

LXXXVII.—*The Affinity Values of Certain Alkaloids.*

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It is a matter of common knowledge that determinations of the affinity values of most naturally occurring alkaloids present considerable experimental difficulties; their insolubility in water, and in most cases the very slight hydrolysis of their salts at the ordinary temperature, preclude determinations by the electric conductivity or ester catalysis methods, and, except in a few cases, by the methyl-orange method. Bredig (*Zeitsch. physikal. Chem.*, 1894, **13**, 289) gave certain results obtained by the electric conductivity method for the hydrochlorides of a few alkaloids, from which the general conclusion was arrived at that the velocity of their ions was of a comparatively low order.

On the other hand, it is well known that the greater number of alkaloids are precipitated or displaced by solutions of ammonia, although a few are not so precipitated, but only by solutions of sodium hydroxide.

To express the matter in its most general form if the functions of the affinity values of an alkaloid be represented by $\phi(b')$ and that of ammonia by $\phi(b)$, in terms of the acids, $\phi'(a)$, then in the one case $\phi'(a)\phi(b) > \phi'(a)\phi(b')$, and in the other, $\phi'(a)\phi(b) < \phi'(a)\phi(b')$; in any equilibrium equation $\phi'(a)$ disappears if the acid is the same in all cases. It is also known that some alkaloids will displace others from their salts, so that a classification of a general type has been arrived at.

In the present communication it is desired to give an account of results obtained (1) by the methyl-orange method in a few cases, and (2) by a precipitation method, together with a few prefatory remarks on each.

Methyl-orange Method.—Since the date of my last publications (*Trans.*, 1908, **93**, 652, 2114, 2122; this vol., 1) Lundén (*Samml. Chem.-u. Chem-techn. Vorträge*, 1908, **14**, 32, *et. seq.*), alluding to my method in the course of a discussion on the relative accuracy of the methods proposed for the determinations of hydrolysis and affinity values, expresses the opinion that as methyl-orange is the sodium salt of an aminosulphonic acid, some of the hydrochloric acid, whether free or liberated by the hydrolysis of a hydrochloride, is used up in the neutralisation of the amino-group to form a hydrochloride. Accepting this view, which sets forth a possible contingency, if the proportion of hydrochloric acid thus used up varies with the relative masses of acid and methyl-orange, there would be an error dependent on the mass of acid liberated by hydrolysis, but, as a matter of fact, it is found that

whether the hydrolysis is 90 per cent. or 1 per cent. the results obtained by my method are concordant with those obtained by other methods against which no such objection is possible. Lundén also alludes to the possibility that the proportion of acid used up may be the cause of my result, that Arrhenius' hydrolysis formula is not applicable to the ultimate point ($\lim.$) $x=1$, $v=\infty$, which I have attributed to a possible reversal of hydrolysis at extreme dilutions. Until some method has been devised for the accurate determination of hydrolysis values when $v < 10^4$, it will not be possible to decide between the two views.

I desire to take this opportunity of replying to queries as to simple examples which are suitable for demonstrating to large classes of students the methyl-orange method as applied to illustrate differences of hydrolysis and hence of affinity values. Such examples might be (1) *o*-toluidine and benzylamine hydrochlorides, both in *N*/20 solution, as illustrating the effect of isomerism, and (2) the hydrochlorides of glycine and its ethyl ester, both in *N*/20 solution, as illustrating the effect of substitution of carboxylic hydrogen by a hydrocarbon grouping, namely, the alteration of an amphoteric electrolyte to a strongly basic substance. Both these illustrations are quite simple, and require no tintometer; 2 c.c. of the hydrochloride solutions can be added to 200 c.c. of a methyl-orange solution, which may be conveniently prepared by diluting the reagent as made up for laboratory purposes, namely, 1:1000, up to 1:100,000. The diluted solution is best when freshly prepared, but the 1:1000 solution appears to remain unaltered for several months.

Suitable examples for individual students, working with a tintometer,* can be selected from my papers, such as *m*-phenylenediamine hydrochloride, giving half the value of hydrochloric acid, both solutions being of same concentration; betaine or caffeine hydrochlorides, giving approximately identical values as hydrochloric acid, and others. I would only suggest the advisability of previously testing persons with coloured skeins of wool or slips of glass, as there are many, by no means colour blind, who are more or less unable to differentiate changes of tint (compare Burch, *Phil. Trans.*, 1908, *B*, 199, 231).

Precipitation Method.—This method, described in outline in my former communication (this vol., p. 5—6), is based on the determination of the mass of sodium hydroxide contained in a hydrolysed aqueous solution of borax which is required to produce an initial precipitation of the alkaloids in aqueous solutions of their hydrochlorides; it is only applicable if the solubility of the alkaloid in water is less than 1/800, and if the hydrochloride is sufficiently

* An improved form of instrument applicable for such work and designed according to my specifications can be obtained from Messrs. Baird and Tatlock.

soluble in water to form a $N/40$ -solution at least. In detail it consists of dropping the borax solution from a burette, or in the case of smaller quantities, from a 1 c.c. pipette divided into 1/100th (both instruments being calibrated), into a known volume of alkaloid hydrochloride contained in a flask resting on black paper until a permanent precipitate is produced.

The reaction, with the one exception of papaverine, was perfectly sharp. Then, as previously explained, the relative masses of sodium hydroxide contained in the borax solution, and of the alkaloid combined initially with the hydrochloric acid, form a factor of these affinities just at that point at which a homogeneous system, all substances remaining in solution, passes into a heterogeneous system, namely, precipitation of alkaloid. Hence, therefore, if $\phi(b)$ and $\phi(b)'$ be functions of the affinities of the soda and alkaloid respectively for hydrochloric acid (or of their ions for the chlorine ion), and M and M' their respective masses, then

$$\phi(b)/\phi(b') = M/M' \quad . \quad . \quad . \quad . \quad . \quad . \quad (1).$$

The same result could be arrived at by the hydrolysis equations :

$$k_b/k_w = \frac{1-x}{x^2 M} \text{ and } k_b'/k_w = \frac{1-x'}{x'^2 M'} \quad . \quad . \quad . \quad (2),$$

hence
$$k_b/k_b' = x'^2(1-x)M'/x^2(1-x')M \quad . \quad . \quad . \quad (3).$$

But as the hydrolysis both of the sodium chloride and alkaloid hydrochloride is very small, equation (3) resolves itself into equation (1) with an inappreciable error.

In order to convert the functions $\phi(b)$, $\phi(b)'$ in equation (1) into affinity values k_b , k_b' in equation (3), the following data have been utilised.

The hydrolysis of a $N/10$ -sodium borate solution is taken at 1 per cent. (compare preceding communication); the relative affinities of sodium and ammonium hydroxides are, according to the mean of Ostwald's determinations by various methods, in the ratio 100:1.8. The affinity value of ammonia $k_{b(15)} = 1.7 \cdot 10^{-5}$ according to Lundén (*J. Chim. Phys.*, 1907, 3, 574), according to Denham (*Trans.*, 1908, 93, 50) $k_{b(25)} \text{ calc.} = 4 \cdot 10^{-5}$, which corrected for temperature is $k_{b(15)} = 3.7 \cdot 10^{-5}$, and the mean of these two values, namely, $k_{b(13)} = 2.7 \cdot 10^{-5}$, has been taken. The value $k_{b(20)} = 5 \cdot 10^{-5}$, obtained by Moore (*Trans.*, 1907, 91, 1382) by the chloroform extraction method, is probably too high. Hence, therefore, $M'/M \times 1.8/100$ gives the factor (f) of the relative affinities of ammonia and an alkaloid, and also $2.7 \cdot 10^{-5}/f$ gives the actual affinity value of the latter.

The errors of the method depend on (i) the correctness of all the data given above; (ii) the tendency of supersaturation taking place

before initial precipitation; (iii) the relative solubilities of the alkaloids, which introduces an indeterminable function, and (iv) the accuracy in reading small volumes of solutions.

As regards (iii), results obtained with *N*/20- and *N*/40-solutions of the alkaloid hydrochlorides were concordant within experimental error; as regards (ii), two to three minutes were allowed, the solutions being agitated if supersaturation was suspected. It is, of course, only desired to put forward the method as an *attempt at approximations*, since other methods are not applicable, unless an ester can be found, which is hydrolysed by a base of high affinity value within a reasonable limit of time, and is not hydrolysed by water under the same conditions. But, however this may be, it will be shown in the sequel that such approximations are in complete accordance with general conclusions which have been arrived at by physical and analytical data.

Classification of Alkaloids.

It will be proposed, for the sake of convenience only, to divide the alkaloids (including the artificially-prepared stovaine and its homologues) into three classes, as follows:

(1) Relatively weak alkaloids, the hydrochlorides of which show traces (about 1 per cent.) by the methyl-orange method at the ordinary temperature, or when their solutions are heated for a certain time (three hours) at 60°; the affinity value of these is rather less than $1 \cdot 10^{-7}$.

(2) Stronger alkaloids, the hydrochlorides of which show no hydrolysis by the methyl-orange method under above conditions (although a few show hydrolysis when solutions are heated to 100°); the affinity value of these varies from $3 \cdot 10^{-5}$ to $1 \cdot 10^{-7}$ (roughly in ratio 1:30). It will be seen in the sequel that one or two alkaloids of affinity value less than $1 \cdot 10^{-7}$ (and hence should belong to Class I) come in this category. Members of this class are precipitated by ammonia solution.

(3) Strongest alkaloids, not precipitated by ammonia, but precipitated by sodium hydroxide solutions, although not in all cases by a hydrolysed borax solution. The affinity value of these is greater than $3 \cdot 10^{-5}$.

The above classification is not, of course, intended to be arbitrary.

EXPERIMENTAL.

Class I.—Narcotine.—A solution of the hydrochloride of this alkaloid was prepared by dissolving a weighed quantity of *N*/20-hydrochloric acid so as to form a *N*/20 solution of salt, presuming no hydrolysis to

take place; this process required several days for completion. A few results were obtained by the methyl-orange method (series I); the solution was heated for three hours at 60° and again examined (series II), when a slight separation of alkaloid took place.

I (temp. 17°).*	II (temp. 20°).
$V=4 \times 10^3$.	$V=4 \times 10^3$.
0.4	0.75
0.7	1.4
1.0	2.1
	2.7

* The methods of stating results and factors are those adopted in my previous communications.

Value of k for I = 0.35, for II = 0.7; hydrolysis values 1.1 and 2.2; $k_{b(17)}$ from I = 7.9×10^{-8} .

Hydrastine.—The hydrochloride of this alkaloid in $N/20$ -solution gave no measurable value with methyl-orange at the ordinary temperature; after heating the solution for three hours at 60° the following results were obtained:

$V=4 \times 10^3$ (temp. 20°).
0.6
1.1
1.6

Value of $k=0.55$; hydrolysis value = 1.7. Hence hydrastine is a stronger base than narcotine; its affinity value is probably about 1×10^{-7} .

Papaverine.—The behaviour of a $N/20$ -solution of the hydrochloride of this alkaloid was precisely similar to that of hydrastine solution; after heating for three hours at 60° the following results were obtained:

$V=4 \times 10^3$ (temp. 20°).
0.6
1.2
1.7

Value of $k=0.6$; hydrolysis value = 1.9. Papaverine is therefore intermediate between hydrastine and narcotine, and its affinity value $k_b=9 \times 10^{-8}$ approximately.

The sodium borate precipitation method was not available in the case of papaverine, as the reaction was not sharp; the precipitate at first formed slowly dissolved, the rapidity of the re-solution decreasing with increase of borate solution added.

On comparison of the two allied alkaloids, narcotine and papaverine, it is evident from the above that the order is papaverine > narcotine; this result is in complete accordance with the thermochemical investigations of Leroy (*Compt. rend.*, 1899, 129, 220), who obtained values

Papaverine + 1 mol. HCl	$\phi=41.5$
Narcotine + ,, HCl	$\phi=23.3$

although both numbers are lower than might be expected.

As both papaverine and narcotine consist of conjoint benzyl and isoquinoline residues (Freund and Becker, *Ber.*, 1903, 36, 152: narcotine. Goldschmidt, *Monatsh.*, 1884, 7, 495; Pope and Peachey, *Trans.*, 1898, 73, 893: papaverine), it is clear that the high affinity value of benzylamine, $k_b = 2.4 \cdot 10^{-5}$, is modified by that of the isoquinoline, $k_b = 3.6 \cdot 10^{-10}$, the nitrogen atom being common to both, the affinity values, $k_b = 8$ to $9 \cdot 10^{-8}$, of the alkaloid not being widely removed from the mean of the values of the two component bases. Their case is precisely analogous to that of tropine (compare former communication).

Narceine.—The hydrochloride was not sufficiently soluble in water for the purpose of this investigation.

Class II.—Of the alkaloids of this class, only cocaine hydrochloride showed any measurable trace of hydrolysis by the methyl-orange method when the solution was heated for three hours at 100° . This alkaloid was dealt with in my previous communication as a derivative of tropine; it is only desired to alter the value of k_b from 2.5 to $4 \cdot 10^{-7}$ on account of alteration of ammonia factor.

Aconitine.—The affinity value of this alkaloid was found to be about $3 \cdot 10^{-8}$ by the borax precipitation method; it would therefore be expected that its hydrochloride would be sufficiently hydrolysed to give a reaction by the methyl-orange method, but none could be detected even after prolonged heating of the solution at 60° . In any case the comparatively high affinity value is remarkable, having regard to the presence of the acidic groupings, namely, benzoyl and acetyl, as shown by Dunstan (*Trans.*, 1894, 65, 292); but until the constitution of the aconine residue becomes a matter of more accurate knowledge the above result cannot be duly interpreted.

Stovaine and its Homologues.—These compounds, although not strictly alkaloids, can be considered under this class. The values obtained by the borax precipitation method for (1) stovaine or (dimethylaminomethyl)methylethylcarbinol benzoate hydrochloride, $\text{OBz} \cdot \text{CMeEt} \cdot \text{CH}_2 \cdot \text{NMe}_2 \cdot \text{HCl}$, and (2) the corresponding methyl derivative, $\text{OBz} \cdot \text{CMe}_2 \cdot \text{CH}_2 \cdot \text{NMe}_2 \cdot \text{HCl}$, are given in the following table, in which M' = mass of base, dissolved as hydrochloride, in decimilligrams, M = mass of sodium hydroxide contained in the volume of borax solution required to produce precipitation, f the factor in terms of ammonia, namely, $M'/M \times 1.8/100$ (compare *supra*), and k_b the derived affinity value at temperature, approximately 15° . (The figures given in succeeding tables will have the same significance.)

	M .	M .	f .	$k_b \cdot 10^{-7}$.
(I.)	1185	0.12	179	1.51
(II.)	1115	0.24	84	3.22

The corresponding isoamyl and phenyl derivatives gave precipitates

with the borax solution so immediately that accurate results could not be obtained; their affinity values are, therefore, about $1 \cdot 10^{-7}$.

Two points appear to be of interest, (i) that the dimethyl derivative is a stronger base than the methylethyl derivative, and both are stronger than the *iso*amyl and phenyl derivatives, and (ii) the relatively high affinity value of all the bases having regard to the presence of the benzoyl grouping, thus presenting cases analogous to that of aconitine, which they further resemble in that their solutions, after heating for some hours at 100° , show no hydrolysis measurable by the methyl-orange method.

The results obtained for stovaine illustrate in a quantitative manner the necessity, insisted upon in writings* on anaesthetics for washing out syringes, previously used for borax solutions, before introducing stovaine solutions.

The Cinchona Alkaloids.—In my former communication it was pointed out that the affinity value of the stronger or piperidine residue was less than that of ammonia and greater than $1 \cdot 10^{-7}$ (Trans., 1908, 93, 2116); on applying the borax precipitation method, this conclusion was confirmed.

In two cases experiments were conducted with *N*/20- and *N*/40-solutions of the hydrochlorides, and the results obtained were within the limits of experimental error. In the following table the details are given:

	<i>M</i> '.	<i>M</i> .	<i>f</i> .	<i>k_b</i> 10^{-7} .
Quinine	1524	0.24	125 (mean)	2.16
„	762	0.14		
Quinidine	762	0.12	114	2.36
Cinchonine	1471	0.16	165.5	1.63
Cinchonidine ...	1471	0.28	91.5 (mean)	3.72
„ ...	735.5	0.15		

The only point in the above figures which calls for comment is the low value obtained for cinchonine, as it would be expected from thermochemical determinations that the order would be cinchonine = cinchonidine > quinine = quinidine, which is that found with the exception of the first named.

But, however this may be, the cinchona alkaloids, as a class, present cases analogous to that of tropine, in that the high affinity value of the piperidine nucleus is modified by being conjoined to the weaker quinoline nucleus.

Strychnine.—The following values were obtained with a *N*/20-solution of the hydrochloride:

<i>M</i> '.	<i>M</i> .	<i>f</i> .	<i>k_b</i> 10^{-7} .
1670	0.16	189	1.43

* The references in clinical journals published in this country, France, and Germany are too numerous to give in detail.

In this case, also, the affinity value of the stronger hydropyridine nucleus is modified by being conjoined to another grouping, probably that of *isoquinoline*, the nitrogen atom of which forms part of an acidic residue (compare *Trans.*, 1908, **93**, 2120).

Gelsemine.—A *N*/40-solution of the hydrochloride was used, owing to the sparing solubility of the salt; the values obtained are as under:

<i>M'</i> .	<i>M</i> .	<i>f</i> .	<i>k_b</i> 10 ⁻⁶ .
2230	2.64	15.2	1.8

Emetine.—I am indebted to Mr. W. C. Reynolds for a sample of the hydrobromide (C₁₅H₂₂O₁₁N, HBr, 2H₂O) of this alkaloid, which is the salt most conveniently obtained, the free base, as also its solution in hydrochloric acid, turning a yellow colour quickly owing to absorption of oxygen from the air. The following values were obtained with a *N*/20-solution of the salt, three quite concordant determinations being made:

<i>M'</i> .	<i>M</i> .	<i>f</i> .	<i>k_b</i> 10 ⁻⁵ .
2380	33.6	1.22	1.98

The above result may not, of course, be quite strictly comparable with the others given, as the hydrobromide, instead of the hydrochloride, was used.

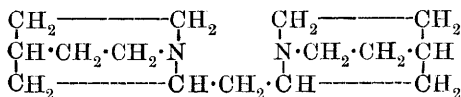
Class III.—Alkaloids of affinity value greater than ammonia.

Brucine.—The following values were obtained:

<i>M'</i> .	<i>M</i> .	<i>f</i> .	<i>k_b</i> 10 ⁻⁴ .
1672	80	0.376	7.2

Attention was called in my previous communication to the great difference between the affinity values of brucine and its congener, strychnine.

Sparteine.—No precipitation or turbidity was produced by the *N*/10-borax solution; hence its affinity value is greater than about 1 10⁻⁴. This result is in accordance with the most recent views of Moureu and Valeur (*Compt. rend.*, 1903, **141**, 261 and 328), who regard this alkaloid as a dipiperidyl derivative of constitutional formula:



As both the residues are alike, there would be no modification, the one of the other, hence the affinity of both would be approximately that of piperidine, 1 10⁻³.

Cotarnine.—Experiments with the hydrochloride of this alkaloid by the borax precipitation method led to a negative result; it would

appear that under such conditions the salt would be converted mainly into the ammonium base form, and into a small proportion only of the carbinol form (Dobbie, Lander, and Tinkler, *Trans.*, 1903, 83, 605; compare Hantzsch and Kalb, *Ber.*, 1899, 32, 3109).

But, however this may be, it is evident that cotarnine should be placed among the alkaloids of high affinity value, a conclusion which is confirmed by the observations of Dobbie and his co-workers as to the difference of the amount of change produced on the hydrochloride by ammonia as compared with the alkaline and alkaline earth hydroxides.

The affinity values k_b (about 15°), as determined by the methods adopted, of the naturally occurring alkaloids are put together in the following table (that of ammonia being introduced for the sake of comparison); in column N_1 the values in ascending order are given for mono-nitrogen bases, and those of the stronger grouping of the di-nitrogen bases; in column N_2 , the values of the weaker grouping of the latter. The wide difference between the N_1 and N_2 values is very remarkable, and illustrates the difficulty of obtaining salts of the general type B_2HCl .

Name.	N_1 .	N_2 .
Aconitine	3 10^{-8}	—
Narcotine	7.9 10^{-8}	—
Papaverine	ca 9 10^{-8}	—
Hydrastine	ca 1 10^{-7}	—
Pilocarpine	ca 1 10^{-7}	4.2 10^{-11}
Strychnine	1.42 10^{-7}	6 10^{-11}
Cinchonine	1.63 10^{-7}	3.32 10^{-10}
Quinine	2.16 10^{-7}	3.32 10^{-10}
Quinidine	2.36 10^{-7}	3.19 10^{-10}
Cinchonidine	3.72 10^{-7}	3.32 10^{-10}
Cocaine	4 10^{-7}	—
Gelsemine	1.8 10^{-7}	nil
Emetine	1.98 10^{-5}	—
Ammonia	2.7 10^{-5}	—
Brucine	7.2 10^{-4}	2.52 10^{-11}
Sparteine }	> 10 10^{-4}	—
Cotarnine }		

Summary.

(i) Determinations are given of the affinity values of some of the important alkaloids by the methyl-orange method, as described in former communications and the borax precipitation method, only put forward as giving approximate results for cases in which the insolubility and high affinity value preclude the application of the electric conductivity and ester catalysis methods.

(ii) It is shown that the affinity values of only a few alkaloids, mainly those derived from opium, are less than $1 \cdot 10^{-7}$, those of the greater number are between the limits of $1 \cdot 10^{-7}$ and $3 \cdot 10^{-5}$ (value of

ammonia), and lastly, only a few have a value higher than the last figure, and hence may be classed with the tetra-alkylammonium hydroxides. Possibly some further information as to the last class might be obtained by a study of the relative absorptive power of carbon dioxide.

(iii) It appears in most cases that when alkaloids consist of two conjoint residues, which, if considered each by itself, would give affinity values of a widely different order, such as piperidine or benzylamine, on the one hand, and quinoline or pyrrolidine, on the other, the stronger residue is modified by the presence of the weaker. It seems to be immaterial whether each residue contains a nitrogen atom (case of cinchona alkaloids) or whether a nitrogen atom is common to both (cases of tropine, papaverine, narcotine, etc.).

(iv) The affinity values of certain mono- and di-nitrogen alkaloids, as determined by the methods applied, are collected together in a table for the sake of comparison.

I have again to express my obligations to the Research Fund Committee of the Chemical Society for a grant for purchase of materials, and also to Messrs. Burroughs Wellcome & Co., for kindly supplying me with certain samples of alkaloids and their salts for the purpose of this investigation.
