218. *The Properties of Nicotine and its Derivatives. Part VI. Electrical Conductivities. Part VII. Electrometric Titrations.*

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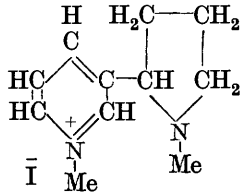
PART VI. ELECTRICAL CONDUCTIVITIES.

IN the preceding papers of this series the optical properties of nicotine and its derivatives have been described and discussed. The two papers now submitted are concerned with the electrical properties of the base and of some of the iodides and hydroxides derived from it. The only available quantitative data on electrical conductivities are those of Nasini and Pezzolato (*Gazzetta*, 1893, **23**, i, 43), in which values are given for aqueous solutions of the base. The substances used in the present investigation were as follows :—



(I.) Nicotine *iso*methiodide.

$C_5H_4\overset{+}{N}MeI\cdot C_4H_7\overset{+}{N}HMeI^-$

(II.) Hydriodide of *iso*methiodide.

$C_5H_4\overset{+}{N}MeI\cdot C_4H_7\overset{+}{N}Me_2I^-$

(III.) Dimethiodide.

$C_5H_4\overset{+}{N}HI\cdot C_4H_7\overset{+}{N}HMeI^-$

(IV.) Dihydriodide.

In Table I, v shows the dilution (in litres), $\sqrt{c}$ the square root of the concentration, κ the specific conductivity, and Λ the molecular conductivity.

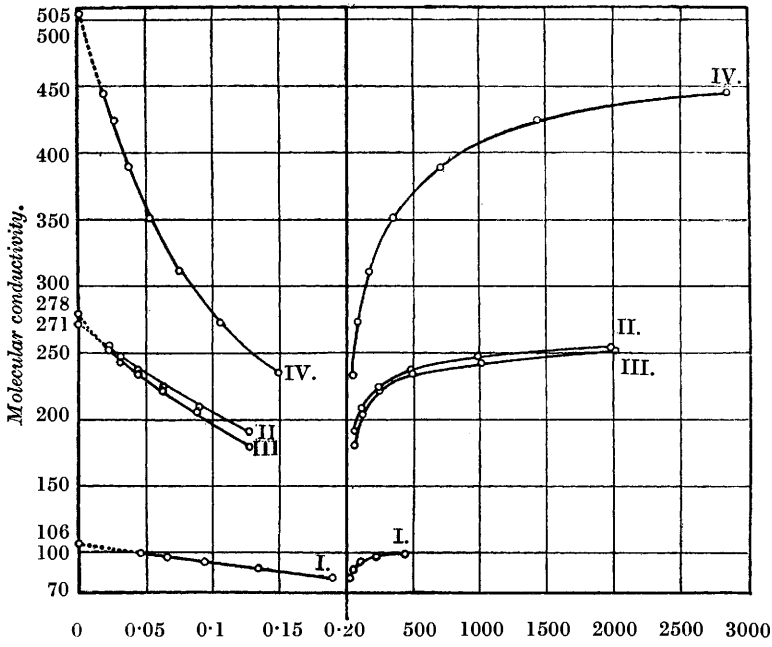
TABLE I.

Molecular Conductivities at 25°.

v.	$\sqrt{c}$.	κ.	Λ.	v.	$\sqrt{c}$.	κ.	Λ.
I. *Nicotine* iso*methiodide.*				III. *Nicotine dimethiodide.*			
27·74	0·1900	0·002920	81	63·1	0·1260	0·002980	188
55·48	0·1343	0·001578	87	126·2	0·0890	0·001633	206
111·0	0·0949	0·000836	93	252·4	0·0630	0·000881	222
221·9	0·0672	0·000433	96	504·8	0·0445	0·000464	234
443·84	0·0475	0·000223	99	1009·6	0·0315	0·000241	243
∞	0	—	106	2019·2	0·0223	0·000125	252
				∞	0	—	278
II. *Hydriodide of* iso*methiodide.*				IV. *Nicotine dihydriodide.*			
62·01	0·1270	0·003081	191	44·51	0·1499	0·005276	235
124·02	0·0898	0·001679	208	89·02	0·1060	0·003059	272
248·04	0·0635	0·000896	222	178·04	0·0750	0·001750	311
496·08	0·0449	0·000477	237	356·08	0·0530	0·000987	351
992·16	0·0318	0·000249	247	712·16	0·0375	0·000547	390
1984·32	0·0225	0·000128	254	1424·3	0·0265	0·000298	424
∞	0	—	271	2848·6	0·0187	0·000156	444
				∞	0	—	505

These four compounds were prepared and purified according to the method of Pictet (*Ber.*, 1897, **30**, 2118). Their conductivities were measured at 25° with a Wheatstone bridge by the method of Kohlrausch, a conductivity cell of capacity 0·1190 being used. The conductivity water was fractionally condensed on a tin-plated copper condenser, but was not good enough ($\kappa = 4$—6 gemmho) to permit of measurements at high dilutions. The integral values of the molecular conductivities which are recorded in Table I are, however, outside the limits of error from this source.

FIG. 1.



Molecular conductivities of iodides derived from nicotine.

The molecular conductivities were plotted against the square root of the concentration (Fig. 1). With the exception of the dihydriodide, the curves are nearly straight, and lead to trustworthy values for the molecular conductivities at infinite dilution. These range from 106 in the *iso*methiodide to 505 in the dihydriodide, but can be explained in a very simple way, as follows:

(i) The *iso*methiodide (I) is a simple binary salt, which behaves as a strong electrolyte, since it gives a linear relationship when its molecular conductivities are plotted against the square roots of the concentrations. The limiting value for the iodide at infinite dilution

is $\Lambda_{\infty}^{25°} = 106$. If the mobility of the iodide ion, 77·2 at 25°, is subtracted from this, the mobility of the kation is found to be 29.

(ii) The *iso*methiodide can be converted into a di-iodide by the addition either of hydrogen iodide or of methyl iodide. The two salts, (II) and (III), do not give a strictly linear relation between Λ and $\sqrt{c}$; but it is easy to deduce by graphical extrapolation the values for infinite dilution, $\Lambda_{\infty} = 271$ and 278 respectively. These are normal values for a ternary electrolyte, and, by subtracting the mobilities of *two* iodide ions, we obtain for the mobilities of the bivalent kations the values 117 and 124. If these are divided by four, in order to allow for the influence of the double charge which they carry, the mobilities of the ions with a single charge would be 29 and 31, in close agreement with the value 29 for the univalent kation of the *iso*methiodide.

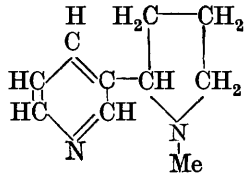
(iii) The enormous conductivity of nicotine dihydriodide (IV), as contrasted with the methylated iodides, (I), (II), and (III), recalls the behaviour of the trimethylstibine dihalides, $SbMe_3X_2$ (Hantzsch and Hibbert, *Ber.*, 1907, **40**, 1513; Lowry and Simons, *Ber.*, 1930, **63**, 1595), and of the dimethyltelluronium dihalides, $TeMe_2X_2$, which gave molecular conductivities ranging from 513 to 520 at 4096 litres (Lowry, Goldstein, and Gilbert, J., 1928, 307). These were explained by the hydrolysis of one iodine atom of the di-iodide and the ionisation of the other :

$$TeMe_2I_2 + H_2O \rightleftharpoons [TeMe_2\overset{+}{O}\overset{-}{H}]I + \overset{+}{H}\overset{-}{I}.$$

The behaviour of nicotine dihydriodide can be explained in a similar way, by supposing that the iodine attached to the *pyrrolidine* nitrogen is ionised, but that the iodine attached to the *pyridyl* nitrogen is liberated as hydrogen iodide by the hydrolytic action of water. In the case of nicotine, this conclusion is justified by the observations of Kolthoff (*Biochem. Z.*, 1925, **162**, 289) on the behaviour of the base towards indicators, and more precisely by the electrometric titrations described in Part VII (below). The dissociation constant of the pyrrolidine nitrogen is there shown to be $4{\cdot}90 \times 10^{-7}$, whilst that of the pyridyl nitrogen is only $7{\cdot}94 \times 10^{-12}$. The latter is therefore so weakly basic that the alkaloid can only be titrated as a monoacid base. This statement obviously implies also that the hydriodides formed by the pyridyl nitrogen are hydrolysed to such an extent that the formation of dihalides in aqueous solution can be ignored, although the corresponding methiodides are stable salts and strong electrolytes. The observed molecular conductivities of nicotine di-iodide are therefore only a little less than those of, *e.g.*, the *iso*methiodide, $\Lambda_{\infty} = 106$, plus a molecule of hydrogen iodide, $\Lambda_{\infty} = 427$.

Part VII. Electrometric Titrations.

The compounds used in the present investigation were as follows



(I.) Nicotine.

$C_5H_4N \cdot C_4H_7\overset{+}{N}Me_2 \cdot \overset{-}{O}H$
(II.) Methohydroxide.

$C_5H_4\overset{+}{N}Me(\overset{-}{O}H) \cdot C_4H_7NMe$
(III.) *iso*Methohydroxide.

$C_5H_4\overset{+}{N}Me(\overset{-}{O}H) \cdot C_4H_7\overset{+}{N}Me_2 \cdot \overset{-}{O}H$
(IV.) Dimethohydroxide.

The nicotine was purified by the zinc chloride method as described in Part I, and was redistilled in a current of nitrogen before use. The methylated bases were prepared by grinding the methiodides (J., 1929, 1381) for ½ hour with three times the theoretical quantity of freshly-prepared and well-washed silver oxide and just enough water to make a thick paste; the base was then extracted with water and titrated.

The potential curves were plotted with the help of a hydrogen electrode, whilst drops of *N*-hydrochloric acid from a burette were being added to the base in a glass vessel closed with a rubber bung and provided with a glass stirrer. The glass vessel was connected to a beaker of saturated potassium chloride by an agar-agar bridge, also saturated with potassium chloride. The cell was completed by a saturated calomel electrode dipping into the potassium chloride beaker, and its *E.M.F.* was determined at room temperature by means of a potentiometer calibrated to read directly in millivolts. The results are shown in Figs. 2—5. The basic dissociation constants of the two nitrogen atoms were then deduced from the values of p_H at half-neutralisation as follows:

	Pyridyl nitrogen.	Pyrrolidine nitrogen.
(I.)	$7{\cdot}94 \times 10^{-12}$	$4{\cdot}90 \times 10^{-7}$
(II.)	$2{\cdot}00 \times 10^{-6}$	$\mathbf{6{\cdot}31 \times 10^{-3}}$
(III.)	$\mathbf{3{\cdot}0 \times 10^{-3}}$	$1{\cdot}3 \times 10^{-9}$
(IV.)	$\mathbf{7{\cdot}08 \times 10^{-7}}$	$\mathbf{1{\cdot}59 \times 10^{-4}}$

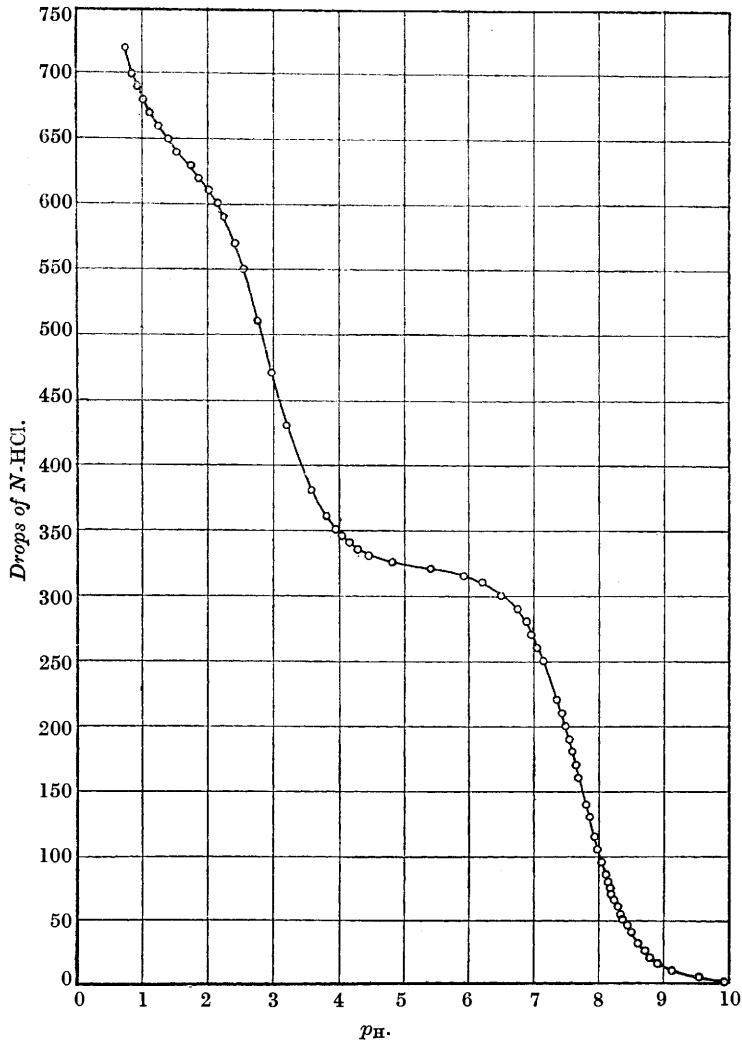
The figures shown in heavy type refer to quaternary nitrogen, the others being tertiary. It will be seen that methylation increases the strength of the base to an enormous extent, since the resulting quaternary radical is probably ionised completely and may therefore be expected to conform to the laws of strong electrolytes, just like a caustic alkali. Further, the basicity of the pyridyl nitrogen is increased when the pyrrolidine nitrogen is methylated, although the converse statement is not true.

The electrometric titration of nicotine itself proceeded in the manner that might have been foreseen for a combination of a fairly

weak with a very weak base. The neutralisation of the mono- and di-methylated bases, however, was accompanied by a " drift " of potential towards higher values of p_H. Thus, in Fig. 5 the initial

FIG. 2.

Electrometric Titration of Nicotine (I).



readings are marked by a heavy line, whilst the final readings are represented by a broken curve. The " drift " was observed only over a limited range of potentials, generally in the second stage of

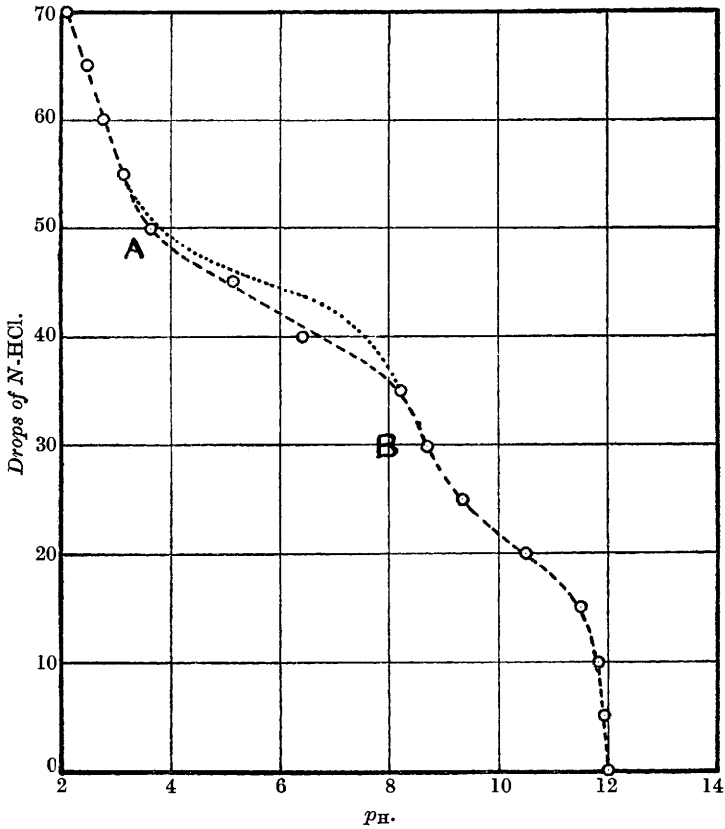
the process of neutralisation. A similar drift in the same direction had already been encountered during the electrometric titration of the dicyclic tellurium base,

$$H\bar{O}\,CH_2\langle\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\rangle\overset{+}{T}e\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot CH_2\cdot\overset{+}{T}e\langle\begin{matrix}CH_2\cdot CH_2\\CH_2\cdot CH_2\end{matrix}\rangle CH_2\,\bar{O}H$$

FIG. 3.

Electrometric Titration of Nicotine Methohydroxide (II).

(*Time allowed for alkaline drift over AB to cease.*)

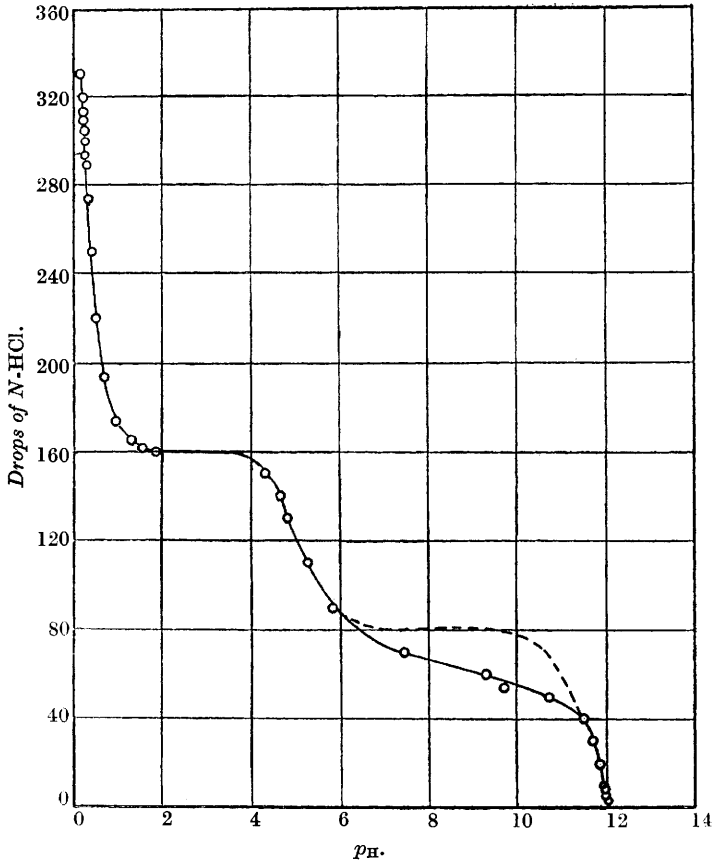


where " at about 75% neutralisation the readings became unstable and began to drift towards the alkaline side " (Gilbert and Lowry, J., 1928, 2664). Since " poisoning " of the electrode would have produced a drift in the opposite direction, it was then suggested that " these anomalies are clearly due to a locking-up of the basic properties of the hydroxide by a reversible process which may be compared with the formation of a pseudo-base." This deduction

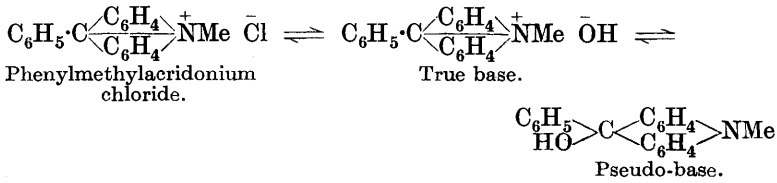
was based upon Hantzsch's observation in the phenylmethylacridinium series (*Ber.*, 1899, **32**, 594, 3109, 3132; 1900, **33**, 278), where a solution of the chloride after treatment with silver oxide

FIG. 4.

Electrometric Titration of Nicotine iso*Methohydroxide* (III).



slowly lost its conductivity and deposited a pseudo-base, which in turn neutralised hydrochloric acid only gradually.



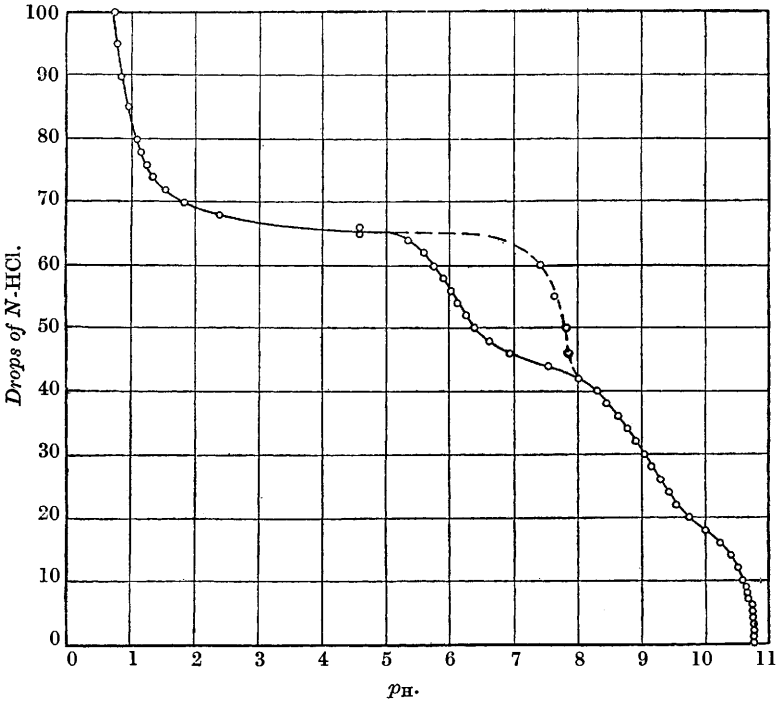
No structure was suggested for the non-conducting form of the tellurium base, but, in view of the readiness with which the pentamethylene group in this series of compounds undergoes a reversible ring formation with tellurium, it is possible that the pseudo-base was a dihydroxyalkyl ditelluride:

$$CH_2[CH_2{\cdot}CH_2{\cdot}Te{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH]_2$$

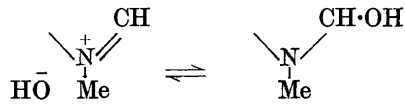
In the present series of compounds, the formation of a pseudo-base had already been invoked (Part I, J., 1929, 1380) in order to account

FIG. 5.

Electrometric Titration of Nicotine Dimethohydroxide (IV).



for the fact that nicotine loses 90% of its absorptive power when dissolved in water, but without developing the strong basicity that would be expected if an ionised hydroxide had been formed, and without the reversal of sign of its optical rotatory power which accompanies ionisation in the nicotinium salts. The formation of a pseudo-base from nicotine was justified by the observations of Decker and Kaufmann (*J. pr. Chem.*, 1911, **84**, 825) in the methyl *iso*quinolinium series and was represented by the following scheme:



True-base. Pseudo-base.

This scheme not only accounts for the occurrence of a drift of potential and for the direction in which it occurs, but it also provides a satisfactory explanation of the compounds in which it is observed, and of the part of neutralisation curve in which the drift takes place. The relevant details are set out and discussed below.

I. *Nicotine.* Temperature 26°; 10 c.c. of 1·333*N*-solution titrated with *N*-HCl; neutralisation points at 320 drops, $p_H = 5{\cdot}52$ (6·61*), and 640 drops, $p_H = 1{\cdot}52$ (3·04*). The first section of the potential curve shows the changes produced by neutralising the pyrrolidine nitrogen, and has the characteristic form for the neutralisation of a weak base. The second section shows the neutralisation of the pyridyl nitrogen; but this is so weak that the possible formation of a pseudo-base is of no importance, and no drift was observed in the strongly acid solutions in which the dichloride is formed.

II. *Methohydroxide.* Temperature 18·2°; 5 c.c of 0·219*N*-solution titrated with *N*-HCl; neutralisation points at 23 drops, $p_H = 9{\cdot}8$, and 46 drops, $p_H = 5{\cdot}4$. In this case, the pyrrolidine nitrogen is quaternary, and is therefore again neutralised before the pyridyl nitrogen, which is still tertiary. The first section of the curve, however, has the form that is characteristic of strong bases, since it rises steeply from $p_H = 12$ instead of rising only slowly from $p_H = 10$. The second section of the curve corresponds with the neutralisation of the pyridyl nitrogen, which is now more strongly basic than in nicotine itself, since neutralisation occurs at $p_H = 5{\cdot}4$ instead of 1·52. During the second stage of neutralisation a drift was observed in the range between $p_H = 8$ and 3, indicating that some pseudo-base had been formed in the strongly alkaline solution. The broken line shows the potentials recorded after 1—4 hours, but the drift was so slow that the final form of the curve may, perhaps, have the more usual form indicated by the dotted line shown on the right of AB in Fig. 3.

III. iso*Methohydroxide.* Temperature 18°; 18 c.c. of 0·178*N*-solution titrated with *N*-HCl; neutralisation points at 80 drops, $p_H = 8{\cdot}8$, and 160 drops, $p_H = 3{\cdot}0$. In the *iso*-compound, the pyridyl nitrogen is quaternary, and is therefore more basic than the pyrrolidine nitrogen, which is still tertiary. The order of neutralisation is therefore reversed, the pyridyl nitrogen being neutralised before the pyrrolidine nitrogen. The first portion of the curve,

* Values deduced by Kolthoff with the help of indicators.

rising steeply from $p_H = 12$, represents the conversion of the methylated pyridyl radical into a chloride. No drift of potential was observed; but this part of the potential curve has the same abnormal form as the second part of the curve in Fig. 5, where a strong drift was observed. This abnormality may be accounted for by the formation of a pseudo-base, which is too stable to show any appreciable drift in these strongly alkaline solutions. We have therefore inserted a broken line to represent the normal form of the neutralisation curve, as it is observed, for instance, in the second stage of the neutralisation, where the relatively weak unmethylated pyrrolidine nitrogen is being neutralised without any of the complications which arise from the formation of a pseudo-base.

The two end-points were so sharp that the base could be titrated in two stages by the use of suitable indicators. The approximate values of the hydrogen-ion concentration deduced in this way were as follows:

Phenol-red, $p_H = 7{\cdot}1$.	Cresolphthalein, $p_H = 9{\cdot}0$.
Thymol-blue, $p_H = 8{\cdot}8$.	Methyl-orange, $p_H = 3{\cdot}8$.

IV. *Dimethohydroxide.* Temperature 24°; 15 c.c of 0·0903*N*-solution titrated with *N*-HCl; neutralisation points at 32 drops, $p_H = 8{\cdot}9$, and 63 drops, $p_H = 4{\cdot}9$.

In this base both nitrogens are quaternary, but the pyrrolidine nitrogen is still the stronger and is neutralised first. The curve therefore rises steeply in the normal way from $p_H = 10{\cdot}8$. In the second stage of the neutralisation, a very strong drift of potential was observed, corresponding with the gradual reconversion of the pseudo-base into a salt of the quaternary methylated pyridyl base. This drift was relatively slow in the more alkaline (or less acid) solutions, but became much more rapid as the second neutralisation point was approached. The total time required for the attainment of a steady value, however, was never more than an hour, so that it was possible to plot two independent curves, the initial readings being represented by a full line, and the final readings by a broken line, in Fig. 5. Outside the region covered by the loop in Fig. 5, the two curves became identical, since steady values for the potential were reached immediately both in the earlier stages of neutralisation, and in the final stages where an excess of acid had been added to the solution.

V. (a) *Ethylenediamine and* (b) N-*diethylethylenediamine.** (a) Temperature 25°; 10 c.c. of 0·169*N*-solution titrated with *N*-HCl; neutralisation points at 40 drops, $p_H = 8{\cdot}2$, and 81 drops, $p_H = 3{\cdot}95$. Basic dissociation constants $7{\cdot}41 \times 10^{-5}$ and $8{\cdot}32 \times 10^{-8}$.

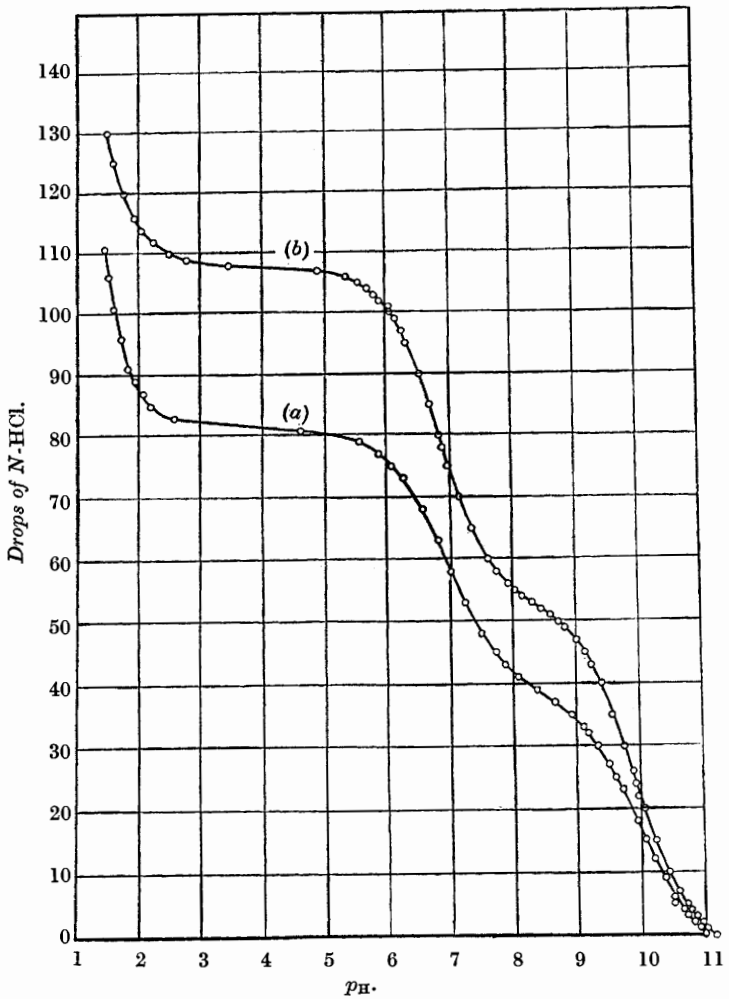
(b) Temperature 23°; 10 c.c. of 0·223*N*-solution titrated with

* A specimen of this compound was kindly provided by Dr. F. G. Mann.

N-HCl; neutralisation points at 53 drops, $p_H = 8{\cdot}30$, and 107 drops, $p_H = 4{\cdot}45$. Basic dissociation constants $7{\cdot}59 \times 10^{-5}$ and $6{\cdot}61 \times 10^{-8}$.

For the purpose of comparison, electrometric titrations were also made of these two simple aliphatic diamines. The results of the

FIG. 6.



Electrometric titrations of (a) *ethylenediamine*, (b) N-*diethylethylenediamine*.

titration are shown in Fig. 6. No drift of potential was observed at any stage of the neutralisation, thus confirming the conclusion that this phenomenon is a peculiarity of the pyridyl nucleus of nicotine.

Summary.

(*a*) Measurements have been made of the molecular conductivities of four mono- and di-iodides derived from nicotine. (i) The *iso*methiodide behaves as a strong binary electrolyte with $\Lambda_{\infty}^{25^{\circ}} = 106$, the mobility of the kation being about 29. (ii) The hydriodide and methiodide derived from it behave as strong ternary electrolytes, the mobility of the doubly-charged kation being approximately 4×30. (iii) The dihydriodide of nicotine, however, loses a molecule of hydrogen iodide, and (like $TeMe_2I_2$ and $SbMe_3Cl_2$) gives conductivities ranging up to about 500.

(*b*) Electrometric titrations have been made of nicotine and of two isomeric monomethylated quaternary bases and one dimethylated diquaternary base derived from it. A drift of potential in the direction of increased alkalinity was observed in some of the solutions during a part of the neutralisation, in the same way as in solutions of a dicyclic telluronium base examined by Gilbert and Lowry in 1928. This drift can be explained by the formation of a pseudo-base, as already postulated in order to account for the optical properties of aqueous solutions of nicotine. The conditions under which the drift was observed are explained by the fact that a pseudo-base can be formed by the pyridyl radical (as in the methyl*iso*quinoline series), but not by the pyrrolidine radical of nicotine.

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