

Examination showed that the portion of the lead cathode in the electrolyte had increased slightly in volume, and that it had lost its former malleability and firmness. Its bright color had changed to gray. On rubbing the lower part of the electrode between the fingers, it was found to have been completely transformed into small particles, which could be rubbed into a fine powder, or pressed together into a soft mass.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA.]

## THE RATE OF CONVERSION OF CINCHONINE INTO CINCHOTOXINE.<sup>1</sup>

(ON CATALYSES WITH WEAK ACIDS. VI.)

BY H. C. BIDDLE AND O. L. BRAUER.

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**i. Introduction.**—The most carefully investigated cases of catalysis in aqueous solution are those reactions of hydrolysis in which the accelerating influence of an acid is largely determined by the concentration of the hydrogen ions. Such, for example, are the familiar inversion of cane sugar and the saponification of an ester in the presence of an acid. In the case of the remarkable conversion of the cinchona alkaloids into their poisonous isomers in the presence of weak organic acids we are, however, dealing with a catalysis of a different nature. In this catalysis, as has been previously shown, the speed of the reaction is apparently a direct function of the molecular concentration of the undissociated acid and an inverse function of the concentration of the hydrogen ion.

The rate of the conversion of cinchonine to cinchotoxine was measured by Biddle and Rosenstein<sup>2</sup> for the alkaloid in two concentrations of acetic acid. In the present paper is given a detailed study of this catalysis in the presence of various acids through a wide range of concentration of the several acids studied and in mixtures of acetic acid and hydrochloric acid presenting also a wide range in concentration of H<sup>+</sup> ion. The data obtained in conjunction with like data from the study of the stereoisomeric cinchonidine and the two stereoisomers, quinine and quinidine, would, it was believed, afford a basis for a more thorough investigation of this extraordinary catalysis. Such data might naturally among other things be expected: first, to show with some greater degree of certainty not only what molecular species are involved in each reaction, but also

<sup>1</sup> Biddle, *Ber.*, 45, 526, 2832 (1912); *THIS JOURNAL*, 34, 500 (1912); 35, 273 (1913); 36, 84 (1914); Biddle and Rosenstein, *Ibid.*, 35, 418 (1913).

<sup>2</sup> *THIS JOURNAL*, 35, 418 (1913).

in what quantity each is concerned; second, to make clear to some extent the nature of the retarding influence of the hydrogen ion, as well as that of the accelerating influence of the organic acid; third, to furnish through a comparative study of the reaction velocities observed, some definite information regarding the influence of optical isomerism upon the speed of the conversion. As will be shown in a later article (the eighth in this series) on the nature of this catalysis, these expectations have been fully realized in the interpretation of the data presented in this paper and the following one on "The Rate of Conversion of Cinchonidine into Cinchotoxine."

**2. The Method of Analysis.**—In the separation of cinchotoxine from cinchonine, the method first used in these investigations<sup>1</sup> involved an extraction with ether and a subsequent dehydration of the ethereal solution, the cinchonine being difficultly soluble in dry ether. The method, however, in addition to the error due to a slight solubility of cinchonine in ether, presented experimental difficulties which rendered it somewhat objectionable. Of the two methods employed by Biddle and Rosenstein,<sup>2</sup> a gravimetric and a polarimetric, the latter proved so accurate and at the same time so expeditious that it was used by them largely in their determinations. In the present investigation<sup>3</sup> this method is employed almost exclusively. The polarimetric method<sup>4</sup> is based upon the fact that the rotatory power of solutions of cinchonine salts is much greater than that of the corresponding cinchotoxine salts. The change in the rotatory power of a solution of a cinchonine salt becomes, then, a measure of the extent to which change to cinchotoxine has taken place.

In view of the isomeric rearrangements which cinchonine and the cinchona alkaloids in general may undergo in the presence of excess of strong mineral acids,<sup>5</sup> and the consequent effect that slight changes in these directions might exert upon the optical activity of the solution, it was necessary to compare the gravimetric and polarimetric methods of measuring the conversion of cinchonine to cinchotoxine to determine whether or not the results were strictly comparable. In a previous paper<sup>6</sup> the optical method was checked with a gravimetric method depending on the solubility of cinchotoxine in ammonium salts. The reaction velocities as

<sup>1</sup> Biddle, *THIS JOURNAL*, 34, 504 (1912).

<sup>2</sup> *Ibid.*, 35, 418 (1913).

<sup>3</sup> The greater portion of the experimental work presented in this paper was carried on at about the same time as that of Rosenstein and Biddle, the polarimetric method of measurement being used in common by all those engaged in making the determinations.

<sup>4</sup> See Landolt, "The Optical Rotation of Organic Substances," 2nd Ed., pp. 500, 680, 687.

<sup>5</sup> Skraup, *Monatsh.*, 20, 571, 585 (1899); 22, 171, 253 (1901); Böttcher and Horowitz, *Ibid.*, 32, 793 (1911).

<sup>6</sup> Biddle and Rosenstein, *THIS JOURNAL*, 35, 418 (1913).

determined by the two methods agreed within the limits of experimental error.

A further comparison was made (Table I) by estimating the amount of conversion of cinchonine into cinchotoxine in a given time under like conditions. In this case the results of the polarimetric method were compared with those of the earlier ether-extraction method already mentioned. In applying this procedure the cinchonine was precipitated, freed as far as possible from cinchotoxine and weighed as the free alkaloid, the cinchotoxine being determined by difference. The results as in the previous case point to the conclusion that under the conditions of the experiments the gravimetric and polarimetric methods are comparable within the limits of experimental error.

TABLE I.—SOLUTIONS CONTAINING ACETIC ACID AND CINCHONINE (0.25 MOLAL) WERE HEATED FOR 15 HOURS AT 99.7° ( $\pm 0.2^\circ$ ).

Strength of acid.	Cinchonine recovered from 7.35 g.	Cinchotoxine by difference.	Average per cent. of cinchotoxine.	Per cent. of cinchotoxine from polarimetric reading.
0.75 molal.....	2.4535	4.8965	66.92	66.50
	2.4070	4.9430		
1.25 molal.....	1.0395	6.3105	86.82	86.86
	0.9997	6.4503		
1.50 molal.....	0.8320	6.5180	89.14	88.60
	0.7624	6.5876		
1.75 molal.....	0.5225	6.8275	92.46	92.60
	0.5666	6.7834		

The measurements presented in this article were made like those recorded in the previous paper by means of a Franz Schmidt and Haensch quartz wedge saccharimeter. The source of light was a Welsbach burner, a bichromate cell being used as a light filter. All readings were taken after the solutions had stood for a time in the dark room. In all cases in which the optical method was used the rotations were determined in terms of the arbitrary scale of the instrument (Ventzke degrees), it being unnecessary for all purposes of calculation to reduce the readings to angular degrees.

In general it may be noted that the initial readings of similar cinchonine solutions vary a trifle in rotation. This may be due to slight variations in the quality of the cinchonine (*e. g.*, minute changes to cinchotoxine) but is probably in part to be ascribed to small experimental errors. Since the same variation would naturally persist throughout any one set of readings, the error introduced into the calculation is negligible. It may be noted, further, that there is a slight increase in optical activity with increasing amount of acid present. On the other hand the rotatory power of cinchotoxine salts appears to vary to a negligible extent with varying concentration of acid. The angular variation observed in this case, however, is somewhat larger than that noted

by Biddle and Rosenstein. They obtained, for a solution of base containing 0.1 molal cinchotoxine and 1.5 molal acetic acid in a dm. tube, a reading of  $2.08^\circ$ , and, for a similar solution containing 3.0 molal acetic acid, a reading of  $2.7^\circ$ .

The cinchotoxine employed in the determinations recorded in Table II was heated with an excess of acetic acid for two days to insure the conversion of any unchanged cinchonine into the alteration product. It was thereupon precipitated as the free base, dissolved in ether and the ethereal solution dried with calcium carbide. After the evaporation of the ether, the base was dried in a vacuum desiccator over sulfuric acid for one week and was finally heated under diminished pressure for two hours at  $100^\circ$ . Readings were made by two observers, ( $x'$ ) and ( $x''$ ). The objection might be raised that the cinchotoxine thus obtained was not absolutely pure. Since, however, it represents the total alteration product, the optical rotation of which is the value to be determined, the objection may be waived.

TABLE II.  
Length of tube—0.25 dm.  
Concentration of cinchotoxine—0.1 molal.

Acetic acid, 0.4 molal.		Acetic acid, 1.0 molal.	
( $x'$ ).	( $x''$ ).	( $x'$ ).	( $x''$ ).
0.82	0.766	0.72	0.716
0.82	0.816	0.72	0.696
0.70	0.716	0.82	0.696
0.67	0.766	0.72	0.746
0.82	0.736	0.72	0.816
			0.716
Mean, 0.766		0.74	0.731

From Table II it will be noted that the difference between the readings for 0.4 equivalent of acid and 1.0 equivalent is not greater than the experimental error involved. The average of all the readings is  $0.75^\circ$ , or for a 1 dm. tube as used by Biddle and Rosenstein,  $3.00^\circ$ —a little higher than their higher value. If we ignore the objection which may be raised to the employment of the shorter tube, the angular rotation of cinchotoxine in the presence of acetic acid of concentration varying from 0.4 molal to 1.0 molal, may be regarded as practically constant.

**3. Experimental Details.**—In determining the rate of conversion of cinchonine into cinchotoxine in various acid solutions, the reaction mixture was kept at a constant temperature (in the greater number of cases at  $99.7^\circ$  ( $\approx 0.2$ )), during the course of the experiment. In some instances the reaction was carried on in small flasks, fitted with a siphon and a reflux condenser. In most cases the reaction mixture was enclosed in a series of hermetically sealed tubes. This method of procedure not only simplified the operation, but also precluded any chance of error due to loss through evaporation or of inaccuracy due to insufficient stirring when

the sample was taken. In the first case, at different time intervals, after quickly stirring the mixture by blowing air back through the siphon, 10 cc. samples were drawn off, rapidly chilled and placed in a dark room until the reading was taken; in the second, at each time interval, a tube was removed and treated as the sample in the previous case. The results obtained by the two methods for solutions of equal concentration were practically identical.

The heating was carried out in a copper water bath about 2 feet square and 8 inches high, fitted with a constant level and heated by means of a quadruple burner. When placed in a small hood to shield the apparatus from currents of air, it was found that the rapidly boiling bath could be readily maintained at a temperature presenting variations in any one set of experiments not exceeding  $\pm 0.2^\circ$ . In a thermostat of this size it became possible to run a number of determinations practically simultaneously.

As previously indicated,<sup>1</sup> if the reaction is a monomolecular one with respect to the alkaloid, then the rate of the reaction for any particular strength of the catalyzer is expressed by the equation,

$$-d(c)/dt = K(c),$$

where  $c$  is the concentration of the alkaloid at the time  $t$ , and  $K$  is the specific reaction rate. On integration this gives for the value of the specific reaction rate,

$$K_1 = 1/t \log c_0/c_1, \quad (1)$$

where  $K_1$  is the specific reaction rate,  $t$  is the time,  $c_0$  is the concentration of the alkaloid at the beginning of the experiment, and  $c_1$  its concentration after the time  $t$ . Or, if the calculation is made during different time intervals,

$$K_2 = \frac{1}{t_2 - t_1} \log \frac{c_1}{c_2}, \quad (2)$$

where  $c_1$  is the concentration after the time  $t_1$ , and  $c_2$  the concentration after the time  $t_2$ .

If concentrations are replaced by polarimetric readings, Formula 1 becomes,

$$K_1 = \frac{1}{t} \log \frac{a_0 - a_\infty}{a_1 - a_\infty}, \quad (3)$$

and Formula 2 becomes,

$$K_2 = \frac{1}{t_2 - t_1} \log \frac{a_1 - a_\infty}{a_2 - a_\infty}. \quad (4)$$

In these formulas,  $a_0$  is the instrument reading for the unchanged cinchonine solution,  $a_1$  and  $a_2$  the readings for the solution after the time intervals  $t_1$  and  $t_2$ , and  $a_\infty$  the reading for the solution when the cinchonine is completely converted into cinchotoxine.

<sup>1</sup> Biddle and Rosenstein, *THIS JOURNAL*, 35, 421 (1913).

**4. Rate of the Reaction with Acetic Acid.**—In the previous measurements of Biddle and Rosenstein<sup>1</sup> the concentrations of the acid were tabulated as molal concentrations above the acid necessary to form the diacid salt of cinchonine. In recording the present experiments, it has seemed preferable to give the molal concentration of the *total* acid, present including as well that which is naturally in combination with the cinchonine to form a salt. In the following tables, *Cin.* represents the molal concentration of the cinchonine, *L* the length of the polarimeter tube, *T* the temperature of the thermostat, *t* the time in hours and *a* the polarimetric reading of the solution after being heated for time *t*. The polarimetric reading of the solution in which complete conversion to cinchotoxine has been effected is determined from the data given in Table II, it being assumed that the variations in readings due to varying concentration of acid are negligible. These values are given under  $\infty$ .

Under Tables III to XIV are given the actual measurements made in the case of 0.1 molal cinchonine with concentrations of acetic acid ranging from 0.15 to 17.24 molal. Under Tables XV and XVI are recorded simply the resulting rates ( $K_1$  and  $K_2$ ) obtained for 0.25 molal and 0.01 molal cinchonine, respectively, with varying concentrations of acetic acid.

TABLE III.

Acetic acid, 0.15 molal.  
Cin. = 0.1 molal. *L* = 2.0 dm.  
*T* = 99.7° ( $\pm 0.2^\circ$ )\*

<i>t</i>	<i>a</i>	$K_1$	$K_2$
0 hr.	34.70	...	...
4 hrs.	33.25	0.00563	0.00563
6 hrs.	32.50	0.00577	0.00606
8 hrs.	31.80	0.00578	0.00581
10 hrs.	31.20	0.00564	0.00511
$\infty$ hrs.	6.00	Mean, 0.00570	0.00565

TABLE IV.

Acetic acid, 0.175 molal.  
Cin. = 0.1 molal. *L* = 1.0 dm.  
*T* = 99.7° ( $\pm 0.2^\circ$ ).

<i>t</i>	<i>a</i>	$K_1$	$K_2$
0 hr.	18.03	...	...
4 hrs.	17.10	0.00713	0.00694
8 hrs.	16.18	0.00713	0.00732
12 hrs.	15.35	0.00711	0.00706
16 hrs.	14.56	0.00713	0.00717
$\infty$ hrs.	3.00	Mean, 0.00708	0.00712

TABLE V.

Acetic acid, 0.2 molal.  
Cin. = 0.1 molal. *L* = 1.0 dm.  
*T* = 99.7° ( $\pm 0.1^\circ$ ).

<i>t</i>	<i>a</i>	$K_1$	$K_2$
0 hr.	17.81	...	...
5 hrs.	16.40	0.0087	0.0087
7 hrs.	15.75	0.0093	0.0108
9 hrs.	15.26	0.0091	0.0085
11 hrs.	14.73	0.0092	0.0096
16 hrs.	13.54	0.0093	0.0093
$\infty$ hrs.	3.00	Mean, 0.0091	0.0094

TABLE VI.

Acetic acid, 0.4 molal.  
Cin. = 0.1 molal. *L* = 0.5 dm.  
*T* = 99.7° ( $\pm 0.2^\circ$ ).

<i>t</i>	<i>a</i>	$K_1$	$K_2$
0 hr.	9.39	...	...
2 hrs.	8.55	0.0244	0.0244
4 hrs.	7.92	0.0224	0.0203
6 hrs.	7.17	0.0239	0.0269
8 hrs.	6.55	0.0242	0.0252
11 hrs.	5.81	0.0238	0.0229
$\infty$ hrs.	1.50	Mean, 0.0238	0.0239

\* All temperatures reached in this and other papers, it is scarcely necessary to mention, are in the centigrade scale.

<sup>1</sup> THIS JOURNAL, 35, 418 (1913).

TABLE VII.

Acetic acid, 0.8 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	19.80	...	...
2 hrs.	16.68	0.0446	0.0446
4 hrs.	14.20	0.0440	0.0434
6 hrs.	12.05	0.0448	0.0463
8 hrs.	10.36	0.0448	0.0449
$\infty$ hrs.	3.00	Mean, 0.0445	0.0448

TABLE VIII.

Acetic acid, 1.0 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.1^\circ$ ).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	20.32	...	...
2 hrs.	16.41	0.0557	0.0557
3 hrs.	14.90	0.0544	0.0520
4 hrs.	13.46	0.0548	0.0560
5 $\frac{1}{4}$ hrs.	11.90	0.0551	0.0561
8 $\frac{3}{4}$ hrs.	8.34	0.0584	0.0634
$\infty$ hrs.	3.00	Mean, 0.0557	0.0566

TABLE IX.

Acetic acid, 1.7 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	20.35	...	...
2 $\frac{3}{4}$ hrs.	13.57	0.0782	0.0782
3 $\frac{3}{4}$ hrs.	11.93	0.0768	0.0732
7 hrs.	8.05	0.0767	0.0762
8 hrs.	6.87	0.0817	0.0867
10 hrs.	5.65	0.0816	0.0838
$\infty$ hrs.	3.00	Mean, 0.0790	0.0796

TABLE X.

Acetic acid, 2.0 molal.

Cin. = 0.1 molal. L = 0.5 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	10.19	...	...
1 hr.	8.70	0.0817	0.0817
2 hrs.	7.40	0.0841	0.0865
3 hrs.	6.14	0.0908	0.1043
5 $\frac{1}{2}$ hrs.	4.22	0.0917	0.0928
6 $\frac{1}{2}$ hrs.	3.91	0.0916	0.0901
$\infty$ hrs.	1.50	Mean, 0.0880	0.0901

TABLE XI.

Acetic acid, 3.2 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	20.99	...	...
2 hrs.	13.68	0.1132	0.1132
4 hrs.	8.66	0.1255	0.1378
6 hrs.	5.76	0.1357	0.1559
8 hrs.	4.61	0.1310	0.1171
10 hrs.	3.80	0.1352	0.1518
$\infty$ hrs.	3.00	Mean, 0.1281	0.1351

TABLE XII.

Acetic acid, 4.0 molal.

Cin. = 0.1 molal. L = 0.5 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	10.50	...	...
1 hr.	8.04	0.1387	0.1387
2 hrs.	6.16	0.1429	0.1472
3 hrs.	4.68	0.1506	0.1659
5 $\frac{1}{4}$ hrs.	2.99	0.1487	0.1463
6 hrs.	2.66	0.1483	0.1450
$\infty$ hrs.	1.50	Mean, 0.1458	0.1486

The specific reaction rates as given in the preceding tables (IX and XI) are in agreement with the corresponding values obtained by Biddle and Rosenstein through a slightly different method of heating. If the mean

TABLE XIII.

Acetic acid, 8.0 molal.  
Cin. = 0.1 molal. L = 1.0 dm.  
T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	20.31	...	...
1 hr.	13.29	0.2259	0.2388
2 hrs.	9.15	0.2247	0.2135
3 hrs.	6.71	0.2230	0.2195
4 hrs.	4.97	0.2359 <sup>1</sup>	0.2749 <sup>1</sup>
5 hrs.	3.92	0.2549 <sup>1</sup>	0.3307 <sup>1</sup>
$\infty$ hrs.	3.00	Mean, 0.2245	0.2229

TABLE XIV.

Acetic acid, 17.24 molal (glacial).<sup>2</sup>  
Cin. = 0.1 molal. L = 0.5 dm.  
T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	10.20	...	...
1 hr.	7.23	0.1814	0.1814
2 hrs.	5.31	0.1793	0.1772
3 hrs.	4.06	0.1771	0.1727
4 hrs.	3.36	0.1675	0.1387
5 hrs.	2.72	0.1706	0.1832
$\infty$ hrs.	1.50	Mean, 0.1751	0.1706

values of the reaction rate as obtained by them are calculated with  $t$  expressed in hours, we obtain the following comparison:

Conc. of acid.	K (Biddle and Rosenstein).	K (Tables IX and XI).
1.7 molal	0.0780 <sup>3</sup>	0.0783 <sup>4</sup>
3.2 molal	0.1296 <sup>3</sup>	0.1216 <sup>4</sup>

In the experiments whose results alone are recorded under Tables XV and XVI, it may be noted that solutions containing the higher concentration of cinchonine (0.25 molal) were sooner discolored by heating, and the readings in most cases were made in a short tube (0.25 dm.). In solutions containing a lower concentration of the alkaloid (0.01 molal), a longer tube (4.0 dm.) was employed. K<sub>1</sub> and K<sub>2</sub> have the same significance as given in the preceding tables.

TABLE XV.

Acetic acid. Cin. = 0.25.  
T = 99.7° ( $\pm 0.2^\circ$ ).

No.	Normality of total acid.	K <sub>1</sub> .	K <sub>2</sub> .
1.....	0.50	0.0200	0.0192
2.....	0.75	0.0310	0.0327
3.....	1.00	0.0414	0.0434
4.....	1.25	0.0563	0.0566
5.....	1.50	0.0721	0.0721
6.....	2.00	0.0880	0.0901
7.....	2.50	0.1072	0.1112

TABLE XVI.

Acetic acid. Cin. = 0.01.  
T = 99.7° ( $\pm 0.2^\circ$ ).

No.	Normality of total acid.	K <sub>1</sub> .	K <sub>2</sub> .
1.....	0.05	0.0056	0.0058
2.....	0.10	0.0086	0.0089
3.....	0.15	0.0116	0.0127
4.....	0.20	0.0153	0.0162
5.....	0.40	0.0252	0.0256
6.....	0.80	0.0340	0.0347

<sup>1</sup> Readings for close of fourth and fifth hours were inexact on account of increased color of solution. Corresponding values of K<sub>1</sub> and K<sub>2</sub> are consequently not considered in determining mean value of these constants.

<sup>2</sup> 97.85 cc. of glacial acetic containing 0.1 molal cinchonine gave at ordinary temperature a volume of 100 cc.

<sup>3</sup> Temperature of experiment, 99.6° ( $\pm 0.1^\circ$ ).

<sup>4</sup> Temperature of experiment, 99.7° ( $\pm 0.2^\circ$ ).



TABLE XVII.

COMPARATIVE SUMMARY OF DATA DERIVED FROM PRECEDING DETERMINATIONS.

A.				B.				C.			
No.	$ac$ .	$K_2$ .	$K_2/ac$ .	No.	$ac'$ .	$K_2$ .	$K_2/ac'$ .	No.	$ac''$ .	$K_2$ .	$K_2/ac''$ .
1	0.05	0.0058 <sup>1</sup>	0.116	1	0.04	0.0058 <sup>1</sup>	0.145	1	0.00	0.0094	...
2	0.10	0.0089 <sup>1</sup>	0.089	2	0.05	0.0057	0.104	2	0.00	0.0192 <sup>2</sup>	...
3	0.15	0.0127 <sup>1</sup>	0.085	3	0.075	0.0071	0.095	3	0.03	0.0058 <sup>1</sup>	0.193
4	0.15	0.0057	0.038	4	0.09	0.0089 <sup>1</sup>	0.099	4	0.08	0.0089 <sup>1</sup>	0.111
5	0.175	0.0071	0.041	5	0.10	0.0094	0.094	5	0.13	0.0127 <sup>1</sup>	0.098
6	0.20	0.0162 <sup>1</sup>	0.081	6	0.14	0.0127 <sup>1</sup>	0.091	6	0.18	0.0162 <sup>1</sup>	0.090
7	0.20	0.0094	0.047	7	0.19	0.0162 <sup>1</sup>	0.085	7	0.20	0.0239	0.119*
8	0.40	0.0239	0.060	8	0.25	0.0192 <sup>2</sup>	0.081	8	0.25	0.0327 <sup>2</sup>	0.131
9	0.40	0.0256 <sup>1</sup>	0.064	9	0.30	0.0239	0.080	9	0.38	0.0256 <sup>1</sup>	0.067
10	0.50	0.0192 <sup>2</sup>	0.041	10	0.39	0.0256 <sup>1</sup>	0.066	10	0.50	0.0434 <sup>2</sup>	0.085
11	0.75	0.0327 <sup>2</sup>	0.044	11	0.50	0.0327 <sup>2</sup>	0.065	11	0.60	0.0448	0.075
12	0.80	0.0448	0.056	12	0.70	0.0448	0.067	12	0.75	0.0566 <sup>2</sup>	0.076
13	0.80	0.0347 <sup>1</sup>	0.043	13	0.75	0.0434 <sup>2</sup>	0.058	13	0.78	0.0347 <sup>1</sup>	0.045
14	1.00	0.0566	0.057	14	0.79	0.0347 <sup>1</sup>	0.044	14	0.80	0.0566	0.071
15	1.00	0.0434 <sup>2</sup>	0.043	15	0.90	0.0566	0.063	15	1.00	0.0721 <sup>2</sup>	0.072
16	1.25	0.0566 <sup>2</sup>	0.045	16	1.00	0.0566 <sup>2</sup>	0.057	16	1.50	0.0796	0.053
17	1.50	0.0721 <sup>2</sup>	0.048	17	1.25	0.0721 <sup>2</sup>	0.058	17	1.50	0.0901 <sup>2</sup>	0.059
18	1.70	0.0796	0.047	18	1.60	0.0796	0.050	18	1.80	0.0901	0.050
19	2.00	0.0901	0.045	19	1.75	0.0901 <sup>2</sup>	0.051	19	2.00	0.1112	0.055
20	2.00	0.0901 <sup>2</sup>	0.045	20	1.90	0.0901	0.047	20	3.00	0.1351	0.045
21	2.50	0.1112 <sup>2</sup>	0.045	21	2.25	0.1112 <sup>2</sup>	0.049	21	3.80	0.1486	0.039
22	3.20	0.1351	0.042	22	3.10	0.1351	0.044	22	7.80	0.2229	0.029
23	4.00	0.1486	0.037	23	3.90	0.1486	0.038	23	17.04	0.1706	0.010
24	8.00	0.2229	0.028	24	7.90	0.2229	0.028				
25	17.14	0.1706	0.010	25	17.14	0.1706	0.010				

In the accompanying table (Table XVII) are brought together the various specific reaction rates ( $K_2$ ) given on the preceding pages, for 0.25, 0.1 and 0.01 molal cinchonine in various concentrations of acetic acid, the latter being tabulated as total acid concentrations under A, as concentrations above the monoacetate under B, and as concentrations above the diacetate under C. Under  $K_2/ac$ ,  $K_2/ac'$  and  $K_2/ac''$ , are given the values obtained by dividing the specific reaction rate, respectively, with the total acid concentration  $ac$ , the concentration above the monoacetate  $ac'$ , and that above the diacetate  $ac''$ .

In the preceding paper of Biddle and Rosenstein,<sup>3</sup> it was suggested that the conversion of cinchonine into cinchotoxine involves at least two elements, of which one is independent of the presence of a weak acid and the other is dependent upon the presence of such an acid. In the study of the catalysis the concentration of the acid was expressed in terms of

<sup>1</sup> Values from solutions 0.01 molal with respect to cinchonine.

<sup>2</sup> Values from solutions 0.25 molal with respect to cinchonine. Unmarked values from solutions 0.1 molal with respect to cinchonine.

<sup>3</sup> THIS JOURNAL, 35, 418 (1913).

the "free" acid, *i. e.*, in terms of the amount in excess of that needed to form the diacetate. A consideration of the summary in Table XVII leads unavoidably to the conclusion that the rate of the reaction is more correctly represented as a function of the acid concentration in excess of that necessary to form the *monoacetate*. This concentration of acid may, consequently, be provisionally designated as "free" acid, although as will be pointed out in a later paper, even this value does not exactly represent the factor in the organic acid responsible for the catalyzing action. Indeed, as will be later shown the rate of the reaction is a linear function of the molecular concentration of the undissociated organic acid in the solution—a value which while in most cases approaching that of the concentration of the acid in excess of the monoacetate is not exactly represented by this concentration, nor by that of the acid in excess of the diacetate.

Since, however, increasing concentration of acid above the monoacetate is accompanied by increasing rate of reaction, it becomes of interest to study the graph presented by plotting these values against each other, as shown in Fig. 1. This is of particular interest in seeking for some ex-

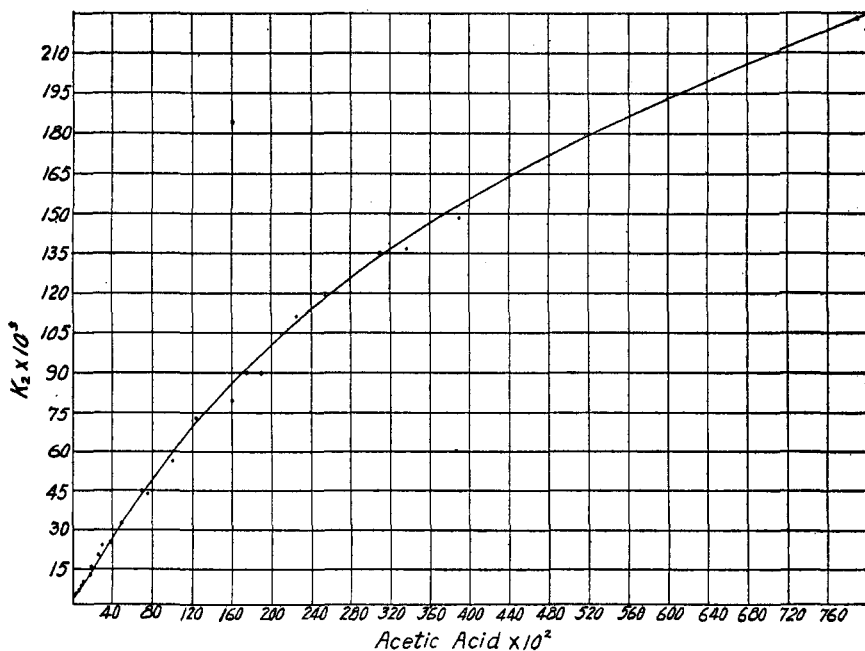


Fig. 1.

planation for the apparent anomaly observed in the specific reaction rates of cinchonine diacetate, where different concentrations of the alkaloid lead to widely divergent values for  $K_2$  (compare values for  $K_2$  under Nos.

1 and 2, C, Table XVII). If the reaction is monomolecular with respect to the cinchonine salt, and the catalyzer obeys the ordinary mass law, the values of  $K_2$  for different concentrations of cinchonine salt should not differ appreciably in like concentrations of the catalyzing acid. If now, in the cases considered, the reaction is regarded as monomolecular with respect to the cinchonine monoacetate and the acid in excess of that necessary to form this salt is regarded as representing the concentration of the catalyzer, the values of  $K_2$  will be found in general to increase with increasing concentration of acid (see B, Table XVII).

It will be observed, furthermore, that the increasing values of  $K_2$  correspond with fair uniformity in the case of all three different concentrations of cinchonine. It may, consequently, be assumed that the first equivalent of acid needed to form the monacid salt does not exert a large catalyzing influence upon the speed of the reaction. This is in accord with an observation already made in a previous paper<sup>1</sup> that the catalyzing influence of acetic acid upon different monacid salts of cinchonine is apparently not greatly different. In stating this, however, attention must be called to the fact that the catalytic action of a given concentration of an organic acid upon different monacid salts of cinchonine does not lead to *identical* reaction rates. This is clearly shown on comparing the action of acetic acid on cinchonine monoacetate and cinchonine monohydrochloride, respectively (see Table XXXIV).

It is of further interest to note the general relation between the speed of the reaction and the concentration of the organic acid. In the fourth column of B, Table XVII, are presented under  $K_2/ac'$ , as shown, the quotient of the specific reaction rate divided by the concentration of the acid in excess of that forming the monoacetate. As is seen the value of  $K_2/ac'$  gradually decreases with increasing concentration of acid.

**5. Rate of the Reaction with Acids other than Acetic.**—Biddle<sup>2</sup> found that under like conditions the amount of cinchonine changed into cinchotoxine was less with strong acids than it was with weak. In the following tables are given the results obtained from a study of this catalysis in the presence of acids of quite different dissociation constants. In Tables XVIII to XXV inclusive, the actual measurements are given in detail. In Table XXVI are summarized the results presented in the preceding tables, together with the resulting rates of other experiments, the details of which, to conserve space, have been omitted. Chloroacetic acid is inadmissible in this study on account of its ready hydrolysis under the conditions of the experiment into hydrochloric and oxyacetic acids. This will account for the low catalyzing influence of this acid already observed.<sup>3</sup>

<sup>1</sup> Biddle, *Ber.*, 45, 2836 (1912).

<sup>2</sup> *THIS JOURNAL*, 34, 500 (1912).

<sup>3</sup> Biddle, *Ibid.*, 34, 501 (1912).

TABLE XVIII.

Formic acid, 0.2 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	20.20	....	....
6 hrs.	19.03	0.0051	0.0051
10 hrs.	18.23	0.0053	0.0056
12 hrs.	17.73	0.0056	0.0072
16 hrs.	16.81	0.0060	0.0070
28 hrs.	14.70	0.0060	0.0060
$\infty$ hrs.	3.00 <sup>1</sup> Mean,	0.0056	0.0062

TABLE XX.

Propionic acid, 0.2 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	17.77	....	....
2 hrs.	17.10	0.0101	0.0101
4 hrs.	16.41	0.0105	0.0109
5 <sup>1</sup> / <sub>2</sub> hrs.	15.81	0.0112	0.0133
8 <sup>1</sup> / <sub>4</sub> hrs.	14.94	0.0111	0.0111
11 <sup>1</sup> / <sub>4</sub> hrs.	13.91	0.0117	0.0130
$\infty$ hrs.	3.00 Mean,	0.0109	0.0117

TABLE XXII.

Oxalic acid, 0.2 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	20.88	....	....
4 hrs.	20.14	0.0046	0.0046
8 hrs.	19.54	0.0042	0.0039
12 hrs.	19.00	0.0040	0.0036
16 hrs.	18.43	0.0040	0.0039
24 hrs.	17.33	0.0040	0.0040
$\infty$ hrs.	3.00 Mean,	0.0042	0.0040

TABLE XIX.

Formic acid, 0.8 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	21.73	....	....
4 hrs.	19.35	0.0148	0.0148
8 hrs.	17.29	0.0147	0.0146
12 hrs.	15.13	0.0157	0.0178
16 hrs.	13.33	0.0161	0.0174
24 hrs.	10.41	0.0168	0.0180
$\infty$ hrs.	3.0   Mean,	0.0156	0.0165

TABLE XXI.

Propionic acid, 0.8 molal.

Cin. = 0.1 molal. L = 0.5 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	9.87	....	....
2 hrs.	7.91	0.0579	0.0579
4 hrs.	6.42	0.0577	0.0574
5 <sup>1</sup> / <sub>2</sub> hrs.	5.40	0.0603	0.0673
7 hrs.	4.70	0.0597	0.0573
11 <sup>1</sup> / <sub>4</sub> hrs.	3.18	0.0620	0.0658
$\infty$ hrs.	1.50 Mean,	0.0595	0.0611

TABLE XXIII.

Oxalic acid, 0.3 molal.

Cin. = 0.1 molal. L = 1.0 dm.

T = 99.7° ( $\pm 0.2^\circ$ ).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	21.02	....	....
8 hrs.	20.70	0.0010	0.0010
12 hrs.	20.22	0.0016	0.0030
16 hrs.	19.87	0.0018	0.0022
24 hrs.	19.20	0.0019	0.0022
30 hrs.	18.96	0.0017	0.0011
$\infty$ hrs.	3.00 Mean,	0.0016	0.0019

In the presence of 0.25 *N* hydrochloric acid the rate but slightly exceeds 0.0001, the conversion after several hours being so slight as to render the experimental results more or less inexact. With concentrations of 0.4 molal and above with respect to the acid, there was no decrease in rotation after heating. Indeed, with these concentrations, an apparent slight *increase*

<sup>1</sup> This is the reading for the corresponding cinchotoxine solution in acetic acid, it being assumed that the variation due to the presence of different acids is sufficiently small to be negligible.

TABLE XXIV.

Hydrochloric acid, 0.15 molal.  
Cin. = 0.1 molal. L = 4.0 dm.  
T = 99.7° (±0.2°).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	78.42	....	....
2 <sup>3</sup> / <sub>4</sub> hrs.	77.83	0.00141	0.00141
4 <sup>3</sup> / <sub>4</sub> hrs.	77.44	0.00136	0.00129
7 hrs.	76.70	0.00163	0.00219
∞ hrs.	12.00	Mean, 0.00147	0.00163

TABLE XXV.

Hydrochloric acid, 0.175 molal.  
Cin. = 0.1 molal. L = 4.0 dm.  
T = 99.7° (±0.2°).

t.	a.	K <sub>1</sub> .	K <sub>2</sub> .
0 hr.	84.01	....	....
6 hrs.	83.41	0.00061	0.00061
8 hrs.	83.09	0.00070	0.00097
12 hrs.	82.60	0.00072	0.00075
∞ hrs.	12.00	Mean, 0.00068	0.00077

in rotation is generally observed, which, however, gradually falls to the original reading. Thus, with 0.8 molal hydrochloric acid the following readings were obtained:

Time:	0 hr.	4 hrs.	8 <sup>1</sup> / <sub>4</sub> hrs.	12 hrs.	15 <sup>3</sup> / <sub>4</sub> hrs.	23 <sup>3</sup> / <sub>4</sub> hrs.	28 hrs.
	20.96	21.30	21.30	21.46	21.09	21.03	20.85

The cause of this phenomenon was not determined. It scarcely seems due to mutarotation, nor is it probably to be ascribed to the formation of isomers of cinchonine such as isocinchonine prepared by Hesse.<sup>1</sup>

TABLE XXVI.

Nor- mality of total acid.	Propionic acid.		Acetic acid.		Formic acid.		Oxalic acid.		Hydrochloric acid.	
	K <sub>1</sub> .	K <sub>2</sub> .	K <sub>1</sub> .	K <sub>2</sub> .	K <sub>1</sub> .	K <sub>2</sub> .	K <sub>1</sub> .	K <sub>2</sub> .	K <sub>1</sub> .	K <sub>2</sub> .
I 0.15	....	....	0.00570	0.00565	....	....	....	....	0.00147	0.00163
2 0.175	....	....	0.00708	0.00712	....	....	....	....	0.00068	0.00077
3 0.20	0.0109	0.0117	0.0091	0.0094	0.0056	0.0062	....	....	0.0003 <sup>2</sup>	0.0003 <sup>2</sup>
4 0.25	....	....	....	....	....	....	....	....	0.0001 <sup>2</sup>	0.0001 <sup>2</sup>
5 0.40	0.0278	0.0296	0.0238	0.0239	0.0118	0.0121	0.0042	0.0040	....	....
6 0.60	....	....	....	....	....	....	0.0016	0.0019	....	....
7 0.80	0.0595	0.0611	0.0488	0.0499	0.0156	0.0165	....	....	....	....
8 1.00	....	....	0.0567	0.0574	....	....	....	....	....	....
9 1.20	0.0750	0.0760	....	....	....	....	....	....	....	....
10 1.70	....	....	0.0790	0.0796	....	....	....	....	....	....
11 2.00	....	....	0.0880	0.0901	....	....	0.0007 <sup>2</sup>	0.0007 <sup>2</sup>	....	....
12 3.20	....	....	0.1275	0.1351	....	....	....	....	....	....

In Table XXVI is presented a comparative summary of the results obtained with different acids. In the results here tabulated it is interesting to note that the speed of the conversion in every instance decreases with acids of increasing dissociation constant—a fact to which attention has already been called in an earlier article.<sup>3</sup> In the presence of any one of the three acids, propionic, acetic, or formic, increasing concentration of acid leads to increasing speed of conversion; in the presence of oxalic acid or hydrochloric acid, the reverse is true. In the case of the first three

<sup>1</sup> *Ann.*, 276, 91 (1893).

<sup>2</sup> Approximate value only.

<sup>3</sup> Biddle, *THIS JOURNAL*, 34, 500 (1912).

acids the rate of increase of speed with equal increments in concentration of acid is greatest with the acid of lowest dissociation constant, and least with the acid of highest dissociation constant. If now this is due primarily to the increasing concentration of  $H^+$  ion in the case of the more highly dissociated acids, it would be natural to expect that, in studying acids of increasing dissociation constant the effect of the increasing concentration of  $H^+$  ion with increasing concentration of acid would eventually exceed that of the positive catalytic influence of the organic acid. In this case, as with oxalic acid, the speed would diminish with increasing concentration of acid. In the case of an acid such as oxalic it would be of interest to study the effect of still lower concentrations to determine whether the speed passes through a maximum value, below which increasing concentration of acid would exhibit the same positive catalyzing action shown in the case of organic acids less dissociated.

In the case of hydrochloric acid, if we assume that this acid has no positive catalytic influence similar to that of an organic acid, then the decreasing speed of the reaction with increasing concentration of acid becomes a measure of the influence of the  $H^+$  ion—a matter which will be considered in detail in a later paper.

**6. Rate of the Reaction with Mixtures of Hydrochloric Acid and Acetic Acid.**—The inhibiting influence of increasing concentration of  $H^+$ , as previously noted,<sup>1</sup> upon the catalysis renders the determination of the reaction velocity in solutions containing mixtures of the two acids, hydrochloric and acetic, of particular interest. Since dilute hydrochloric acid may be regarded practically as completely dissociated, we may, to a certain extent, vary as desired the concentration of  $H^+$  ion by choosing a suitable mixture of the two acids. Furthermore, since solutions of cinchonine in dilute hydrochloric acid exhibit no large velocity of conversion, as is shown in solutions of like  $H^+$  ion concentration containing acetic acid,<sup>2</sup> it seems safe, as already indicated, to disregard any *positive* catalyzing influence of the halogen acid. It then becomes possible through a study of mixtures of the two acids to gain some idea of the retarding influence of the  $H^+$  ion upon the positively accelerating action of the acetic acid. The experimental results of such a study are presented in the following determinations in which are first considered the reaction rates in the case of cinchonine in molal acetic acid with varying amounts of hydrochloric acid.

In Table XXXIII is presented a summary of the results obtained in the following measurements (Tables XXVII–XXXII) together with the results of similar experiments, the detailed measurements of which have been omitted.

<sup>1</sup> Biddle, *THIS JOURNAL*, 34, 505 (1912).

<sup>2</sup> *Ibid.*, *Loc. cit.*

TABLE XXVII.

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

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	20.73	....	....
3 hrs.	16.73	0.0370	0.0370
5 hrs.	14.31	0.0391	0.0421
6 hrs.	13.24	0.0397	0.0432
8 <sup>1</sup> / <sub>2</sub> hrs.	11.39	0.0382	0.0346
9 <sup>26</sup> / <sub>30</sub> hrs.	10.36	0.0382	0.0379
∞ hrs.	3.00	Mean, 0.0384	0.0389

TABLE XXVIII.

Hydrochloric acid, 0.125 molal.  
Acetic acid, 1.0 molal.  
Cin. = 0.1 molal. L = 1.0 dm.  
T = 99.7° (±0.1°).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	21.13	....	....
2 hrs.	18.61	0.0325	0.0325
4 hrs.	16.92	0.0287	0.0249
5 hrs.	15.79	0.0303	0.0367
6 hrs.	14.80	0.0311	0.0349
8 <sup>1</sup> / <sub>2</sub> hrs.	12.83	0.0313	0.0317
∞ hrs.	3.00	Mean, 0.0308	0.0321

TABLE XXIX.

Hydrochloric acid, 0.15 molal.  
Acetic acid, 1.0 molal.  
Cin. = 0.1 molal. L = 1.0 dm.  
T = 99.7° (±0.1°).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	21.30	....	....
2 hrs.	19.47	0.0229	0.0229
4 hrs.	17.90	0.0223	0.0217
6 hrs.	16.36	0.0228	0.0237
8 <sup>1</sup> / <sub>2</sub> hrs.	14.71	0.0228	0.0229
10 <sup>1</sup> / <sub>2</sub> hrs.	13.58	0.0226	0.0220
∞ hrs.	3.00	Mean, 0.0227	0.0227

TABLE XXX.

Hydrochloric acid, 0.175 molal.  
Acetic acid, 1.0 molal.  
Cin. = 0.1 molal. L = 1.0 dm.  
T = 99.7° (±0.1°).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	21.62	....	....
2 <sup>1</sup> / <sub>4</sub> hrs.	20.48	0.0122	0.0122
4 hrs.	19.47	0.0133	0.0148
6 hrs.	18.38	0.0138	0.0149
7 <sup>1</sup> / <sub>4</sub> hrs.	17.77	0.0138	0.0141
10 <sup>1</sup> / <sub>4</sub> hrs.	16.39	0.0139	0.0142
∞ hrs.	3.00	Mean, 0.0136	0.0140

TABLE XXXI.

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

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	21.72	....	....
2 hrs.	21.31	0.0048	0.0048
4 hrs.	20.95	0.0046	0.0043
6 hrs.	20.51	0.0048	0.0054
8 <sup>1</sup> / <sub>2</sub> hrs.	20.06	0.0048	0.0046
14 hrs.	19.40	0.0041	0.0031
∞ hrs.	3.00	Mean, 0.0046	0.0044

TABLE XXXII.

Hydrochloric acid, 0.21 molal.  
Acetic acid, 1.0 molal.  
Cin. = 0.1 molal. L = 1.0 dm.  
T = 99.7° (±0.1°).

<i>t.</i>	<i>a.</i>	<i>K</i> <sub>1</sub>	<i>K</i> <sub>2</sub>
0 hr.	21.41	....	....
4 hrs.	21.10	0.0018	0.0018
7 <sup>1</sup> / <sub>2</sub> hrs.	20.81	0.0019	0.0020
10 <sup>1</sup> / <sub>2</sub> hrs.	20.52	0.0021	0.0024
14 <sup>1</sup> / <sub>2</sub> hrs.	20.19	0.0021	0.0021
∞ hrs.	3.00	Mean, 0.0020	0.0021

In Table XXXIV is given a comparative summary of the specific reaction rates of cinchonine monoacetate, cinchonine monohydrochloride and cinchonine dihydrochloride in the presence of varying quantities of acetic acid. To conserve space the detailed measurements in the case of the two hydrochlorides have been omitted and the results alone recorded.

TABLE XXXIII.

No.	Molality of cinchonine.	Normality of acetic acid.	Normality of hydrochloric acid.	K <sub>1</sub> .	K <sub>2</sub> .
1.....	0.1	1.0	...	0.0557	0.0566
2.....	0.1	1.0	0.100	0.0384	0.0389
3.....	0.1	1.0	0.125	0.0308	0.0321
4.....	0.1	1.0	0.150	0.0227	0.0227
5.....	0.1	1.0	0.175	0.0136	0.0140
6.....	0.1	1.0	0.200	0.0046	0.0044
7.....	0.1	1.0	0.210	0.0020	0.0021
8.....	0.1	1.0	0.220	0.0013	0.0015
9.....	0.1	1.0	0.230	0.0009	0.0011
10.....	0.1	0.5	0.15	0.0131	0.0136
11.....	0.1	0.5	0.25	0.0003	0.00035
12.....	0.01	0.5	0.010	0.0158	0.0163
13.....	0.01	0.5	0.015	0.0115	0.0114
14.....	0.01	0.5	0.020	0.0054	0.0056

TABLE XXXIV.

No.	Molality of cinchonine.	Normality of acetic acid.	Normality of hydrochloric acid.	K <sub>1</sub> .	K <sub>2</sub> .
1.....	0.1	0.2	....	0.0091	0.0094
2.....	0.1	0.4	....	0.0238	0.0239
3.....	0.1	0.8	....	0.0445	0.0448
4.....	0.1	1.0	....	0.0557	0.0566
5.....	0.1	1.7	....	0.0790	0.0796
6.....	0.09	0.1	0.09	0.0069	0.0076
7.....	0.09	0.2	0.09	0.0125	0.0115
8.....	0.09	0.4	0.09	0.0215	0.0216
9.....	0.09	0.8	0.09	0.0325	0.0339
10.....	0.09	1.6	0.09	0.0545	0.0548
11.....	0.1	0.1	0.20	0.00066	0.00066
12.....	0.1	0.2	0.20	0.0011	0.0010
13.....	0.1	0.4	0.20	0.0018	0.0017
14.....	0.1	0.8	0.20	0.0029	0.0030
15.....	0.1	2.0	0.20	0.0065	0.0068
16.....	0.1	0.2	0.30	0.0000	0.0000
17.....	0.1	2.0	0.30	0.0000	0.0000

A consideration of Tables XXXIII and XXXIV clearly reveals the effect of varying concentrations of hydrochloric acid under widely divergent conditions. With increasing concentration of the halogen acid, the acetic acid remaining constantly normal, the speed of the reaction falls from a maximum value of  $K_2 = 0.0566$  in the presence of normal acetic acid alone to  $K_2 = 0.00$  when the concentration of hydrochloric acid has reached a value of 0.3 *N*. While the hydrochloric acid, even if it were completely dissociated, cannot on account of its partial use to neutralize the cinchonine be regarded as exactly representing the concentration of  $H^+$  ion, yet the general inhibiting effect of increasing concentration of this ion in solutions



of constant concentration with respect to the organic acid is clearly seen from the data presented.

The inhibiting action of the  $H^+$  ion appears no less clearly in the results obtained with constant concentration of halogen acid and varying amounts of acetic acid (Table XXXIV). As will be seen, increasing concentration of organic acid effects increasing speed of reaction in the case of cinchonine acetate, cinchonine monohydrochloride and cinchonine dihydrochloride, and for any given concentration of organic acid, the speed is greatest in the first instance, less in the second and least in the third.

It is of further interest to observe that the ratio between speeds in the case of different salts with equal concentrations of organic acid appears to approach a constant, as is shown in a comparison of the monohydrochloride with the dihydrochloride in Table XXXV.

TABLE XXXV.

No.	Normality of acetic acid.	Ratio of speed, monohydrochloride: dihydrochloride.
1.....	0.1	$\frac{0.0076}{0.00066} = 11.5$
2.....	0.2	$\frac{0.0115}{0.0010} = 11.5$
3.....	0.4	$\frac{0.0216}{0.0017} = 12.7$
4.....	0.8	$\frac{0.0339}{0.0030} = 11.3$

From these considerations and others which have been presented in this paper, it will be evident that a definite interpretation of this catalysis involves a fairly exact determination on the one hand of the concentration of the  $H^+$  ion in the solution and on the other of the concentration of the nonionized organic acid. The methods employed in such determination, and the results obtained, will be presented in a later paper by the senior author of the present article. In this it will be shown that the conversion of cinchonine into cinchotoxine is fundamentally dependent upon the presence of the univalent cinchonine ion and that the speed of the reaction is a function of the concentration of the undissociated organic acid.

#### Summary.

1. The rate of conversion of cinchonine into cinchotoxine gradually increases with increasing concentration of an organic acid such as acetic acid, the range of concentration of acid through which this was studied and found to be true extending from 0.05 molal to and beyond 8.0 molal. Within this range the speed of the reaction appears to be some direct function of the concentration of the nonionized organic acid. In glacial acetic acid (17.24 molal), the rate decreases somewhat, falling considerably below that shown in 8.0 molal acid.

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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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA.]

## THE RATE OF CONVERSION OF CINCHONIDINE INTO CINCHOTOXINE.<sup>1</sup>

(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.<sup>2</sup> 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,<sup>3</sup> 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,<sup>4</sup> both may be converted into the common product, cinchotoxine.

<sup>1</sup> See preceding article on "Rate of Conversion of Cinchonine into Cinchotoxine."

<sup>2</sup> *Rep. f. Pharm.*, **85**, 392; **98**, 384; **99**, 1.

<sup>3</sup> *Ber.*, **29**, 2185 (1896).

<sup>4</sup> *Jahresb.*, **1853**, 422; *Compt. rend.*, **37**, 110 (1853); *Ann.*, **88**, 209 (1853).