On Adsorption of Alkaloids

C. O. BJÖRLING and A. BERGGREN

Laboratories of Pharmacia Ltd., Uppsala, Sweden

Experiments on the behaviour of alkaloidal salts on columns of the artificial permutit Decalso F have given the following results:

1. In alkaloidal and similar salts in aqueous solution the cations are exchanged for potassium, and monovalent anions go straight through. Multivalent anions are retained stronger.
2. Alkaloidal salts soluble in organic solvents, *e.g.* chloroform, are most often retained as a whole.
3. Subsequent elution with water releases the anion.
4. Free alkaloidal bases dissolved in *e.g.* chloroform are adsorbed to the Decalso.

Decalso and other permutoid compounds have frequently been used for water softening by ion exchange, calcium and magnesium being exchanged for sodium or potassium. It seems likely that alkaloidal salts in aqueous solution will behave in a similar way. In recent papers ^{1,2} it has been established that the cations of such salts are adsorbed by the Decalso and in the present paper evidence is given that both ions follow the general rules valid for ion exchange processes.

Hyoscine hydrobromide, atropine sulphate, and codeine phosphate were adsorbed on Decalso columns from aqueous solutions ^{1,2}. The recoveries of the anions are shown in Table 1.

The bromide is very easily eluted, the sulphate requires much more water and some losses appear. The phosphate is most strongly adsorbed and could only be recovered in 83 % yield with twenty times as much water as for the bromide. Subsequent elution with 0.2 *N* hydrochloric acid did only add 7 % to the yield of phosphate in the eluate, and 0.2 *N* acetic acid nothing. For alkaloidal cations these acids are very effective eluants ^{1,2}. These findings concord with the general ion exchange experience.

As cation only potassium could be detected in the water effluent from columns charged with hyoscine hydrobromide. The recoveries were between 121 and 129 % calculated on the amount equivalent to the alkaloid. The values are difficult to explain but might be due to a slight decomposition of the Decalso lattice. We are, however, sure that the discrepancy is not due to experimental errors.

Previously we have shown¹ that the free bases of atropine and hyoscyne extracted from their salts could be adsorbed by Decalso from ethereal solutions. The bases were in those cases liberated with ammonia or sodium carbonate. Now, a similar technique has been applied to a number of other bases. Most bases investigated were quantitatively retained by the Decalso from solutions in chloroform or ethyl ether and could be eluted in excellent yields with acids as before (Table 2). It did not matter whether the organic solvents were dry or saturated with water or whether the Decalso column was prepared with the exclusion of water or not. If, however, the organic solvent contained too much ammonia the alkaloid leaked through: the more ammonia the more leakage.

Some organic salts, *e.g.* some alkaloidal salts of inorganic acids, are soluble in organic solvents such as chloroform and ether. Such solutions were applied to Decalso columns and the effluents were tested for cations and anions. Most of the salts investigated were retained by the Decalso, *i.e.* not only the cation but also the anion. This is a most interesting fact which indicates that the process involved is hardly a common ion exchange.

If the column charged with the salt is washed with water the anion is eluted as before. The cation sticks to the Decalso but can as usual be eluted with acids.

An inspection of the Tables 2 and 3 and the previous paper¹ reveals that some bases and some salts do not behave in the same way as the majority of the compounds tested. Bases as atropine¹, hyoscyne¹, codeine, quinine, strychnine, and even 2-aminopyridine (pK_b in water ranging from 3.3 to 6.9) were adsorbed by the Decalso both as free bases and salts from chloroform, ether, or water. Weaker bases, however, as *N*-diethylaniline, pyridine, and 1-naphthylamine (pK_b in water 7.4–10.0) leaked through, the weaker the more. Thus, there seems to be a certain limit as to the strength of the bases which can be taken up by the Decalso.

EXPERIMENTAL

Table 1. Desorption of anions.

Alkaloidal salt	Elution with water ml	Recovery of anion %
Hyoscyne hydrobromide	15	99.1; 98.7
Atropine sulphate	40	95.0; 98.7
Codeine phosphate	50–300	45–83

10–15 mg of the alkaloidal salt was adsorbed on 2.0–2.5 g of Decalso* in a column 1 cm wide¹. The column was washed with varied amounts of water and the anion determined in the effluents. Blanks were always run.

Bromide. The eluate was evaporated to near dryness after the addition of 0.50 ml of 0.1 *M* sodium bicarbonate solution and titrated with 0.1 *N* silver nitrate according to Volhard in the presence of nitrobenzene.

* Decalso F, obtained from the Permutit Company, Gunnersbury Av., London, W. 4. through Rudolph Grave, Stockholm.

Sulphate. The eluate was acidified with 1.0 ml of 2 *M* hydrochloric acid and the sulphate precipitated with 5.00 ml of 0.2001 % barium chloride solution. The mixture was evaporated to dryness on the waterbath, 5.00 ml of 0.1316 % potassium dichromate solution and 3.0 ml of 5 % sodium acetate solution were added. After evaporation to dryness on the waterbath the residue was stirred with 25.00 ml of water, centrifuged and 10.00 ml of the supernatant liquid withdrawn and after evaporation to about 2 ml the excess of potassium dichromate was titrated iodometrically with 0.1 *N* sodium thiosulphate.

Phosphate. The phosphate was determined both colourimetrically⁴ and acidimetrically⁵. As the values obtained were very irregular and low we tried wet ashing with a mixture of nitric and sulphuric acids and dry ashing with sodium carbonate and potassium chlorate. These attempts did not improve the results on the effluents. When the various techniques were applied on plain codeine phosphate or potassium phosphate however good results were obtained.

Potassium was determined with a Zeiss flame spectrophotometer. Standard curves were made with solutions of potassium bromide. To all solutions lithium chloride was added to a final concentration of 0.1 mg per ml, *i.e.* about 10–20 times the amount of potassium.

During determinations frequent standards were run and in each sample also the sodium content was determined. In no case, however, measurable amounts of sodium were detected.

Preliminary experiments showed that it was impossible to obtain a potassium-free effluent from plain Decalso with water. However, after copious washing the potassium leakage became constant under the conditions of each experiment. Hence, the Decalso (2.50 g) was soaked overnight in water, and then washed in the column with 3–4 50 ml portions of water until the potassium content of the effluent had become constant. About 15.00 mg of hyoscine hydrobromide dissolved in 10 ml of water was adsorbed on the Decalso. The column was washed with water, the effluent being collected in 50.0 ml volumetric flasks. The potassium concentration was high in the first 50 ml eluate, but dropped in the second to the same value as before the adsorption. As checks blank columns were run parallel.

<i>Example:</i>	Uncorrected recovery	39.5	μg K/ml
	Constant leakage	1.5	„
	Corrected value	38.0	„
	Theory	32.45	„

As the values were always 20–30 % high wet ashing with perchloric and nitric acids was tried, but the same results were obtained.

The substance was dissolved in some ml of the solvent in question and the solution passed through the decalso column^{1,2}. The column was washed, first with 10–15 ml of the solvent, then with 10–15 ml of water. If an organic solvent was used it was displaced

Table 2. Adsorption of bases on Decalso, 0.5 or 0.6 g.

Alkaloid	pK _b (water)	Amount mg	Solvent	Recovery (%) after elution with 0.2 <i>N</i> acetic or hydrochloric acid	
Codeine	6.05	4.8	Ether	100.2	99.2
„		5	Chloroform	99.5	100.3
Quinine	5.9	1.3	Ether	100.3	99.7
„		1.5	Chloroform	99.0	99.5
Strychnine	6.0	1.0	Chloroform	99.5	99.6
2-Aminopyridine	6.9	0.3	Chloroform	100.2	99.7
N-Diethylaniline	7.4	1.0	Chloroform	15–20	
Pyridine	8.9	1.1	Water	Total leakage	
1-Naphthylamine	10.0	1.5	Chloroform	2–17	

Table 3. Adsorption of salts on Decalso.

Alkaloidal salt	pK _b base in water	Amount		Solvent	Recovery (%) after elution with 0.2 N acetic or hydrochloric acid		
		Alka- loidal salt mg	Decalso g				
Dimethylammonium chloride	3.3	8	3	Chloroform	97.6	100.5	100.5
Hyosine hydro- bromide	6.2	1.4	0.25	»	97.0	97.5	
Papaverine hydro- chloride	8.1	1.3	0.6	»	99.0	99.6	
		1.6	0.6	»	98.8	99.2	
2-Aminopyridine hydrochloride	6.9	0.2	0.5	Water	100.1	101.6	100.6
N-Diethylaniline hydrochloride	7.4	1.0	0.5	»	94.4	92.6	
Pyridine hydro- chloride	8.9	1.1	0.5	»	Total leakage		
1-Naphthylamine hydrochloride	10.0	0.8	0.5	Ether	72.8	73.7	
		0.7	0.5	Water	Total leakage		
Tetraphenylboron compound of methylhyosine ³	strong	30	2.5	Acetone	100.9	100.6	

by some alcohol prior to the water. If the solvent was water the first 10–15 ml of effluent was examined separately. When chloroform or ether were used the organic phase and the alcoholic-aqueous phases were separately examined. The organic effluents were evaporated together with some water and the aqueous residue was investigated.

The cations were eluted from the columns with acids ^{1,2} and determined in the acid solution with the aid of their ultraviolet absorption. Diethylaniline was extracted with 2,2,4-trimethylpentane from the alkalized effluent and measured in the hydrocarbon. Dimethylamine was determined by a micro-Kjeldahl procedure.

In addition to the quantitative experiments listed in Table 3 qualitative tests were made on chloroform solutions of the following salts:

Hyosine hydrobromide	pK _b for the base in water	6.2
Papaverine hydrochloride		8.1
Narcotine hydrochloride		7.8
Atropine sulphate		4.4
Dimethylammonium chloride		3.3
Physostigmine salicylate		6.1
Allypine hydrochloride		4.5
Homatropine hydrobromide		~ 4.7

The chloroform effluents were evaporated with some water and the water tested for the anion in question, in each case with a negative result. On the other hand the anions were present in the subsequent aqueous eluates.

In one case, hyosine hydrobromide, the anion was quantitatively determined in the aqueous eluate as previously described. The recoveries were: 100.6, 99.1, and 99.3 %.

We are indebted to Messrs. Pharmacia Ltd. for permission to publish this paper and to Mr. L. Magnusson who carried out most of the experimental work.

REFERENCES

1. Björling, C. O. and Berggren, A. *J. Pharm. and Pharmacol.* **5** (1953) 169.
2. Berggren, A. and Björling, C. O. *Ibid.* **5** (1953) 615.
3. Schulz, O. E. and Mayer, G. *Deut. Apoth. Ztg.* **92** (1952) 358.
4. Snell, F. D. and Snell, C. T. *Colorimetric Methods of Analysis*, vol. II, New York 1949, p. 630.
5. Fernlund, U., Zechner, S. and Andersson, T. *Z. anal. Chem.* **138** (1953) 41.

Received January 18, 1955.