CXXXVI.—*The Absorption Spectra of Cinchonine, Quinine, and their Isomerides.*

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THE investigation described in this paper was undertaken originally with the object of ascertaining whether the absorption spectra of cinchonine and its isomerides α -, β -, and allocinchonine differ from one another in such a way as to imply differences in the structure of these alkaloids, or are identical, as one would expect them to be if the alkaloids possessed the same structure. We found the spectra to be indistinguishable, but, for reasons to be explained hereafter, it is impossible to infer from their identity that the alkaloids in question are stereoisomerides. The investigation, however, has yielded results of considerable interest in other directions.

The absorption spectra of cinchonine and quinine were first examined by Hartley (*Phil. Trans.*, 1885, 175, 471), and afterwards by ourselves (*Trans*, 1903, 83, 605).

In the course of the present investigation we had occasion to

examine the spectra of solutions of these alkaloids and of some of their compounds and derivatives in a variety of solvents. It then became evident that each alkaloid, with its related compounds and derivatives, exhibits two distinct series of spectra, one agreeing with, and the other differing considerably from, the spectra described in connexion with our earlier work on the subject.

In the case of cinchonine the spectra of an alcoholic solution or of salts containing one equivalent of acid to one of the base, for example, $C_{19}H_{22}ON_2 \cdot HCl$, may be taken as representing the one series, and the spectra of salts containing two equivalents of acid to one of base, for example, $C_{19}H_{22}ON_2 \cdot 2HCl$, the other (Fig. 1).

FIG. 1.

Oscillation frequencies.

For convenience we shall refer hereafter to the former as spectrum "A," and to the latter as spectrum "B."

In spectrum "A" the absorption band is neither well defined nor persistent; with a layer 20 mm. thick of $N/5000$ -solution the band lies between $1/\lambda$ 3220 and $1/\lambda$ 3824. In spectrum "B," on the other hand, the general absorption is greater, and the absorption band is well defined and much more persistent; with a layer of 20 mm. thick of a $N/5000$ -solution the band lies between $1/\lambda$ 3000 and $1/\lambda$ 3488.

The clue to the explanation of the difference between the two series of spectra was afforded by the study of the alkyl derivatives. According to von Miller and Rohde's formula for cinchonine,* this

* The recent work of Rabe on cinchonine shows that the formulæ here given for cinchonine and quinine probably require modification; the alterations, however, which he suggests do not affect the points dealt with in this paper.

alkaloid contains two atoms of nitrogen, one belonging to the quinoline nucleus, the other to that part of the molecule commonly referred to as the "second half":

Both atoms of nitrogen are capable of combining with an equivalent of acid or with a molecule of alkyl haloid. The "second half" of the cinchonine molecule is, however, more basic than the quinoline nucleus, and if only one equivalent of acid be added to a molecule of the alkaloid it is to the nitrogen of the "second half" that it attaches itself. Skraup and Konek von Norwall (*Monatsh.*, 1894, **15**, 37) established this point in the following manner. By heating cinchonine hydriodide, $C_{19}H_{22}ON_2 \cdot HI$, with ethyl iodide, and treating the compound formed with ammonia, they obtained a yellow-coloured ethiodide, which differs entirely from the earlier known colourless ethiodide obtained by heating a solution of cinchonine in alcohol with ethyl iodide. The yellow ethiodide possesses the properties of a true quinoline compound. That the alkyl haloid group which it contains is attached to the nitrogen of the quinoline nucleus is placed beyond doubt by the fact that when heated with silver nitrate to remove the iodine and then oxidised with permanganate in the cold, it yields cinchoninic acid ethyl nitrate, $CO_2H \cdot C_9H_6N \cdot C_2H_5 \cdot NO_3$. It follows that the colourless ethiodide obtained by the direct action of ethyl iodide on cinchonine has the alkyl haloid united to the nitrogen of the "second half," and that it is to this nitrogen atom that acids attach themselves when present only in the proportion of one equivalent.

lent to one molecular weight of the alkaloid. The relation of the two ethiodides is easily seen from the following formulæ:

We have repeated Skraup's experiments, and have photographed the spectrum of his ethiodide, and compared it with that of the α -ethiodide with the following results.

Cinchonine α -ethiodide gives the spectrum "A" in alcoholic solution, but the spectrum "B" in acid solution. On the other hand, Skraup's β -ethiodide gives spectrum "B" in alcoholic solution, and the spectrum remains unchanged on the addition of acid. The diethiodide of cinchonine, $\text{C}_{19}\text{H}_{22}\text{ON}_2, 2\text{C}_2\text{H}_5\text{I}$, gives the spectrum "B."

Having regard to the results obtained from the examination of the salts and of the alkyl haloid derivatives of cinchonine, it is clear that so long as the nitrogen of the quinoline nucleus is not in combination with acid or alkyl haloid, the spectrum "A" is obtained, but that when it is so combined the spectrum "B" is obtained, whether the nitrogen of the "second half" is in combination with acid or alkyl haloid or not. In other words, whether the spectrum "A" or "B" is produced depends entirely on the condition of the nitrogen of the quinoline nucleus as regards valency. Spectrum "A" is associated with the tervalent, spectrum "B" with the quinquevalent condition.

In his paper on the absorption spectra of the alkaloids (*loc. cit.*), Hartley pointed out that the position of the absorption band in the spectra of the cinchona alkaloids agrees with that of quinoline. As, however, the curves in his paper and those illustrating the paper in which the spectrum of quinoline is described (*Trans.*, 1885, **47**, 685) were not drawn on the same system, no exact comparison of them was possible.

It was not until we had engaged in the present investigation and re-photographed the spectra, both of quinoline and of cinchonine (Figs. 2 and 3), that the close agreement of the absorption curves of the two substances became evident to us.

On comparing them it will be seen that they coincide almost exactly, and that the only difference is that the absorption is a little greater in the case of cinchonine than in that of quinoline. The spectrum "A" of cinchonine, as well as of certain of its derivatives and salts, is practically the same as the spectrum of quinoline, whilst the spectrum "B" of other cinchonine salts and derivatives is practically the same as that of the quinoline salts. The character,

therefore, of the cinchonine spectrum depends almost entirely on the quinoline part of the molecule, and is hardly at all affected by the "second half."

FIG. 2.

Oscillation frequencies.

This result, at first sight surprising, is in no way at variance with our previous knowledge of the relations existing between

FIG. 3.

Oscillation frequencies.

absorption spectra and chemical constitution. Although some of the details of the structure of cinchonine are still the subject of controversy, it has been established that the ring or rings of the

'second half' of the molecule are completely reduced. It is also a well ascertained fact that reduced rings produce no absorption band, but act like open chains so far as absorption is concerned. The only effect, therefore, which, a priori, we should expect the "second half" of the molecule to produce on the absorption spectrum of the quinoline nucleus would be to increase somewhat the amount of general absorption, and this is what we actually find to be the case. The only matter for surprise is that the effect in this direction is so slight.

We are now in a position to explain why it is that a change within the "second half," such as the alteration of the valency of the nitrogen atom, produces no effect on the spectrum, while the corresponding change in the case of the nitrogen atom of the quinoline nucleus produces so marked an effect. The fact that the vinyl group in cinchonine belongs to the "second half" of the molecule affords a more complete explanation of the practical identity of the spectrum of cinchotenine with that of cinchonine than the one formerly advanced by us (*loc. cit.*).

It is interesting to note that whilst the quinoline alkaloids derived from the cinchona bark show only one or two types of spectra, the *isoquinoline* alkaloids, nearly all of which have unreduced rings attached to the *isoquinoline* nucleus, possess highly characteristic spectra, differing widely from one another, as well as from those of *isoquinoline*.

The conclusions arrived at from the chemical investigation of the constitution of cinchonine and those derived from the spectrographic examination, are thus seen to be in complete agreement.

Before we had discovered the close connexion which we now know to exist between the spectra of cinchonine and quinoline, or had succeeded in accounting for the difference between the spectra "A" and "B," we had undertaken, with the object explained at the beginning of this paper, a spectroscopic investigation of the artificial isomerides of cinchonine, the claim of which to be regarded as true chemical individuals has been well established, as well as of the naturally-occurring isomerides, cinchonidine and homocinchonidine. All these substances give spectra "A" and "B" practically identical with those of cinchonine; but it is obviously impossible to infer from this that they are stereoisomerides, and not structural isomerides, in view of the fact that the "second half" of the cinchonine molecule as a whole produces such a small effect on the quinoline spectrum, and that such an important change as the conversion of tervalent nitrogen into quinquivalent nitrogen or of a vinyl into a carboxyl group may take place in this part of the molecule without producing any appreciable effect on the spectrum.

Quinine is distinguished from cinchonine by the possession of a methoxy-group in the quinoline nucleus, and, as may be seen from a comparison of the curves in Figs. 1 and 4, there is a considerable difference between the spectra of the two compounds. Like cinchonine, quinine exhibits two series of spectra, "C" and "D," which are related to one another in the same way as the cinchonine spectra.

The spectrum "C" is given by an alcoholic solution of quinine, and by solutions of quinine salts containing one equivalent of acid to one molecular proportion of alkaloid; spectrum "D" by solutions of salts containing two equivalents of acid to one molecular proportion of the alkaloid. In spectrum "C" with layers 20 mm.

FIG. 4.
Oscillation frequencies.

thick of $N/5000$ -solution the principal band lies between $1/\lambda$ 2938 and $1/\lambda$ 3293. In spectrum "D" the general absorption is greater and the band is wider; with layers 20 mm. thick of a $N/5000$ -solution the band lies between $1/\lambda$ 2768 and $1/\lambda$ 3468.

The substances examined were either prepared in the laboratory or purchased from well known makers. In nearly every case two preparations of independent origin were examined. The following table contains a list of the substances the spectra of which were photographed in connexion with the present investigation, and shows the spectrum obtained in each case—(a) when the substance was photographed in alcoholic solution or in a solution containing not more than one equivalent of acid to one molecular proportion of base, and (b) in a solution containing at least two equivalents of

acid to one of the base. The letters A, B, C, and D refer to the figures in the text bearing these letters.

	Spectrum.	
	(a).	(b).
<i>Cinchonine</i> . Recrystallised from alcohol, m. p. 254°.		
Other specimens were also examined with identical results.....	A.	B.
<i>Cinchonidine</i> , m. p. 202°.....	A.	B.
<i>Homocinchonidine</i> , m. p. 201°.....	A.	B.
<i>α</i> -iso <i>Cinchonine</i> . Prepared by Hesse's method (<i>Annalen</i> , 1898, 276 , 91), m. p. 126—127°	A.	B.
<i>β</i> -iso <i>Cinchonine</i> . Prepared by Skraup's method (<i>Monatsh.</i> , 1900, 21 , 393), m. p. 125°	A.	B.
<i>HoCinchonine</i> Prepared by Hlavnicka's method (<i>Monatsh.</i> , 1901, 22 , 191), m. p. 218—220°	A.	B.
<i>Cinchotenerine</i> , m. p. 195°	A.	B.
<i>Cinchonamine</i> , m. p. 186°	A.	B.
<i>α</i> - <i>Cinchonine methobromide</i> . Prepared by Claus and Müller's method (<i>Ber.</i> , 1880, 13 , 2290), m. p. 261—262°	A. (alcoholic solution).	B. (+1 equiv. acid).
<i>Hydriodide of β-cinchonine ethiodide</i> , m. p. 251°	B.	B.
<i>β-Cinchonine ethiodide</i> (C ₂₀ H ₂₁ I attached to quinoline N). Prepared by Skraup's method (<i>Monatsh.</i> , 1894, 15 , 37), m. p. 184°	B.	B.
<i>Cinchonine diethiodide</i> . Prepared by Skraup and Konek von Norwall's method (<i>Monatsh.</i> , 1894, 15 , 43), m. p. 264°	B.	B.
<i>Cinchonine chloride</i> , C ₁₉ H ₂₁ N ₂ Cl. Prepared by Com- stock and König's method (<i>Ber.</i> , 1884, 17 , 1984), m. p. 72—73°	A.	B.
<i>Quinoline</i> . (1) Synthetical; (2) Prepared from cinchonine	A. (alcoholic solution).	B. (+1 equiv. acid).
<i>Quinoline methiodide</i>	B.	B.
<i>Quinine</i> , m. p. 175·5°	C.	D.
<i>Quinine methiodide</i> , m. p. 98°.....	C. (alcoholic solution).	D. (+1 equiv. acid).
<i>Quinine dimethiodide</i> . Prepared by Claus and Mall- mann's method (<i>Ber.</i> , 1881, 14 , 76), m. p. 167—168°	D.	D.

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