2. The speed of the reaction in the presence of different organic acids of equal concentration diminishes with increasing values of the dissociation constants of the respective acids.

3. The function of the organic acid is that of a true catalytic agent, accelerating but not causing the reaction, as is shown by the fact that cinchonine dihydrochloride gives a low but measurable rate of conversion.

4. The effect of H^+ ion is to inhibit the rate of the reaction. In solutions of uniform concentration with respect to cinchonine (0.1 molal) and acetic acid (1.0 molal), increasing concentration of H^+ ion, as effected by the introduction of hydrochloric acid, produces a decrease in the rate of conversion until the reaction practically ceases when the solution contains 0.3 molal hydrochloric acid. In solutions of different salts of the alkaloid, such as cinchonine acetate, cinchonine monohydrochloride and cinchonine dihydrochloride, increasing concentration of organic acid effects increasing rate of reaction. The rates for equal concentration of organic acid, however, are less in the case of the salts naturally presenting through partial hydrolysis in solution the greater concentration of H^+ ion.

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THE RATE OF CONVERSION OF CINCHONIDINE INTO CINCHOTOXINE.[1]

(ON CATALYSIS WITH WEAK ACIDS, VII.)

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1. Introduction.—Cinchonidine was isolated from the bark of the cinchona trees by Winkler in 1847.[2] The alkaloid crystallizes from alcohol in white prisms which melt at 202–203°. It is isomeric in composition with cinchonine, but unlike this base is strongly laevorotatory. As shown by Königs and Hussmann,[3] it is possible to convert one alkaloid directly into the other. Thus, on prolonged heating with amyl alcohol and potassium hydroxide, cinchonine is converted into cinchonidine.

The properties of the two alkaloids indicate that they are of like constitution, the relation between the two being one of stereoisomerism. As was early shown by Pasteur,[4] both may be converted into the common product, cinchotoxine.

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[1] See preceding article on "Rate of Conversion of Cinchonine into Cinchotoxine."

[2] *Rep. f. Pharm.*, **85**, 392; **98**, 384; **99**, 1.

[3] *Ber.*, **29**, 2185 (1896).

[4] *Jahresb.*, **1853**, 422; *Compt. rend.*, **37**, 110 (1853); *Ann.*, **88**, 209 (1853).

If, in the light of the numerous investigations[1] of Königs, v. Miller, Rabe, Rhode and Skraup, the constitutions of cinchonine, cinchonidine and cinchotoxine are represented as in Fig. 1, the conversion of the first two alkaloids into the third involves the loss of asymmetry of the two asymmetric carbon atoms starred. The difference between cinchonine and cinchonidine must, consequently, lie in the stereoisomeric arrangement about one or both of these two carbon atoms.

According to Rabe[2] the difference between the two alkaloids is determined solely by the difference in stereoisomeric arrangement about the asymmetric carbon atom within the ring.

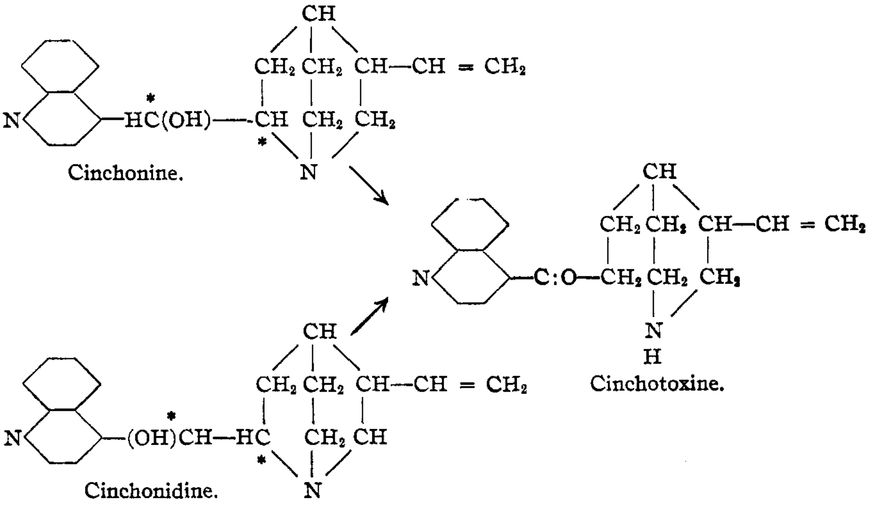

Fig. 1.

An investigation of the conversion of cinchonidine into cinchotoxine in comparison with the similar conversion of cinchonine into this base under like conditions thus becomes of interest as casting light upon the influence of stereoisomerism upon this conversion.

2. The Conversion of Cinchonidine into Cinchotoxine in the Presence of Organic Acids.—In view of the peculiar catalytic action of organic acids upon the rate of conversion of cinchonine into cinchotoxine, it is of importance to determine first whether the same phenomena obtain in the case of the stereoisomeric cinchonidine. That a like catalyzing influence occurs in this case as well has been indicated in a previous paper[3] and has also been pointed out by Rabe.[4] To obtain a general comparison

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[1] *Ann.*, **347**, 143 (1906); **350**, 180 (1906); **364**, 330 (1909); **365**, 353 (1909); **373**, 85 (1910).

[2] *Ann.*, **373**, 91 (1910).

[3] Biddle and Rosenstein, This Journal, **35**, 419 (1913).

[4] *Ber.*, **45**, 2929 (1912).

of the influence of different acids upon this catalysis, the following experiments were made with hydrochloric, formic and acetic acids: To 2 g. of cinchonidine were added in each case 5 equivalents of acid and then sufficient water to give a solution of 40 cc. The various solutions with the different acids were then heated at 99.7° (±0.2°) for 24 hours. Thereupon the alkaloids were precipitated by the addition of sodium hydroxide, extracted with ether and the solutions dried with calcium carbide. The ethereal solution of cinchotoxine was in each case thus largely freed from cinchonidine which, like cinchonine, is difficultly soluble in dry ether. The weight of the cinchotoxine was obtained on evaporating the ether. The results in each case were checked by isolating and weighing the unchanged cinchonidine. The results obtained are given in Table I.

TABLE I.

Cinchonidine, 2.0 grams. Temp., 99.7° (±0.2°).

No.	Acid.	Dissociation constant at 18°.	Cinchotoxine formed. Grams.	Per cent. conversion.
1.........	Hydrochloric	....	0.05	0.25
2.........	Formic	0.0214	1.15	60.00
3.........	Acetic	0.0018	1.92	96.00

While the results of these experiments are to be regarded as only rough approximations, they show beyond doubt the same catalyzing action observed in the case of cinchonine under like conditions.

For the exact measurement of the speed of the reaction advantage was taken, as in the case of cinchonine, of the variation in the optical rotation of the solution as the conversion progressed. As has been shown in previous papers, the value of the specific reaction rate is,

$$K_1 = \frac{1}{t} \log \frac{a_0 - a_\infty}{a_1 - a_\infty} \tag{1}$$

or, if instead of calculating K from the time when the reaction began, the calculation is made during different time intervals,

$$K_2 = \frac{1}{t_2 - t_1} \log \frac{a_1 - a_\infty}{a_2 - a_\infty}. \tag{2}$$

In these equations, as previously given, a_0 is the reading of the saccharimeter for the cinchonine solution, a_1 and a_2 the readings for the solution after the time intervals t_1 and t_2, and a_∞ the reading for the corresponding cinchotoxine solution. In the results recorded in this paper the calculations were made as in the case of cinchonine, bearing in mind, of course, that the specific rotation of cinchonidine unlike that of cinchonine is negative.

3. The Rate of Conversion in the Presence of Acetic Acid and Formic Acid.—In Tables II and III are given in detail the measurements for two concentrations of acetic acid. In Table IV are recorded the values of K_1 and K_2 for all the experiments carried out with acetic acid alone and formic acid alone. In this table and the remaining tables of the paper, to conserve space, there are given only the resulting values of K_1 and K_2 for the various experiments made.

TABLE II.
Acetic acid, 0.2 molal.
Cin. = 0.1 molal. L = 1.0 dm.
T = 99.7° (±0.2°).

t.	a.	K_1.	K_2.
0 hr.	−11.05	....	....
4 hrs.	−10.25	0.0064	0.0064
6 hrs.	−9.75	0.0070	0.0084
8 hrs.	−9.30	0.0072	0.0078
12 hrs.	−8.35	0.0077	0.0087
∞ hrs.	3.00	Mean, 0.0071	0.0078

TABLE III.
Acetic acid, 0. 3 molal.
Cin. = 0.1 molal. L = 1.0 dm.
T = 99.7° (±0.2°).

t.	a.	K_1.	K_2.
0 hr.	−11.40	....	....
4 hrs.	−9.80	0.0128	0.0128
6 hrs.	−9.20	0.0120	0.0104
8 hrs.	−8.50	0.0122	0.0128
12 hrs.	−7.10	0.0128	0.0141
∞ hrs.	3.00	Mean, 0.0125	0.0125

TABLE IV.
Cin. = 0.1 molal. T = 99.7° (±0.2°).

No.	Normality of total acid.	Acetic acid.		Formic acid.		Oxalic acid.	
		K_1.	K_2.	K_1.	K_2.	K_1.	K_2.
1	0.2	0.0071	0.0078	0.0048	0.0050	....	....
2	0.3	0.0125	0.0125	0.0077	0.0076	....	....
3	0.4	0.0178	0.0180	0.0102	0.0095	....	....
4	0.5	0.0241	0.0238	0.0118	0.0113	0.0033	0.0031
5	0.8	0.0373	0.0370	....	....	....	....
6	1.5	0.0585	0.0586	....	....	....	....
7	3.0	0.1040	0.1053	....	....	....	....

A comparison of the results in Table IV with those obtained under like conditions in the case of cinchonine (see THIS JOURNAL, p. 2077), show that we are dealing with a similar type of catalysis in the two cases. In both instances in the presence of acetic acid and formic acid there is increasing rate of reaction with increasing concentration of acid.

4. The Rate of Conversion with Mixtures of Acetic and Hydrochloric Acids.—In Table V are given the rates of the reaction in the case of cinchonidine monohydrochloride and cinchonidine dihydrochloride in the presence of varying quantities of acetic acid.

TABLE V.

No.	Molality of cinchonidine.	Normality of acetic acid.	Normality of hydrochloric acid.	K_1.	K_2.
1	0.09	0.2	0.09	0.0097	0.0098
2	0.09	0.3	0.09	0.0136	0.0138
3	0.09	0.4	0.09	0.0165	0.0170
4	0.09	0.8	0.09	0.0272	0.0275
5	0.09	1.5	0.09	0.0402	0.0418
6	0.1	0.2	0.2	0.0009	0.00084
7	0.1	0.3	0.2	0.0010	0.0012
8	0.1	0.5	0.2	0.0016	0.0018
9	0.1	0.8	0.2	0.0025	0.0027
10	0.1	1.5	0.2	0.0040	0.0044

A comparison of the specific reaction rates from Table V with those from the corresponding tables under the study of cinchonine (see preceding article), clearly reveals the close resemblance between the results in the two cases. In both instances the catalyzing influence of the organic acid accelerates the rate of reaction, and in both instances this accelerating influence is greatest in the case of the monoacetate, less in the case of the monohydrochloride and least in the case of the dihydrochloride.

It is of further interest to note that here, as in the catalysis of cinchonine, the ratio between rates of conversion in the case of different salts with equal concentrations of organic acid appears to approach a constant, as is shown in Table VI, in which the monohydrochloride is compared with the dihydrochloride.

TABLE VI.

No.	Normality of acetic acid.	Ratio of speed, monohydrochloride: dihydrochloride.
1	0.2	$\frac{0.0098}{0.00084} = 11.7$
2	0.3	$\frac{0.0138}{0.0012} = 11.5$
3	0.8	$\frac{0.0275}{0.0027} = 10.2$
4	1.5	$\frac{0.0418}{0.0044} = 9.5$

5. Relation between the Reaction Rates of Cinchonine and Cinchonidine.—A comparison of the rates of conversion of the two alkaloids in equal concentrations of acid reveals an interesting relation. Since the specific reaction rates obtained in the case of the two alkaloids were not derived in all instances from like concentrations of acid, the comparison in Table VII is naturally confined to the ten examples presenting such identity of concentration. The starred values under K_2'' were not determined experimentally, but are calculated from the mean value of $K_2''/K_2' = 1.21$.

From the results set forth in Table VII, it is apparent that the general rate of conversion of cinchonine into cinchotoxine slightly exceeds that of the conversion of the isomeric alkaloid. If we were to assume that the concentration of H^+ ion in solutions of equal concentration with respect to the acid is the same with either alkaloid, then the conditions affecting the catalysis in the two cases must be identical and the mean ratio of 1 : 1.21 would represent a difference of rate due solely to the stereoisomeric difference between the two alkaloids. The significance of this relation will be discussed by the senior author in the following paper.

TABLE VII.

No.	Molality of cinchonidine or cinchonine.	Normality of acetic acid.	Normality of formic acid.	Normality of hydrochloric acid.	K_2'.	K_2'' cinchonine.	K_2''/K_2'.
1	0.1	0.2	...	....	0.0078	0.0094	1 : 1.20
2	0.1	0.3	...	....	0.0125	0.0151*	
3	0.1	0.4	...	....	0.0180	0.0239	1 : 1.27
4	0.1	0.5	...	....	0.0238	0.0288*	
5	0.1	0.8	...	....	0.0370	0.0448	1 : 1.21
6	0.1	1.5	...	....	0.0586	0.0710*	
7	0.1	3.0	...	....	0.1053	0.1275*	
8	0.1	...	0.2	....	0.0050	0.0062	1 : 1.24
9	0.1	...	0.3	....	0.0076	0.0092*	
10	0.1	...	0.4	....	0.0095	0.0121	1 : 1.27
11	0.1	...	0.5	....	0.0113	0.0137*	
12	0.09	0.2	...	0.09	0.0098	0.0115	1 : 1.17
13	0.09	0.3	...	0.09	0.0138	0.0167*	
14	0.09	0.4	...	0.09	0.0170	0.0216	1 : 1.27
15	0.09	0.8	...	0.09	0.0275	0.0339	1 : 1.23
16	0.09	1.5	...	0.09	0.0418	0.0505*	
17	0.1	0.2	...	0.2	0.00084	0.0010	1 : 1.19
18	0.1	0.3	...	0.2	0.0012	0.0014*	
19	0.1	0.5	...	0.2	0.0018	0.0022*	
20	0.1	0.8	...	0.2	0.0027	0.0030	1 : 1.11
21	0.1	1.5	...	0.2	0.0044	0.0053*	
						Mean,	1 : 1.21 +

Summary.

1. The rate of the conversion of cinchonidine into cinchotoxine in the presence of organic acids is affected in the same general way as that of the conversion of the stereoisomeric cinchonine. With such acids as acetic and formic increasing concentration of acid effects increase in the speed of conversion.

2. The effect of increasing concentration of H^+ ion, as in the case of cinchonine, is to decrease the speed of the reaction. In solutions of uniform concentration with respect to the cinchonidine (0.1 molal) in the presence of such an acid as acetic, increasing concentration of hydrochloric acid leads to a decrease in the speed of conversion until eventually the reaction ceases.

3. The general rate of conversion of cinchonidine into cinchotoxine is less than that of the stereoisomeric cinchonine under the same conditions of temperature and concentration of acid, the ratio between the mean values of the two rates under the same conditions being 1 : 1.21.

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