

2. *Modified Cinchona Alkaloids. Part V. β -isoQuinotoxine and the Stereochemistry of the Parent Bases.*

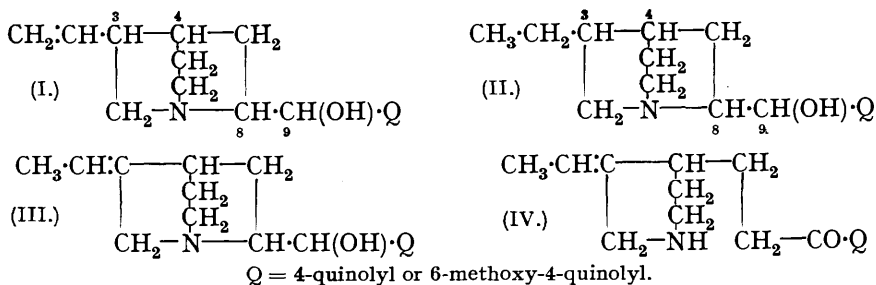
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The relative configurations of three of the four asymmetric carbon atoms in the cinchona alkaloid molecule are known, and evidence is here adduced in favour of a levorotatory configuration of the remaining carbon atom.

THE principal, naturally occurring, stereoisomeric pairs of cinchona alkaloids (I, II) each have four asymmetric carbon atoms, here numbered 3, 4, 8 and 9 in accordance with the system proposed by Rabe and Riza (*Annalen*, 1932, **496**, 152) and adopted in Part IV of this series (J., 1937, 592). The relative configurations of carbon atoms 8 and 9, as first announced by King and Palmer (J., 1922, **121**, 2577), are known to be dextrorotatory in the dextrorotatory alkaloids cinchonine, quinidine, etc., and levorotatory in cinchonidine and quinine [Rabe *et al.*, *Annalen*, 1910, **373**, 85; 1932, **492**, 242; Vereinigte Chininfabriken, Zimmer u. Co., G.m.b.H., G.P. 330,813/1918 (experimental work by Rabe's pupil, Fräulein E. Müller)].

The relative dextrorotatory configuration of carbon atom 3 was established in Part IV (*loc. cit.*) by a comparison of the optical rotations of ordinary dihydroquinine and dihydroquinidine (II, Q = 6-methoxy-4-quinolyl) with those of the corresponding C₃-epimerides, both pairs in each case being obtained by the catalytic hydrogenation of the *iso*-quinines and -quinidines (III, Q = 6-methoxy-4-quinolyl). Although experimentally applicable only to the methoxylated alkaloids quinine and quinidine, this

configuration of carbon atom 3 must be extended also to the other cinchona alkaloids, which, as has been pointed out by Rabe (*loc. cit.*), all have one and the same configuration



at the centres 3 and 4. The dextro-configuration of carbon atom 3 is supported also by a consideration of the optical rotations of α - and β -isoquinine (III, Q = 6-methoxy-4-quinolyl). For, both these geometrical isomerides, which may be regarded as quinine (I) in which the asymmetry of centre 3 has been destroyed, have higher lævorotations than quinine itself.

The preparation, and determination of the optical rotation of β -isoquinotoxine (IV, Q = 6-methoxy-4-quinolyl) to be described herein, constitute the first evidence of the configuration of carbon atom 4. This substance has been prepared previously by Suszko (*Bull. Inter. Acad. Polonaise*, 1925, A, 137), but he did not concern himself with its optical rotation. β -isoQuinotoxine is now found to be lævorotatory, and seeing that it has only one centre of asymmetry, carbon atom 4, the asymmetry of the other three centres (3, 8, 9) in this molecule being destroyed, carbon atom 4 must itself be lævorotatory. This evidence, though not conclusive, is of the same nature as that which has for so many years caused carbon atoms 3 and 4 taken together to be considered as dextrorotatory in total effect.

With this proviso, therefore, the stereochemical picture of the cinchona alkaloids is now complete, and may be tabulated as follows :

Substance.		Relative configurations at C atoms.			
		3.	4.	8.	9.
Cinchonine	} dextro-rotatory series	+	-	+	+
Dihydrocinchonine					
Quinidine					
Dihydroquinidine					
Cinchonidine	} lævo-rotatory series	+	-	-	-
Dihydrocinchonidine					
Quinine					
Dihydroquinine					

Dr. T. A. Henry, whom I desire to thank for his interest in this work, informs me that he has converted *epi*-C₃-dihydroquinine into the corresponding toxine. Although the quantity available is at present too small to enable a complete purification and characterisation of this substance to be made, he has nevertheless succeeded in establishing that it has a pronounced lævorotatory power, a fact which will be readily seen to be in conformity with my own findings concerning the configuration of carbon atom 4.

EXPERIMENTAL.

β -isoQuinotoxine was prepared from β -isoquinine by prolonged boiling with dilute acetic acid by the method of v. Miller and Rohde (*Ber.*, 1894, 27, 1187, 1279; 1895, 28, 1056).

β -isoQuinine (10 g.) was dissolved in 7.5% aqueous acetic acid (200 c.c.), and the pale solution boiled under reflux for 36 hours, either continuously or spread over 5 days. The solution progressively darkened. The base was recovered without loss by means of sodium hydroxide and ethereal extraction. This crude toxine was a dark brown oil. For purification it was converted into the acid tartrate in alcoholic solution, and recrystallised several times, at first from concentrated syrupy alcoholic solution, and finally from 10 parts of alcohol.

The *acid tartrate* so obtained consisted of tiny, loose, cream-tinted needles, m. p. 192—194° (corr., decomp.) after preliminary softening several degrees lower, $[\alpha]_D^{15} - 12.0^\circ$ ($c = M/40$ in water). It was sparingly soluble in alcohol, but readily in water to give a yellow solution. The salt was anhydrous (Found: C, 61.1; H, 6.4; N, 5.8. $C_{20}H_{24}O_2N_2, C_4H_6O_6$ requires C, 60.7; H, 6.4; N, 5.9%). The base obtained from this salt was a viscous, straw-coloured oil which could not be distilled in a high vacuum; neither could it be crystallised. After drying in a vacuous desiccator over sulphuric acid for 4 weeks, it had $[\alpha]_D^{15} - 33.8^\circ$ ($c = M/40$ in 0.1N-sulphuric acid). The *neutral tartrate* crystallised from alcohol and resembled the acid salt in appearance, m. p. 162—166° (corr., decomp.), $[\alpha]_D^{15} - 12.0^\circ$ ($c = M/40$ in water). The air-dried salt contained $2H_2O$ [Found: loss on drying, 5.1. $(C_{20}H_{24}O_2N_2)_2, C_4H_6O_6, 2H_2O$ requires $2H_2O$, 4.3%. Found in anhydrous salt: C, 67.0; H, 7.0; N, 6.8. $(C_{20}H_{24}O_2N_2)_2, C_4H_6O_6$ requires C, 66.1; H, 6.8; N, 7.0%]. The *sulphate* separated from 1 or 2 parts of alcohol as a buff-coloured, granular powder, readily soluble in water and in alcohol, m. p. 198—199° (corr., decomp.), $[\alpha]_D^{15} - 25.2^\circ$ ($c = M/40$ in water) and $- 22.9^\circ$ in 0.1N-sulphuric acid. The salt contained $3\frac{1}{2} H_2O$ [Found: loss on drying, 7.9. $(C_{20}H_{24}O_2N_2)_2, H_2SO_4, 3.5H_2O$ requires $3.5H_2O$, 7.8%. Found in anhydrous salt: C, 63.9; H, 7.0; N, 7.2; S, 4.5. $(C_{20}H_{24}O_2N_2)_2, H_2SO_4$ requires C, 64.3; H, 6.7; N, 7.5; S, 4.3%].

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