RESEARCH PAPERS

THE POTENTIOMETRIC TITRATION OF ALKALOIDAL SALTS

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THE assay of some alkaloidal salts by titration with alkali, using phenolphthalein as an indicator, was reported in 1885 by Leger[1]. In this type of titration, the weak base of the salt plays a minor part. The method is inapplicable to salts of alkaloids which are strong bases; these can, however, often be titrated in aqueous alcohol solutions with phenolphthalein or Porrier blue as the indicator, as was reported by Baggesgaard Rasmussen and Reimers[2] in 1935. These authors recommended that all alkaloidal salt titrations should be carried out in alcoholic solution.

The main difficulty in the titration of alkaloidal salts is the indistinct end-point obtained with colour indicators, due to the buffering effect of the organic base present during the titration. Lyons[3], in 1912, overcame this by carrying out titrations in aqueous solution with a layer of chloroform present to remove the alkaloid as soon as it was liberated by the alkali. Other workers have used other organic solvents, immiscible or only partially miscible with water; for example, Rotondaro[4] used benzyl alcohol. More recently, Jindra[5] has treated an alkaloidal salt solution with an anion exchange resin, replacing the anion of the salt by hydroxyl and then titrating the resulting alkaloid solution with acid in the usual way.

The difficulty of obtaining sharp end-points with colour indicators is increased by the use of aqueous alcohol as a solvent. This can be overcome by carrying out the titration potentiometrically. The end-point of a potentiometric titration can be found quite accurately, with very small personal error, using solution concentrations as low as 0·01N and in aqueous solvents containing 75 per cent. or more of ethanol. Earlier work on the titration of alkaloidal salts in alcohol solutions, such as that of Rasmussen and Reimers, was directed towards the evaluation of suitable colour indicators for these titrations; however colour indicators in alcohol are unsatisfactory and the potentiometric method is essential if a clear estimate of the end-point titre is to be obtained.

Many of the earlier problems of the potentiometric method have now been solved. The very high resistances of the earlier glass electrodes have been reduced and satisfactory deflection *p*H meters have been developed (notably as the result of the work of C. Morton[6]). Since a potentiometric titration involves a number of *p*H readings, a deflection instrument is clearly a valuable time-saver. The labour of potentiometric titration is still further reduced by the use of automatic titro-

meters (see Furman[7]). These instruments plot a titration curve automatically and rapidly, and the operator has only to evaluate the end-point titre from the plotted curve. They should be of great value in routine analytical laboratories.

Kenneth, Albert and Raymond[8] have shown that many alkaloidal salts can be estimated by potentiometric titration in aqueous alcohol.

The work reported here has been undertaken to determine the necessary conditions for accurate assay of a number of alkaloidal salts of the British Pharmacopœia by potentiometric titration.

We have found that the salts of the strongly basic alkaloids such as ephedrine and atropine show no inflection in their titration curves when pure water is used as solvent; all the salts do, however, give an inflection adequate for quantitative estimation, when 50 or 75 per cent. ethanol with water is used as solvent.

Experimental

The following B.P. alkaloidal salts

1. Cocaine hydrochloride
2. Diamorphine hydrochloride
3. Codeine phosphate
4. Hyoscine hydrobromide
5. Morphine sulphate
6. Quinine hydrochloride
7. Quinine sulphate
8. Papaverine hydrochloride
9. Pilocarpine nitrate
10. Strychnine hydrochloride
11. Quinidine sulphate
12. Atropine sulphate
13. Homatropine hydrobromide
14. Emetine hydrochloride
15. Ephedrine hydrochloride
16. Morphine hydrochloride
17. ψ-ephedrine hydrochloride
18. Apomorphine hydrochloride

were obtained from various sources. The titres showed that all were within the B.P. limits for alkaloid content.

Titrations were carried out with solutions at 20°C., in a laboratory whose temperature was controlled at 20± 2°C. A valve potentiometer type of *p*H meter was used in order to obtain the highest accuracy in the *p*H measurements. The meter was standardised at *p*H 3·97 with 0·05M potassium hydrogen phthalate solution in water, using glass and saturated calomel electrodes. This standardisation was repeated for each titration and checked at the end of each titration. Standardisation with aqueous phthalate was used throughout. The meter was also frequently checked in the higher *p*H range with an aqueous 0·05M sodium borate buffer (*p*H 9·18 at 20°C.).

Having standardised the meter, the electrodes were washed off with water and the solvent to be used in the titration. Approximately 0·5 mole of the alkaloidal salt was weighed accurately and dissolved in 100 ml. of solvent (boiled to remove carbon dioxide). A burette, with a carbon dioxide guard tube, containing 100 ml. of standardised carbonate-free 0·01N sodium hydroxide solution made up in the solvent to be used in the titration, was clamped above the titration vessel, together with a mechanical stirrer (screened to prevent interference with the meter) and the electrodes. *p*H readings were taken after each small addition of alkali and from the results *p*H/(volume of alkali added)

curves were constructed. From these curves the following quantities were found; the titre of the alkaloidal salt, the *p*H at one-third, one-half and two-thirds neutralisation ($pH_{\frac{1}{3}}$, $pH_{\frac{1}{2}}$, $pH_{\frac{2}{3}}$), and the maximum slope of the curve at the end-point (s) in *p*H units per ml. of 0·01N sodium hydroxide added to one milliequivalent of alkaloidal salt.

The 0·01N sodium hydroxide solutions were prepared from boiled-out solvents and saturated (15M) caustic soda solution in water in which sodium carbonate is insoluble, taking all precautions to minimise contamination of the solution with carbon dioxide. The solutions were standardised directly by titration with pure potassium hydrogen phthalate and also by titration with 0·01N hydrochloric acid solution which had been standardised with pure sodium carbonate.

Discussion

Some of the experimental titration curves are shown in Figures 1 to 3. These are typical of the 3 groups into which the alkaloidal salts fall.

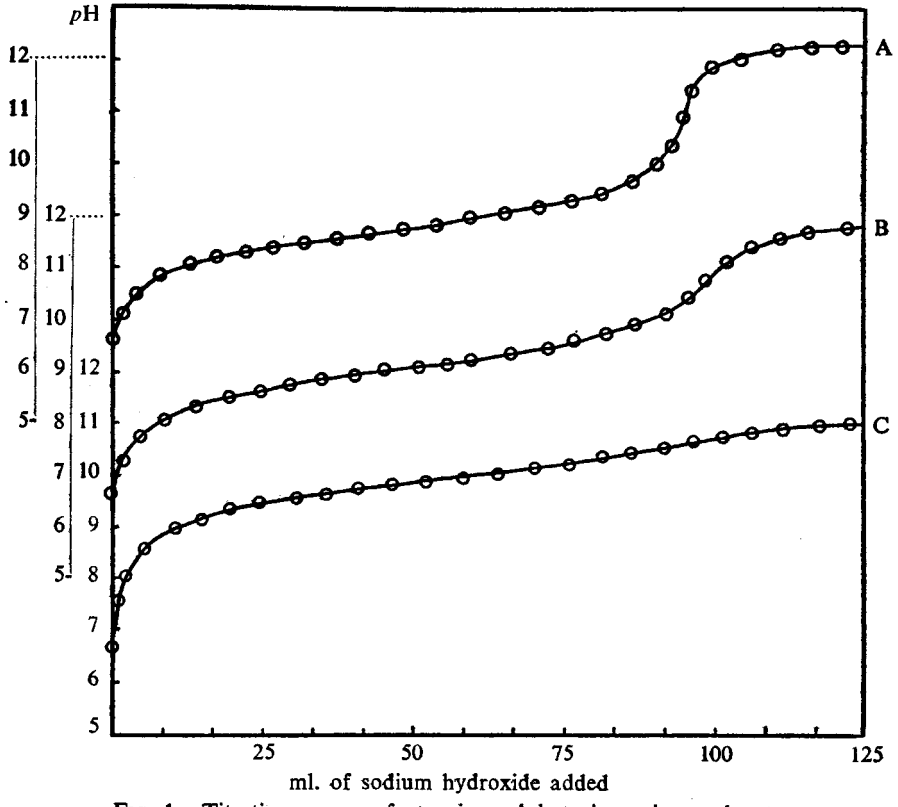

Fig. 1. Titration curves of atropine sulphate in various solvents.
A: against 0·0104 N sodium hydroxide in 75 per cent. ethanol.
B: against 0·01006 N sodium hydroxide in 50 per cent. ethanol.
C: against 0·00956 N sodium hydroxide in water.
No inflection in aqueous solution; typical of salts 12 to 18 in list on page 79.

The basic dissociation constant exponents (pK_B) of the alkaloids in the various solvents were found from the values of $pH_{1/3}$, $pH_{1/2}$, $pH_{2/3}$.

The pK_B values were derived as follows. By definition

$$K_B = \frac{[QH^+][OH^-]}{[Q]} \quad (1) \text{ and } K_A = \frac{[H^+][Q]}{[QH^+]} \quad (2)$$

Q referring to undissociated alkaloid, QH^+ to the alkaloid ion K_A being the "acid" dissociation constant of the latter

From (2) $pK_A = pH + \log. \frac{[QH^+]}{[Q]}$ At 1/2 neutralisation $\frac{[QH^+]}{[Q]} = 1$

At 1/3 neutralisation $\frac{[QH^+]}{[Q]} = 2$ At 2/3 neutralisation $\frac{[QH^+]}{[Q]} = \frac{1}{2}$

Therefore $pK_A = pH_{1/3} + \log. 2$; $pK_A = pH_{1/2}$; $pK_A = pH_{2/3} - \log. 2$ (3)

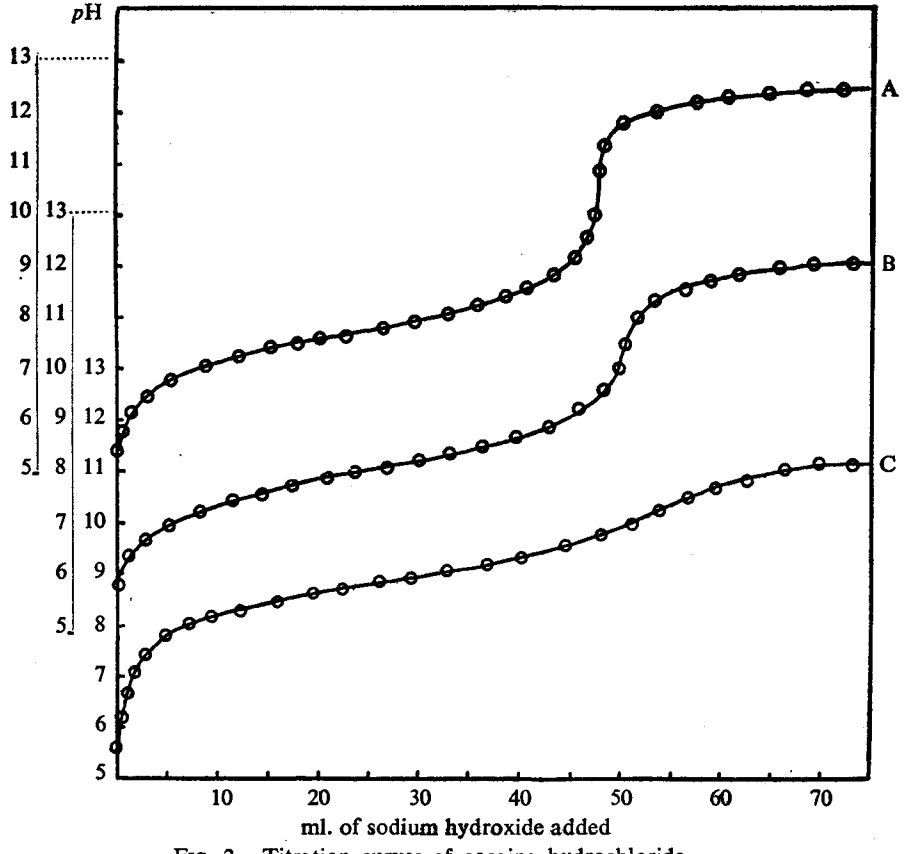

FIG. 2. Titration curves of cocaine hydrochloride.

A: against 0·0104 N sodium hydroxide in 75 per cent. ethanol.
B: against 0·01006 N sodium hydroxide in 50 per cent. ethanol.
C: against 0·00956 N sodium hydroxide in water.
Slight inflection in aqueous solution; typical of salts 1 to 7 and 11 in list on page 79.

In nearly all cases the variation of pK_A with extent of neutralisation was very small though codeine and emetine salts did show some variation. The mean of the three pK_A values for each alkaloid was used to determine pK_B.

From equations (1) and (2).

$$K_B . K_A = (H^+)(OH^-) = Kw \text{ or } pK_B = pK_W - pK_A \quad (4)$$

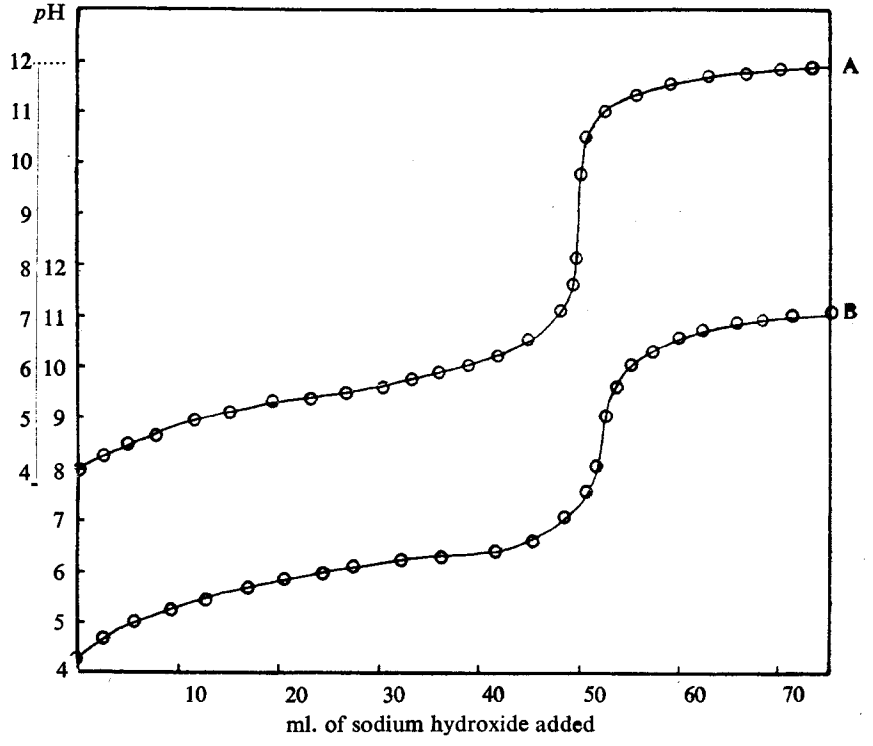

FIG. 3. Titration curves of papaverine hydrochloride.
A: against 0·01006 N sodium hydroxide in 50 per cent. alcohol.
B: against 0·00956 N sodium hydroxide in water.
Sharp inflection in aqueous solution; typical of salts 8 to 10 in list on page 79.

The value of pK_W for pure water[9] is approximately 14·2 at 20°C. In mixed solvents such as aqueous alcohol the value of pK_W will be slightly higher. We have calculated values of pK_W for 50 per cent. and 75 per cent. ethanol as 14·5 and 14·8 respectively at 20°C. assuming that the alcohol only acts by diluting the water and that the dissociation constant of water $\frac{[H^+][OH^-]}{[H_2O]}$ remains unchanged in alcoholic solution.

A small correction for the activity coefficient γ, of the alkaloidal ion in the solutions, should be made to pK_B. The activity coefficient of the undissociated alkaloid can be taken as unity in these very dilute solutions, but that of the alkaloidal ion will differ appreciably from unity by

an amount depending on the ionic strength of the solution (which will not vary greatly during the titration) and the dielectric constant of the solvent. The value of γ can be calculated from the Debye-Hückel theory and by this means we have deduced that in water, under the conditions of our

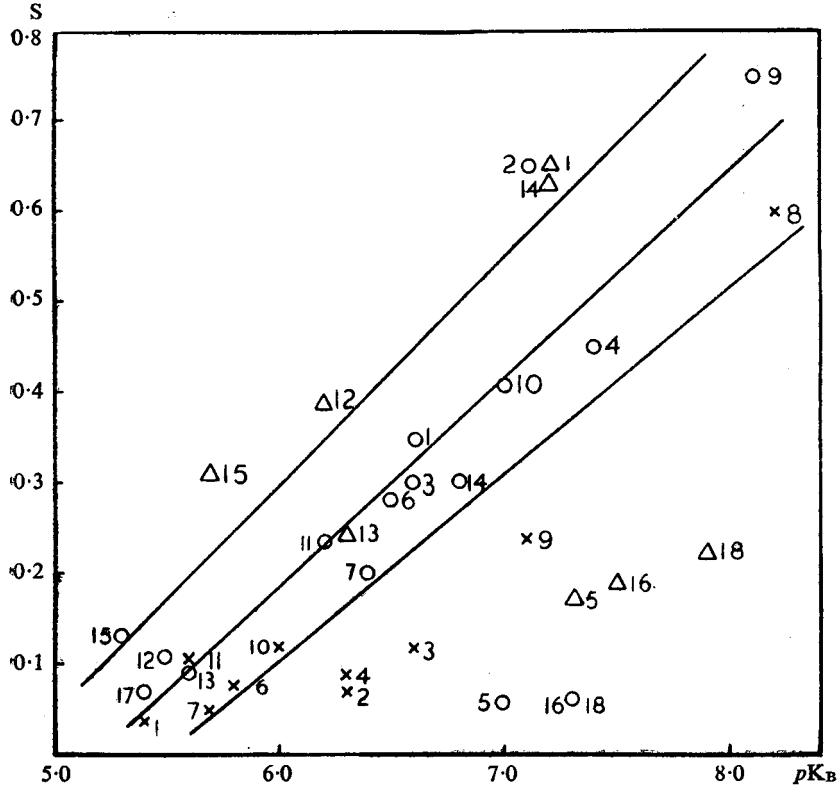

FIG. 4. Regression of s/pK_B. The numbers indicate the salts listed in page 79. Solvents used: x, water; O, 50 per cent. ethanol; Δ, 75 per cent. ethanol.

titrations – log. γ = 0·04; in 50 per cent. ethanol, – log. γ = 0·09 and in 75 per cent. ethanol, – log. γ = 0·14. These small corrections were applied to the calculated values of pK_B.

The values of s, the maximum slopes of the titration curves, represent the rate of change of *p*H with added sodium hydroxide solution, at the end-point, expressed numerically as *p*H change/ml. of 0·01N sodium hydroxide solution added to one milliequivalent of alkaloid salt.

On plotting values of s, the maximum slopes of the titration curves, against pK_B for all the salts in the three different solvents, the scatter diagram shown in Figure 4, was obtained. This indicated a correlation between s and pK_B and in fact, a correlation coefficient (excluding results for morphine and apomorphine salts) of 0·96, was computed indicating that the sharpening of the end-point of the titration curves by alcohol is

largely due to the suppression of the ionisation of the base by the alcohol.

The three lines shown in Figure 4 are the calculated regression lines of s upon pK_B' for the salts, each line representing a different solvent (values for morphine and apomorphine salts have been excluded from the

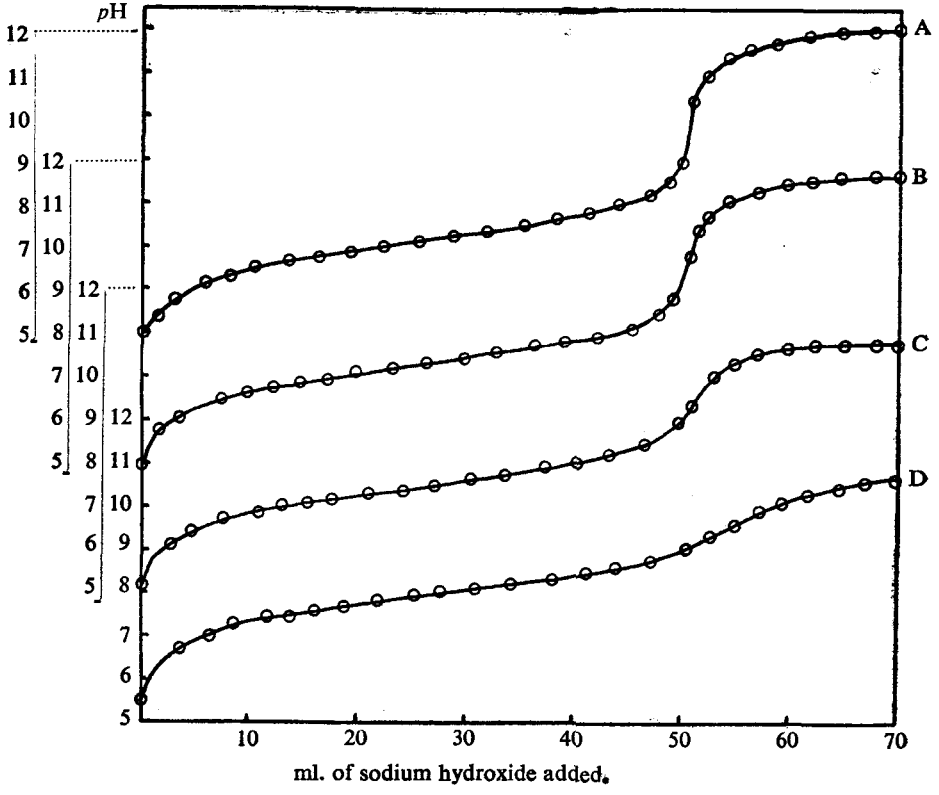

Fig. 5. Titration curves of diamorphine hydrochloride in various solvents.
A: against 0·00990 N sodium hydroxide in 50 per cent. propanol.
B: against 0·01006 N sodium hydroxide in 50 per cent. ethanol.
C: against 0·01001 N sodium hydroxide in 50 per cent. methanol.
D: against 0·00956 N sodium hydroxide in water.

regression calculation). Morphine and apomorphine salts show very wide deviations from these regression lines, the values of s being much smaller than would be expected from their pK_B values. This is due to the phenolic groups in the molecules of these two alkaloids. As the solution becomes slightly alkaline near the end-point, this phenolic group will begin to ionise and a zwitterion effect will appear which will mask the sharpness of the end-point and so reduce s. Codeine and diamorphine, in which these phenolic groups are methylated and acetylated respectively, show much smaller deviations from the regressions.

The scatter of the other results about their regression lines may be

attributed to unavoidable errors in determining s and to specific solvation effects of the solvents on the different organic ions which are not revealed in the value of pK_B.

The lateral displacement of the regression lines (which all have similar slopes) indicates that if s is taken as an ultimate measure of pK_B, the values of the latter derived from *p*H determinations are in error by

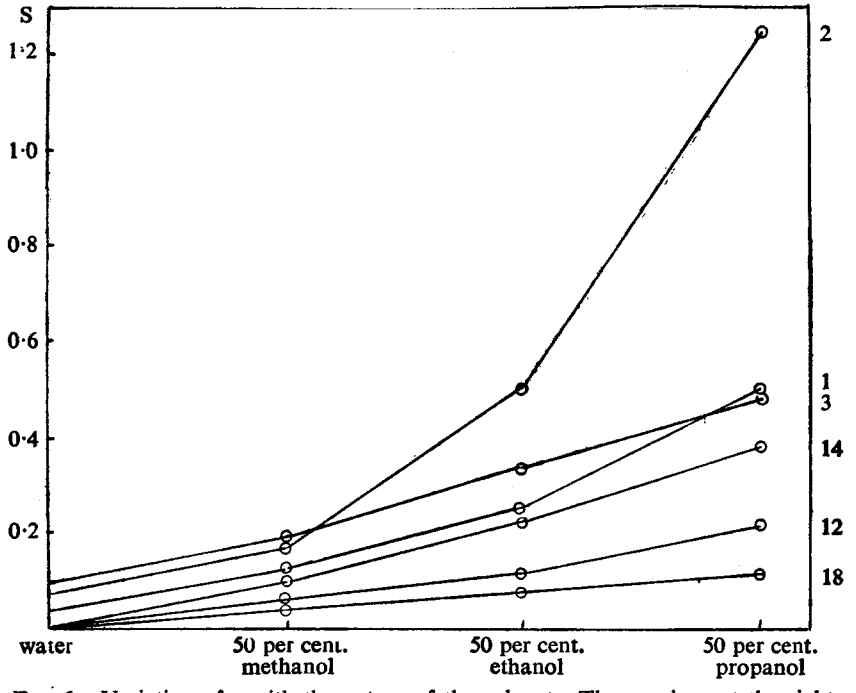

FIG. 6. Variation of s with the nature of the solvent. The numbers at the right-hand side of the graph represent the various salts shown in the list on page 79.

about 0·45 *p*K unit in 50 per cent. ethanol and about 0·9 *p*K unit in 75 per cent. ethanol, accepting the values in water as correct. These results suggest that the use of aqueous alcohol as solvent for the alkaloidal salt, in place of water, in the cell.

Glass electrode	alkaloidal salt solution	saturated KCl	Hg_2Cl_2, Hg

introduces a liquid junction potential of the order of 25 millivolts in the case of 50 per cent. ethanol and about 50 millivolts in the case of 75 per cent. ethanol, acting in the sense that the observed *p*H values in these solvents are too low by 0·45 and 0·9 *p*H units respectively. An alternative explanation for the shift of the lines is that the *p*Kw values calculated for 50 and 75 per cent. ethanol, are in error.

A value of s equal to or greater than 0·15 is adequate for reasonably accurate assay of an alkaloidal salt. Even in the case of morphine, an inflection adequate for assay is obtained by using 75 per cent. ethanol as solvent.

The effect on s of using 50 per cent. methanol and propanol in place of ethanol (the 0·01N sodium hydroxide being made up in the same solvent as the alkaloidal salt, in each case) is shown in Figures 5 and 6. Figure 5 shows the titration curves of diamorphine hydrochloride in the three 50 per cent. alcohols, while Figure 6 shows the s values for a number of salts plotted against the number of carbon atoms in the alcohol molecule. In all cases a progressive sharpening of s is apparent as this number of carbon atoms increases.

SUMMARY

1. Potentiometric titration curves for a number of alkaloidal salts with 0·01N sodium hydroxide solutions in water and various aqueous alcoholic solvents, have been determined. In all cases, sufficient inflection in the titration curves for quantitative assay of the salts, was obtained by using alcoholic solvents.

2. The maximum slopes (s) of the titration curves at the end-points, have been correlated with the basic dissociation constant exponents (pK_B) of the alkaloids in water and in 50 and 75 per cent. ethanol-water mixtures. Morphine and apomorphine salts show marked deviation from the (pK_B, s) points for the other salts, this is attributed to a zwitterion effect produced by the phenolic groups in these alkaloids. The displacement of the s upon pK_B regression lines in the different solvents has been used to assess the liquid junction potential introduced into the pH measuring cell by the use of aqueous alcohol in place of water, as solvent.

3. The sharpening of the end-points of the titration is improved by using propanol in place of ethanol in the mixed solvent, while use of methanol reduces the sharpness of end-point, compared with ethanol.

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REFERENCES

1. Leger, *J. Pharm. Chim.*, 1885, **11**, 425.
2. Baggesgaard Rasmussen and Reimers, *Dansk. Tidsskr. Farm.*, 1935, **9**, 253.
3. Lyons, *J. Amer. pharm. Ass.*, 1912, **1**, 525.
4. Rotondaro, *Amer. J. Pharm.*, 1935, **107**, 237.
5. Jindra, *J. Pharm. Pharmacol.*, 1949, **1**, 87.
6. Morton, *Trans. Farad. Soc.*, 1948, **44**, 588. (See Chemical Abstracts author index for references to earlier work.)
7. Furman, *Anal. Chem.*, 1950, **22**, 33.
8 Kenneth, Albert and Raymond, *J. Amer. pharm. Ass. Sci. Ed.*, 1949, **38**, 14.
9. Glasstone, *Text book of physical chemistry*, 1946, Van Nostrand, New York.