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Adsorption Analysis of Alkaloid Salts of Polyvalent Acids

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Adsorption methods have been used before for the analysis of alkaloids. Merz and Franck [1] and later Björling [2] and Christiansen [3] sucked alcoholic solutions of extracts containing alkaloids through aluminium oxide and eluted with alcohol. In the elute they obtained mainly the free alkaloid bases which could then be titrated. Reimers and Gottlieb [4] and Reimers [5] applied the same principle to pure alkaloid salts in alcoholic solution, and were able, in many cases, to resolve the salt quantitatively into the free base, which was eluted, and the acid, which was adsorbed. The methods of analysis thus worked out were simple and exact. On some alkaloid salts, however, the method failed: the base was eluted slowly or incompletly or else the alkaloid salt passed through the column. Björling and Ehrlén [6] tried to explain these irregularities, and found that a necessary condition for success was apparently that the base should not be too strong. Another condition, naturally, was that the base, once liberated, could be eluted easily. The process was believed to imply an exchange of ions in accordance with the equation:

$$\text{Oxide-O-Na} + \text{BH}^+ = \text{Oxide-O-H} + \text{B} + \text{Na}^+$$

where Oxide-O-Na = hypothetical aluminate in the oxide
B = base.

Ungerer [7] came to similar conclusions in his work on permutite and alkaloid salts.

Most of the experiments had been carried out on hydrochlorides of the bases. Now, even if the base was weak and easily eluble, it could not always be eluted readily from its salts with polyvalent acids. Thus, from codeine hydrochloride codeine was eluted to 100 % with a certain amount of alcohol, but from codeine phosphate this number decreased to 60—70. Similar be-

haviour was observed in the pair of substances atropine hydrochloride — atropine sulphate.

The object of this paper is to attempt to to throw some light on these problems and to work out a method of analysis for salts of bases and polyvalent acids.

There are relatively few earlier investigations on this subject.

Synthetic resins. Bhatnagar, Kapar and Puri [8] found that sulphuric acid was adsorbed more on basic synthetic resins than nitric and hydrochloric acids. Myers [9] and Myers, Eastes and Urquhart [10] showed that an alkylene polyamine resin bound phosphoric, sulphuric, and hydrochloric acids in quantities corresponding to 8.0, 4.1 and 2.46 millimoles per gram adsorbent, quite an important difference.

Coal. Phelps and Peters [11] found that some organic acids were adsorbed on coal only as molecules, not as ions. The adsorption was greatest at the pH of the free acid. Régnier *et al.* [12, 13, 14, 15] showed that various salts of the novocaine base were adsorbed on coal to a different degree. Dibasic citrate was adsorbed best, followed in order by monobasic citrate, phenyl propionate, hydrochloride, and isobutyrate. Base and acid were adsorbed to approximately the same extent, and it seemed probable that the salts were adsorbed as molecules, not as ions. In addition, the sodium salts of the same acids behaved similarly. In mixtures of novocaine salts and sodium salts it was evident that one of the components influenced the adsorption of the other.

Aluminium oxide. Lottermoser and Edelmann [16] revealed considerably different degrees of adsorption for different ammonium salts on aluminium oxide in aqueous solution. Schwab and Dattler [17] were able to separate some inorganic an-ions in aqueous solution by means of »acid» aluminium oxide. The sulphate was adsorbed more than the chloride. Kuhn and Wieland [18] were able to elute a »Wuchsstoff» out of acid aluminium oxide with sodium sulphate, but not with sodium chloride. The sulphate was bound more firmly than the »Wuchsstoff», which was in turn bound better than the chloride.

Grettie and Williams [19] and Whitehorn [20] adsorbed alkaloids, amino compounds, etc., on various adsorbents and found some rules regulating the adsorption.

EXPERIMENTS

As adsorbent was chosen aluminium oxide, standardised by Brockmanns method [21], which has constant properties and is now produced by several factories. It was tested in the following way.

In most of the experiments 10 g of the oxide was placed in a glass-tube, 1 cm wide, fitted at one end with a perforated cork, covered with a plug of cotton-wool.

Blind test. Alcohol of different concentrations was sucked through the column, the filtrate was diluted with an equal volume of water, and titrated with one tenth normal hydrochloric acid using bromphenol blue as an indicator. The amount of acid used up did not exceed 0.01—0.02 ml for every 25 ml of 95 or 85 % (vol.) alcohol. With 75 % alcohol the consumption increased to 0.6 ml.

A low consumption of acid was also obtained when 5 ml of the 95 or 85 % alcohol was mixed with 2 drops of 2 *N* hydrochloric acid or sulphuric acid or with the same amount of sodium hydroxide, and the mixture eluted with the alcohol in question.

The blind consumption was, thus, very small and independent of the presence of moderate quantities of acid or alkali. Too much water in the alcohol must, however, be avoided.

Adsorption test. About 0.1200 g of procaine hydrochloride was dissolved in 5 ml of alcohol, the solution was transferred to the top of the column by small amounts of alcohol, and was sucked into it. The column was then washed with successive amounts of alcohol of 5 ml each. When 10 ml of the elute had been collected it was titrated with one tenth normal hydrochloric acid and the alcohol concentration was adjusted to 50 % at the end of the titration (bromphenol blue, green colour, see Baggesgaard-Rasmussen and Reimers [22]). The next 5 ml of the elute was collected in the same flask and titrated in the same manner, and so on until the consumption of acid decreased to zero. This happened after one or two elutions, when the total quantity of acid corresponded to 100 % of the procaine base contained in the hydrochloride.

As a check the total filtrate was evaporated to 5—10 ml on a water-bath and extracted exhaustively with chloroform, which was drawn off, filtered, and distilled off almost completely. The residue was mixed with 10.00 ml of one tenth normal hydrochloric acid, the rest of the chloroform was evaporated, and the solution was titrated back with one tenth normal sodium hydroxide (methyl red). Again, the results corresponded to 100 % of the procaine base (see *e. g.* table 1).

For the main experiments procaine was chosen as a test substance. Alcoholic solutions of different salts of the base were prepared in the following manner.

A procaine hydrochloride solution was mixed with excess of sodium carbonate and extracted with chloroform which was then dried and distilled off. The resultant procaine base was dissolved in ethanol (99.5 vol. %) and the strength of the solution was adjusted to approximatively 0.12 mol (bromphenol blue). 20.00 ml of this base solution was pipetted into a 25 ml volumetric flask and neutralized with a calculated amount of an acid, 2-normal aqueous solution (about 1.2 ml). The flask was filled with alcohol (95 vol. %) up to the mark. The solution contained procaine in about one tenth molar concentration in 94 vol. % alcohol.

Above all, it seemed necessary to find out what substances were carried down into the elute. For this purpose 5.00 ml of a procaine salt solution was pipetted on the top of the oxide column and sucked into it. Elution was performed with 20 ml of alcohol, the elute was then diluted with 15 ml of water and titrated potentiometrically with one tenth normal hydrochloric

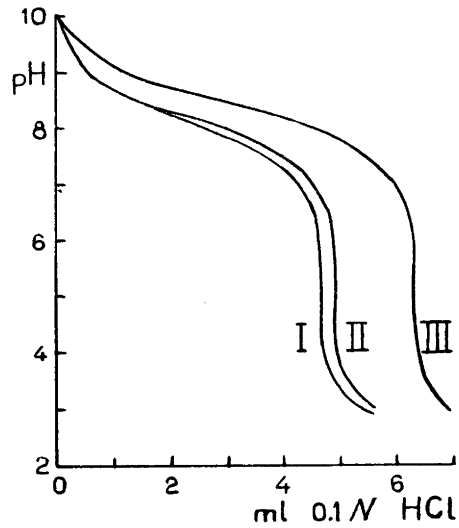

Fig. 1. Potentiometric titration curves.
I. Procaine tartrate eluted with alcohol.
II. Procaine hydrochloride, acetate, or borate eluted with alcohol.
III. Procaine base eluted with alcohol and procaine base titrated directly.
The initial concentrations of the solutions are the same in I and II and somewhat greater in III.

acid (glass electrode-calomel electrode). The titration curves were always congruent, no matter what acid formed the an-ion of the procaine salt. They also ran parallel to the curves obtained on titration of a procaine base solution under the same conditions (fig. 1). Appreciable amounts of interfering substances — *e. g.* aluminium ions or weak acids — could not, therefore, have been eluted.

Qualitatively, no negative ion from the salt could be detected in the elutes. On the contrary, they were all found in the upper parts of the column not in the lower parts. The same was later found to be the case with other alkaloid salts.

After evaporation of the alcohol from the elutes, their contents of procaine base were determined as before by extraction with chloroform. The same values were obtained as with direct titration of the elutes (see table 1).

Thus, it seemed to be fully established that the oxide retains all the acid contained in the procaine salts and that all the alkali titrated in the elutes is procaine base and nothing else.

The next question to be answered was: is the base eluted differently from the various procaine salts? Figure 2 shows that this is the case. The percentage of the base found in 10—20 ml of the elute was 100 % for procaine hydrochloride, nitrate, acetate, borate *, benzoate, and monochloro-acetate. On

* 1 mole of boric acid + 1 mole of the base.

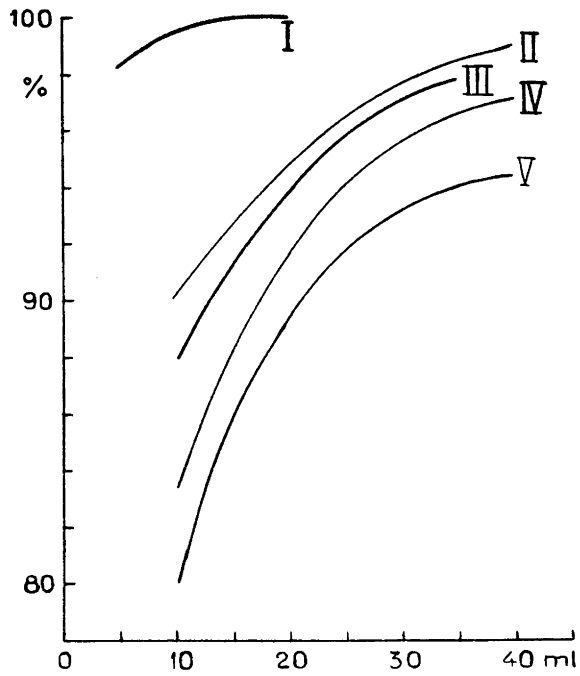

Fig. 2. Procaine base eluted from different salts. Abscissa: Volume of alcohol used for the elution. Ordinata: Yield of procaine base in per cent of the calculated value.
Curve I from procaine hydrochloride, nitrate, acetate, monochloro-acetate, borate, and benzoate.
Curve II from procaine citrate. Curve IV from procaine oxalate.
» III » » sulphate. » V » » tartrate.
The values on which the curves are based are the averages of several experiments.

Table 1. Procaine base eluted from different salts.

Procaine salt investigated	Per cent of the calculated value found		Eluted with ml alcohol
	on direct titration of the elute	after extraction of the elute	
Hydrochloride	100.0	100.0	10
	100.2	100.4	10
Tartrate	94.0	93.6	35
	95.8	95.2	40
Acetate	99.7	99.2	15
Citrate	98.4	98.4	35
Benzoate	100.6	101.0	15
Monochloro-acetate	99.4	98.8	15
Oxalate	97.1	97.1	40
	96.8	97.0	35

the other hand, the neutral procaine salts of sulphuric, tartaric, citric, and oxalic acid behaved differently. The elution of the base was slower, and a 100 % recovery was never attained, or at least only after a very long time. A simple explanation is that these procaine salts are less soluble in alcohol than the salts that behave »normally». This is, indeed, the case with procaine sulphate and procaine oxalate, which formed supersaturated solutions when prepared as described above. The solubilities of some of the salts were determined by shaking for 8 hours and evaporating the saturated solution (for results see table 2).

Table 2. Approximate solubilities of some procaine salts.

Solvent: 95 vol. % alcohol. Temperature: 17—19°.

	Grams of salt in 100 ml solution
Oxalate	0.6
Sulphate	0.8
Hydrochloride	4.4
Tartrate	7.5
Monochloro-acetate	11.8
Benzoate	> 50
Acetate	> 50
Citrate	> 50

It is evident that the solubility of procaine tartrate or citrate has no connexion with their abnormal behaviour. The explanation must be that the salts of these poly-basic acids are bound more firmly to the oxide, depending on the nature of the acid (*cf.* 9—15), so that the exchange of ions cannot take place as easily as with the salts of mono-basic acids.

This theory is supported by the following experiment. In a column used for the analysis of procaine tartrate eluted with 15 ml of alcohol, the procaine and the tartaric acid were found together in the uppermost parts of the oxide. No acid and scarcely any base could be detected in the lower parts of the column.

An important part of the task of solving the problem is obviously to find out some means of eluting the base totally out of the »abnormal» salts. It is impossible to increase the elutive power of the alcohol by diluting it with water. Apart from the fact that the blind consumption of acid will be too great, the diluted alcohol will elute the procaine partly as salt. Addition of the strongly polar base pyridine proved to be of no value as it was eluted together with the procaine, thus causing a considerable error on titrating.

However, the addition of other compounds was more successful. If the procaine tartrate solution was mixed with 2 drops of 2 *M* hydrochloric acid,

Table 3. Elution of procaine base from the tartrate. The influence of certain additions.

To 5 ml of procaine tartrate solution is added			The yield of procaine base in per cent of the calculated value, when eluted with alcohol ml							Per cent found on extraxtion
Compound	Amount	Solvent	10	15	20	25	30	35		
Nil			80.7	85.9	89.6	91.6	91.6			
HCl	0.10 ml 2 *M*	water	83.6	88.3	90.3	92.3	93.7	93.7		
			84.4	90.5	92.3	94.1	96.3	96.3		
HCl	0.25 ml 2 *M*	water	98.9	100.2	100.4	100.4				
			98.0	99.4	100.6	100.6				100.6
HNO_3	0.25 ml 2 *M*	water	92.7	96.7	98.6	99.2	99.2			
			90.9	95.7	98.8	99.4	99.4			
HAc [3])	0.25 ml 2 *M*	water	84.3	89.0	91.1	93.1	94.9	96.1		
HBz [4])	0.25 ml 2 *M*	alcoh.	83.1	87.6	90.9	92.9	96.3			
H_2Ta [5])	0.25 ml 1 *M*	water	66.5	75.0	79.7	83.5				
			65.0	72.4	77.8	80.2	82.1	83.1	89.7 [2])	88.0
NaOH	0.25 ml 2 *M*	water	98.8	99.0						
KOH	1.00 ml *M*/2	alcoh.	95.7	97.6	99.0					
NH_3	0.25 ml 2 *M*	water	96.4	97.4						
LiCl	0.25 ml 2 *M*	water [1])	96.7	98.2	100.6	100.6				100.6
			94.9	97.8	99.8	99.8				98.6
LiCl	0.10 ml 1 *M*	alcoh.	85.0	89.8	91.7	93.7	95.3	97.2		
			81.1	87.0	90.9					
NaJ	1.00 ml 1.3 *M*	alcoh.	100.0	100.0						100.4
			100.0	100.0						
KJ	1.00 ml *M*/2	alcoh.	90.6	100.5	100.5					
			99.8	99.8						
NH_4Br	1.0 ml 0.6 *M*	alcoh.		100.0	100.0					
				100.5	100.5					
$MgCl_2$	1.0 ml 0.7 *M*	alcoh.	92.5	97.2	98.6	99.8	99.8			
			98.4	98.4						
$CaCl_2$	0.5 ml 0.2 *M*	alcoh.	82.9	88.6	92.2	93.7	94.9	96.0		
	1.2 ml		84.8	90.5	92.8	93.5	94.9	96.0		

[1]) + 0.1 ml of water, otherwise precipitate.
[2]) Eluted with 65 ml of alcohol.
[3]) HAc = acetic acid.
[4]) HBz = benzoic acid.
[5]) H_2Ta = tartaric acid.

equivalent to 40 % of the base, the elution of this solution still gave the same result as before, *i. e.* incomplete recovery of the base. But when 5 drops of the acid, corresponding to 100 % of the base, the process was carried out just as easy as with pure procaine hydrochloride. Easy elution was brought about, too, by adding an equal amount of nitric acid, but not by acetic, benzoic, or tartaric acids. Indeed, the latter acid made the elution still more incomplete (see table 3).

Likewise, it was possible to facilitate the elution of the base by adding equivalent quantities of aqueous sodium hydroxide, or of ammonium hydroxide, or of an alcoholic potassium hydroxide solution. In these last cases, however, the time of elution was seriously prolonged, for precipitates were formed which obstructed the passage through the oxide. The precipitates apparently consisted of alkali tartrates, which are little soluble in alcohol.

Good results were also obtained if the procaine tartrate solution was mixed with equivalent amounts of alcoholic solutions of certain salts before entering the column, or if the elution was performed with these salt solutions instead of alcohol. Thus, 100 % of the base was found in elutes of 15 to 20 ml volume with LiCl, $LiNO_3$, NaJ, NaBr, KJ, NH_4Br, and $MgCl_2$. With $CaCl_2$, $Ca(NO_3)_2$, and $SrCl_2$ complete elution failed.

Table 4. Elution of procaine base from the tartrate with alcoholic solutions of certain salts.

Composition of salt solution	The yield of procaine base in per cent of the calculated value, when eluted with salt solution ml						Per cent found on extraction
	10	15	20	25	30	35	
LiCl 0.1 *M*	94.9	99.4	100.6				99.4
	92.3	99.2	100.6				
LiCl 1 *M*	99.6	101.4					
	98.6	100.5	101.6				99.6
$LiNO_3$ 0.06 *M*	99.2	100.2					
	100.2	100.2					
NaBr 0.8 *M*	99.2	100.6	100.6				
	97.2	99.4	100.8	100.8			
$CaCl_2$ 0.2 *M*	73.8	75.3	76.6	77.3			76.1
	73.2	74.1	75.5	76.4	77.6	77.6	78.3
$Ca(NO_3)_2$ 0.05 *M*	79.3	81.3	83.5	85.8	85.8		
	80.3	80.3					
$SrCl_2$ 0.075 *M*	75.0	75.0					
	77.0	77.8	79.9	79.9			

. Nitric acid seems to act more slowly than hydrochloric acid, but the phenomenon has not been investigated further.

Ammonia does not appear to have a full effect.

The addition of magnesium chloride apparently caused precipitates in the strongly basic column, for the surface of the oxide became hard and almost impermeable to the solution. Hard surfaces were also obtained with the alkali hydroxides.

Additions of less than the equivalent of the procaine present (0.5 milliequivalents) did not have the desired effect, *e. g.* hydrochloric acid 0.2 milliequivalents and lithium chloride 0.1 millieq.

Experiments with procaine citrate gave the same results as with the tartrate (*cf.* tables 3 and 4). The addition of hydrochloric acid or sodium iodide gave a full elution of the base with alcohol, as did elution with lithium nitrate. Magnesium chloride had a doubtful effect, calcium chloride acted in a positive manner but »poisoned» the oxide. The figures resemble those obtained with procaine tartrate and are omitted here.

The experience gained from experiments with procaine was applied to other alkaloid salts, some of which have formerly resisted attempts at analysis by means of adsorption. The salts tested hitherto are: codeine phosphate, atropine sulphate, dicodid bitartrate, ephedrine sulphate, benzedrine sulphate, and oxedrine tartrate. Since it is the simplest method, elution with alcoholic salt solutions only has been tested. The results are shown in table 5.

Sodium bromide in alcohol is evidently an excellent eluent. In the case of oxedrine tartrate it failed, owing to the fact that the base itself could not be eluted quantitatively. Addition of salt, however, had a positive effect.

The mechanism of the processes involved in the experiments described on the preceding pages has not yet been fully established. The investigation has been continued on other compounds and under different conditions. Separation analyses will be tried.

SUMMARY

Several organic bases are eluted with alcohol from salts of mono-valent acids by adsorption analysis in an alcoholic medium using aluminium oxide, standardised by Brockmanns method, easily and quantitatively. A volumetric assay has previously been based on this fact. From salts of poly-valent acids the elution of base is slow and incomplete, but can be increased by the addition of certain acids, bases, or salts, or by performing the elution with an alcoholic salt solution. A simple mode of quantitative determination of a number of alkaloid salts is described.

Table 5. Elution of free base from various alkaloid salts by means of salt solutions.

	The yield of free base in per cent of the calculated value after elution with ml							Per cent found on extraction
	5	10	15	20	25	30	45	
0.2 g *codeine phosphate* dissolved in 1 ml H_2O + 10 ml alcohol. Eluted with:								
Alcohol	25.1	53.5	66.0	68.3				
Continued with $LiNO_3$[1])	71.8	82.2	97.2	99.1	100.2			100.2
Alcoh. NaBr 0.1 *M*		89.1	99.6	100.2	100.2			100.4
		96.4	99.8	100.2	100.2			99.5
0.2 g *atropine sulphate* dissolved in 5 ml alcohol. Eluted with:								
Alcohol	72.5	77.3	83.1	89.2	91.1	92.2	94.3	95.1
Alcohol	70.2	80.3	84.8					
Continued with $LiNO_3$[1])	88.5	101.4						
Alcoh. $LiNO_3$ 0.3 *M*	87.1	99.0	100.0	100.9				
Alcoh. NaBr 0.1 *M*	87.0	99.0	99.7	99.7				99.9
	94.0	99.4	99.4					99.2
0.25 g *dicodid bitartrate* dissolved in 1 ml H_2O + 5 ml alcohol. Eluted with:								
Alcohol	29.9	51.6	58.3					
Continued with $LiNO_3$[1])	59.7	81.9	96.8	98.5	100.1			
Alcoh. NaBr 0.1 *M*		90.4	99.8	100.2	100.2			99.1
		98.7	99.3	100.6	100.6			100.8
0.1 g *ephedrine sulphate* dissolved in 1 ml H_2O + 5 ml alcohol. Eluted with:								
Alcohol	47.9	59.8	65.3	71.5	74.5	76.5	84.7[2])	83.6
Alcoh. KI 0.1 *M*	64.5	98.4	100.4	100.4				100.3
Alcoh. NaBr 0.1 *M*	79.2	94.2	99.6	100.7				100.9
0.1 g *benzedrine sulphate* dissolved in 1 ml H_2O + 5 ml alcohol. Eluted with:								
Alcohol	39.1	47.9	53.6	58.9	63.0	64.9	67.7	
Alcoh. NaBr 0.1 *M*	41.9	78.4	94.5	98.1	100.6	100.6		100.6
	39.5	72.4	95.0	100.8	100.8			99.1

[1]) 0.3 *M* alcoholic solution.
[2]) Eluted with 50 ml of alcohol.

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