c.c.) and chloroform (100 c.c.) and the dihydrocinchonine extracted completely by 5 further chloroform extractions (each 50 c.c.). The combined chloroform extracts were evaporated and left a crystalline base (1·75 g.). This was boiled with alcohol (5 c.c.) and gave dihydrocinchonine (0·85 g.). It was crystallised once more from absolute alcohol (40 c.c.), and separated in needles, m. p. 265° not depressed by an authentic specimen of natural dihydrocinchonine which melted at 266° (Found: C, 77·1; H, 8·2. Calc. for $C_{19}H_{24}ON_2$: C, 77·0; H, 8·2%). In N/10-hydrobromic acid (*c*, 0·235) it had $[\alpha]_D^{18°}$ + 220·4°. A specimen of authentic dihydrocinchonine under comparable conditions (*c*, 0·234) had $[\alpha]_D^{23°}$ + 219·7°. Emde (*loc. cit.*) gives $[\alpha]_D^{20}$ + 142° for the dihydrobromide whence for the base $[\alpha]_D^{20°}$ + 219·5° in agreement with the above figures. The dihydrobromide was recovered from each preparation and each specimen crystallised in hexagonal plates, m. p. 284—286° (decomp.), a mixture showing identical behaviour.

Conversion of Cupreine into Cinchonidine.—Cupreine (0·8 g.) was dissolved in warm ethylene glycol (2 c.c.) and the solution was cooled and treated with aqueous ammonia (7·5 c.c., 20%) followed by aqueous ammonium bisulphite (7·5 c.c.). The mixture was heated at 150° for 7·5 hours in a sealed tube. The contents of two such tubes were worked up for amino-base as described above, yield 0·6 g. The amino-base was dissolved in N-sulphuric acid (7·5 c.c.) and diazotised at 0°, and the solution was then run into hypophosphorous acid (30 c.c., 30%) also kept at 0°. After keeping for 48 hours at 0° the base was liberated by ammonia and extracted with chloroform. On removal of the solvent the base crystallised (0·56 g.). It was twice crystallised from benzene and separated in needles, m. p. 201°, undepressed by an authentic specimen of cinchonidine which melted at 202°. The dihydrobromide separated from water in tablets as a dihydrate (Found: C, 45·8; H, 5·8; H_2O, 7·8. Calc. for $C_{19}H_{22}ON_2,2HBr,2H_2O$; C, 46·3; H, 5·3; $2H_2O$, 7·3%). In N/10-hydrobromic acid (*c*, 0·421) the anhydrous salt had $[\alpha]_D^{19°}$ — 110° whence for the base $[\alpha]_D^{19}$ — 170·1°. A specimen of natural cinchonidine dihydrobromide was prepared. It crystallised similarly in tablets as a dihydrate, for the anhydrous salt of which $[\alpha]_D^{19°}$ — 109·9° (*c*, 0·4) whence for the base $[\alpha]_D^{19°}$ — 170·1°.

Emde (*loc. cit.*) describes the dihydrobromide as a monohydrate, which for the anhydrous salt had $[\alpha]_D^{20°}$ — 112·5°, whilst Buttle, Henry, and Trevan (*Biochem. J.*, 1934, **28**, 430) describe the hydrobromide as a dihydrate with $[\alpha]_D$ — 111·4° for the anhydrous salt. Both these values are in substantial agreement with those now recorded. Both salts melted at 268° (decomp.) alone or in admixture.

Ethylene glycol may possess some advantages for the crystallisation of the cinchona alkaloids since both hydrocupreidine and cupreine readily crystallise from this solvent.

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