1.

INTRODUCTION :

1.1 THE PURPOSE AND SCOPE OF THIS STUDY :

The purpose of this series of investigations of which the present work is the first, is to study the ion exchange resins - alkaloid systems in detail, and to utilise these for practical purposes.

The scope of the present work is to study the exchange equilibria, exchange rates and column behaviour of some of the major cinchona alkaloid sulphates. For comparision the exchange equilibria with sodium sulphate and potassium sulphate have also been investigated.

1.2 ION EXCHANGE MATERIALS : (1 to 10)

Introduction :

Ion exchange materials are of a wide variety. These may be inorganic or organic and of different shape and size. The common general structural principle is a frame work with electric surplus charge and mobile counter ions. However, the various types of materials behave markedly differently.

Inorganic ion exchange materials :

Most natural ion exchange materials are crystalline aluminosilicates with cation exchange properties. The zeolites have a rigid three-dimensional framework structure with cavities and channels permeable to counter ions. Clays have a layer structure and the counter ions move in between the layers. Glauconites have a dense, three-dimensional frame work structure and the exchange can occur essentially

only at the crystal surface. A few minerals such as apatite can act as natural inorganic anion exchangers.

Synthetic aluminosilicate cation exchangers have been prepared by fusion and precipitation methods. Recently zeolites with regular crystal structure have been prepared. These are useful as molecular sieves as these can sorb small molecules, but exclude molecules which may be larger than the channel width. Interesting cation and anion exchangers, have also been prepared from zirconium and tin hydroxides.

Organic ion exchangers :

Organic ion exchange resins are the most significant of the ion exchange materials. These are gels and the matrix consists of an irregular, macromolecular, three-dimensional network of hydrocarbon chains. The ionic groups attached to the matrix may be of various types such as,

$-SO_3^-$ $-COO^-$ $-PO_3^{--}$ $-AsO_3^{--}$

for cation exchangers and

$-NH_3^+$ $>NH_2^+$ $\rangle N^+\langle$ $-S^+$

for anion exchangers. Hence, ion exchange resins are cross-linked polyelectrolytes. They are insoluble, but have a limited swelling in water, depending on the cross-linking . The ion exchange behaviour of the resins is mainly dependent on the nature of the fixed ionic groups.

Certain coals are natural weak acid cation exchangers. Others may be converted into ion exchangers by

chemical treatment, such as sulphonation. Many other natural or synthetic materials can act as ion exchangers or can be converted into ion exchangers, by introducing fixed ionic groups or by cross-linking. Ion exchange papers and phosphorylated cotton are of interest.

Commercial ion exchangers are insoluble solids. Recently liquid ion exchangers, such as long chain aliphatic amines and fatty acids or alkyl phosphates have become of great interest.

Organic synthetic resins in general, have superior chemical and mechanical stability, exchange capacity, exchange rates and versatility. Inorganic materials possess better thermal stability and resistance to radiation.

Preparation :

A wide variety of organic ion exchange resins have been prepared and some are available commercially under various trade names. Tables (1.1 and 1.2) give the trade names and the manufacturers of commercially available ion exchange resins.

The synthesis of ion exchange resin should yield a three-dimensional, cross-linked matrix of hydrocarbon chains carrying ionic groups. The resins can be prepared by condensation polymerisation or addition polymerisation and the ionogenic groups can be introduced, before,during or after the polymerisation. These groups may be of one or more types giving mono-functional or multi-functional cation exchange or anion exchange or amphoteric resins.

Table 1.1

Some common commercial cation exchange resins

Matrix	Ionic group.	Trade name	Manufacturer	Physical form.	Remarks
Cross-linked polystyrene.	$-SO_3^-$	Amberlite IR-120	Rohm and Haas Co.	Spherical beads.	Standard resin, 8% DVB.
Strongly acidic.		Amberlite 200	Rohm and Haas Co.	Sph.Beads.	Higher mech.and chem. stability.
		Amberlyst 15	Rohm and Haas Co.	Sph.Beads.	Macroreticular resin.
		Dowex 50	Dow Chemical Co.	Sph.Beads.	Dowex 50 x 2 has 2 % DVB etc.
		Imac C-12	Activit Hollands.	Sph.Beads.	Standard resin,8% DVB.
		Permutit Q	Permutit Co., U.S.A.	Sph.Beads.	Standard resin.
		Zeo-Karb 225	Permutit Co.,England.	Sph.Beads.	Standard resin,8% DVB.
Vinyl addition polymers.	- COOH	Amberlite IRC-50	Rohm and Haas Co.	Sph.Beads.	
Weakly acidic.		Duolite CS-101	Chemical Process Co.	Sph.Beads.	
		Zeo-Karb 226	Permutit Co.England.	Sph.Beads.	

Table 1.1 (Continued)

Matrix	Ionic group.	Trade name	Manufacturer	Physical form.	Remarks
Vinyl addition polymers.		Permutit 200	Permutit A.G. W.Germany	Sph.Beads.	
Weakly acidic		Permutit H-70	Permutit Co., New York.	Sph.Beads.	
Phenolic resins.	$-SO_3$	Duolite C-10	Chemical Process Co	Granules.	More porous
		Zeo-Karb 215	Permutit Co. England.	Granules.	
	-COOH	Duolite CS-100	Chemical Process Co	Granules.	
		Permutit H	Permutit Co., New York.	Granules.	
		Zeo-Karb 216	Permutit Co., England.	Granules.	

Table 1.2

Some common commercial anion exchange resins

Matrix	Ionic group.	Trade name	Manufacturer	Physical form.	Remarks
Cross-linked Polystyrene	$-N^{+}(alkyl)_3$	Amberlite IRA-400	Rohm and Haas Co.	Spherical Beads.	Standard resin, 8% DVB
		De-Acidite FF	Permutit Co. England.	Sph.Beads.	Standard resin, 7-9%DVB
		Dowex 1	Dow Chemical Co.	Sph.Beads.	Standard resin, Dowex 1-X8
		Dowex 21 K	Dow Chemical Co.	Sph.Beads.	Improved mech. stability.
		Duolite A-101	Chemical Process Co.	Sph.Beads.	Improved resins.
		Permutit S-1	Permutit Co., New York.	Sph.Beads.	
	$-N^{+}(alkylol)-(alkyl)_2$	Amberlite IRA-410	Rohm and Hass Co.	Sph.Beads.	Standard resin, 6% DVB.
		Dowex 2.	Dow Chemical Co.	Sph.Beads.	Standard resin, Dowex 2-X8.
		Duolite A-102	Chemical Process Co	Sph.Beads.	Improved resins.
		Permutit S-2	Permutit Co. New York.	Sph.Beads.	

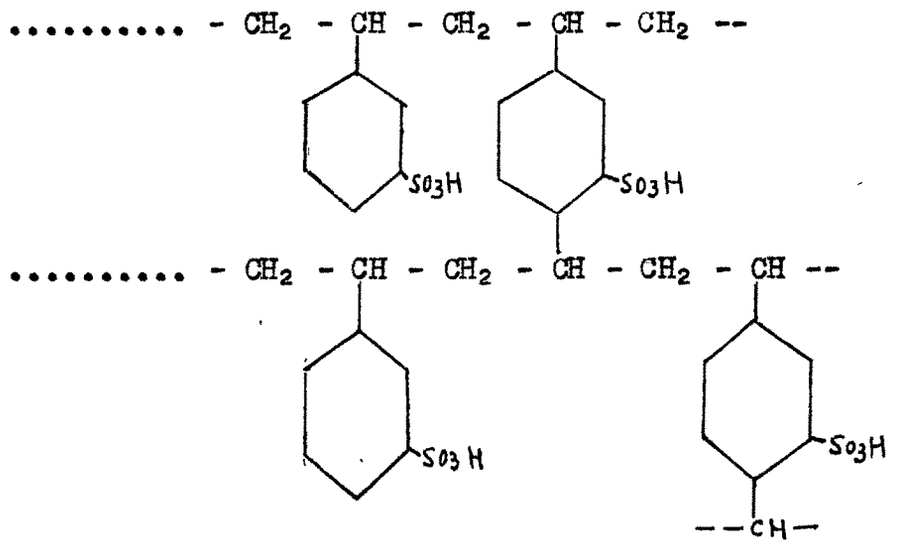
Table 1.2 (Continued)

Matrix	Ionic group	Trade name	Manufacturer	Physical form.	Remarks
"	Weak base Amino groups	Amberlite IR-45	Rohm and Haas Co.	Sph.Beads.	
		De-Acidite M	Permutit Co. England	Sph.Beads.	Polyamine groups.
		De-Acidite G	Permutit Co. England.	Sph.Beads.	$-N(C_2H_5)_2$ groups. only
		Dowex 3	Dow Chemical Co.	Sph.Beads.	
Condensation polymers	$-N^{+}(alkyl)_3$	Imac S-3	Activit Holland	Granules.	Highly porous resi
	Weak base Amino groups	Amberlite IR-4B	Rohm and Haas Co	Granules.	
		Duolite A-2	Chemical Process Co	Granules.	
	Strong and weak base groups.	Permutit A	Permutit Co. N. York.	Granules.	

Most of the earlier cation exchange resins were condensation products of phenol derivatives and aldehydes.

Most of the present commercial resins are addition polymers prepared from vinyl monomers. These resins have a better chemical and thermal stability than the condensation polymers and their degree of cross-linking and particle size can be more easily controlled.

The monofunctional sulphonic acid cation exchange resins available are cross-linked polystyrenes with sulphonic acid groups, introduced by sulphonation of the polymer. The cross-linking agent used is divinyl benzene. Amberlite IR-120, Dowex 50, Nalcite HCR, Permutit Q, Duolite C-20 and C-25 and Lewalit S-100 are resins of this type. The structure may be imagined as :



Pure divinyl benzene is not readily available ; hence the resins are prepared with a commercial product consisting of a mixture of the different divinyl benzene isomers (about 40 to 55 %) and ethylstyrene (~45 to 60 %). Ethylstyrene is also incorporated into the matrix.

By varying the divinyl benzene content, the degree of cross-linking can be adjusted in a simple and reproducible manner. The nominal DVB content is used to indicate the degree of cross-linking ; it refers to mole percent of pure divinylbenzene (not of the commercial product) in the polymerisation mixture. Resins with low degree of cross-linking, swell strongly and are soft and gelatinous. Resins with high DVB content swell much less and are tough and mechanically more stable.

The copolymer beads are prepared by the pearl polymerisation technique. The monomers, from which stabilisers have been removed, are mixed and a polymerisation catalyst, such as benzoyl peroxide is added. The mixture is then added to a thoroughly agitated aqueous solution at a required temperature (usually 85° to $100^{\circ}C$). The mixture forms small droplets, which remain suspended. A suspension stabiliser (gelatin, polyvinyl alcohol etc.) in the aqueous phase prevents agglomeration of the droplets. The size of the droplets depends mainly on the nature of the stabiliser, the viscosity of the solution and the agitation and can be varied within wide limits. The polymer is obtained in the form of fairly uniform beads.

The sulphonation of the beads is simple, if proper preeautions are taken. The cracking of beads may be avoided by first swelling the beads in an organic solvent such as toluene, nitrobenzene etc. It is advisable to transfer the sulphonated beads first to a highly concentrated electrolyte solution, which causes less

swelling and then to dilute the solution stepwise. Sulphonation with concentrated sulphuric acid or chlorosulphonic acid results in practically complete monosulphonation of all the benzene rings.

Highly porous, 'macromolecular ion exchange resins' are prepared by a variation in the conventional pearl polymerisation technique. An organic solvent, which is a good solvent for the monomers, but a poor solvent for the polymer is added to the polymerisation mixture. As polymerisation progresses, the solvent is squeezed out by the growing copolymer regions. In this way, spherical beads are obtained with wide pores which permit access to the interior of the beads even when nonpolar solvents are used. The recent Amberlyst ion exchange resins are of this type.

Cation exchangers with specific preference for certain cations can be made by introducing groups which form strong complexes, preferably chelates with these cations. Resins with chelating iminodiacetic acid are now commercially available.

Most of the earlier anion exchange resins were condensation products of aromatic or aliphatic amines and aldehydes, dihaloparaffins or haloepoxides. Most of these contain weakly basic groups.

The more important anion exchangers are cross-linked polystyrenes, into which strong or weakly basic groups are introduced by chloromethylation and subsequent amination. Reaction with tertiary alkyl amines gives strong base quaternary ammonium groups and reaction with primary

or secondary alkyl amines or ammonia gives weak base amino groups. Anion exchangers with strong base quaternary phosphonium and tertiary sulphonium groups have also been prepared.

Amphoteric ion exchangers contain both acidic and basic groups. 'Snake cage' polyelectrolytes are a novel variety of amphoteric resins. These are prepared from conventional ion exchangers by polymerisation of monomeric counter ions within the resin.

For specific purposes ion exchangers in the form of pellets, rods, belts etc. have been prepared by cementing ion exchange particles together with an inert binder or by impregnating suitable supporting carriers.

Ion exchange membranes have been prepared by various methods. The membranes may be homogeneous or heterogenous and have become of significant interest recently, particularly for desalting of water.

1.3 ION EXCHANGE STUDIES WITH ALKALOIDS :

1.3.a. INTRODUCTION :

Extraction with aqueous acids (11) :

Most alkaloids being basic are extracted when the raw material is treated with aqueous acid. Other water soluble non-alkaloidal matter is also extracted, the removal of which may be rather difficult. Hence, this method of extraction, though cheaper, has a relatively limited use and is usually adopted in cases where raw material is fairly rich in alkaloid content, such as cinchona and opium.

In such cases, a concentrated acid water extract is feasible, which is then made alkaline to liberate the alkaloids. Further purification of the alkaloid is necessary.

Extraction with water miscible solvents :

The raw material is treated with a solvent such as alcohol, to dissolve the alkaloids. Some non-alkaloidal matter is also extracted. If the raw material (seeds) is rich in fat, it has to be first defated by extraction with petroleum solvents. The alcohol used should be free from acetone, since many alkaloids form condensation products with acetone. The alcoholic extract is concentrated to a small volume. Distillation under reduced pressure may be employed, if frothing can be prevented. The concentrated extract is acidified to a pH of two or less and steam distilled to remove the remaining solvent. The aqueous solution contains suspended organic matter, which is suitably removed. The alkaloids are extracted from the aqueous solution by the use of water immiscible organic solvents, such as chloroform ; sometimes the aqueous solution yields the alkaloids when it is made alkaline by addition of ammonia or aqueous sodium carbonate.

Extraction with water immiscible solvents :

The material is extracted with solvents after it has been made alkaline by the addition of ammonia or aqueous sodium carbonate. If the raw material is rich in fats, it should first be defated.

Aqueous acid or water miscible solvent extracts are usually contaminated with non-alkaloidal matter. These solutions tend to foam, are difficult to filter and may form emulsions with organic immiscible solvents. Removal of the non-alkaloidal matter is rather difficult.

Extraction by ion exchange materials (1 to 9) :

Lloyds (12) for the first time used magnesium silicate to purify alkaloids. Fink (13) used a mixture of kaoline and asbestos to absorb alkaloid from an aqueous extract of cinchona. This was followed by several workers and recently, with use of organic ion exchange resins, a number of alkaloids have been isolated and estimated.

Alkaloids, being basic in nature form cations in aqueous or aqueous salt solution. If the solution is passed over a cation exchange resin, the alkaloid is taken up by the resin. To liberate the free alkaloid from the resin, an alkali, such as sodium hydroxide or ammonium hydroxide may be added and the free alkaloid eluted from the resin by a suitable organic solvent such as alcohol or chloroform. The liberation of the free alkaloid and its elution from the resin can also be accomplished in one step, in suitable cases, by using ammonical alcohol. The effluent is evaporated to remove the organic solvent and the residue of the alkaloid is further purified. When an anion exchange resin is used, the exchange of anions occurs. The liberated alkaloid remains in the resin bed and is eluted by using suitable organic solvents.

Ion exchange method has the advantage that an alkaloid can be recovered from a large volume of dilute solution. Some of the difficulties encountered in the conventional methods of extraction are avoided. Ion exchange methods may become cheaper in some cases and it may be possible to effect relatively high recovery.

1.3.b CINCHONA ALKALOIDS :

Ungerer and Kolloid (14) first examined the uptake of salts of quinine, cinchonine and strychnine on the calcium form of synthetic zeolites. Fink (13) took a patent for isolating cinchonine, strychnine and adrenaline from their aqueous extracts by a filtering material having adsorptive properties, such as asbestos and kaolin, cotton and asbestos or asbestos and kieselguhr. The pH of the solution was suitably adjusted to facilitate the separation. Applezweig (15) studied the removal of cinchona alkaloids by a cation exchanger of sulphonic acid type. Three possibilities were explored : (a) recovery of alkaloids from the mother liquor of the acid extracts of the bark after the major portion had been removed by alkaline precipitation, (b) purification of the crude totaquine obtained from alkaline precipitation and (c) application of ion exchange directly to the acid extracts of the bark in a cyclic system. Capacity determinations were carried out on a 200 cc. Zeo-karb column using quinine concentrations of 0.033 and 0.0033 M and flow rates of approximately 5 and 50 cc./min. The capacity of a 200 cc. bed of Zeo-karb for quinine,

from acid solution (.1 % H_2SO_4) was found to be between 7 and 8 grams, before break through (Mayer's Reagent). To liberate the alkaloids from the column ammonical alcohol was used. Purification of totaquine prepared by alkaline precipitation of acid extracts of the bark was attempted by ion exchange. From 20 grams of totaquine precipitate, 2.5 grams of white crystalline material was obtained. This technique was also successfully employed in the isolation of atropine, morphine and scopolamine. Recoveries of totaquine from cinchona bark and scopolamine from datura plants were also effected by Sussman and others (16). The extract containing the alkaloids was brought into contact with a cation exchanger and then the cation exchanger was treated with aqueous alkali and a solvent. In a subsequent paper, Applezweig and Ronzone (17) described a portable unit for extracting usable antimalerial from freshly stripped cinchona bark in the field. Commercially dried cinchona bark was macerated with 0.1 N H_2SO_4. The acid was repeatedly cycled through a sulphonated coal cation exchanger and back into the maceration tank. The exchanger was regenerated with 0.5 N NaOH and stripped with alcohol, the crude alkaloid being recovered by evaporation. Rectified totaquine was obtained by precipitation from aqueous solution. An overall yield of 81.2 % within 82 hours was obtained. Mukherjee and Gupta (18) investigated the extraction of alkaloids from cinchona bark with hydrochloric acid and sulphuric acid over a range of acid concentrations and temperatures

in the presence and absence of sodium chloride with Amberlite IR-100 and Ionac C-284. For elution, alkali was used and after an interval, alcohol was percolated. Ionac C-284 proved to be the best sorbent and showed highest elution effeciency but tended to soften and form a jelly in contact with alkali. Hence Zeo-karb, the next best and free from this defect was used. Applezweig (19) took a patent for the removal of quinine from a dilute solution in acid with Zeo-karb cation exchanger. The juice of the fresh material was passed through a column of Zeo-karb or Amberlite IR-100 or Ionac -C. The sorbed alkaloids were eluted with ammonical ethanol. This method was used for the extraction of atropine, scopolamine and quinine alkaloids. Mukherjee and others (20) examined three cation exchange resins (Zeo-karb, Amberlite IR-100 and Ionac C-284) and two anion exchange resins (Deacidite and Ionac A-293) for the sorption of quinine sulphate, strychnine hydrochloride and other organic bases. The results showed that a resin having high sorption power for one alkaloid may not behave similarly with another alkaloid. The relative sorptive powers of the different resins, for each of the alkaloids studied were given.

Jindra (21) used an anion exchange resin of weakly basic type for the determination of several alkaloids. 0.1 to 0.2 grams of alkaloid salt was dissolved in 20 cc. of alcohol and passed through a prepared column of Amberlite IR-4B. The flask and the column were washed with 50 cc. of alcohol at 50^{0}C and the alkaloidal solution

in alcohol was titrated with 0.1 N hydrochloric acid using a mixture of 10 drops of methyl red and 2 drops of methylene blue as indicator. The method was applied to quinine and cinchonine hydrochlorides and to a number of other alkaloids. Jindra and Pohorsky (22) have given detailed descriptions of the apparatus, reagents, preparations of the ion exchange column and general micro and semi-micro methods of assay, applied to cinchona bark and other alkaloids. Bucke and Furrer (23) have described in detail, the determination of quinine and total alkaloids in the cinchona bark extracts by the use of ion exchange resins. In a subsequent paper they (24) found that sorption from cinchona bark was best with sulphuric acid extracts and the elution was best done with ethanol with or without addition of sodium hydroxide. A quantitative sorption occured within 14 hours by shaking the powdered cinchona bark and Duolite in dilute sulphuric acid but the subsequent separation of alkaloids from the resin was found to be difficult. Sanders and others (25) described an assay process using strongly basic anion exchange columns to separate quinine salts and ephedrine hydrochloride which was capable of giving results within 0.5 %. One and two column procedures are described. Yoshino and Sugihara (26) separated quinine and strychnine chromatographycally by sorption on weakly acidic cation exchange (NH_4-R) resins such as Duolite CS-101 or Amberlite IRC-50 and the subsequent elution with 0.1 - 0.3 M ammonium chloride respectively. H-R exchanger could also be used but then a

large amount of eluting solution was required to separate strychnine. Toshino and others (27) classified some organic bases (a) quinine,cinchonine, ephedrine and berberine (b) nicotine and yohimbine (c) amino pyridine (d) antipyrine (e) acetanilide, caffeine, theobromine and theophylline, according to the facilities of being eluted with water from the cation exchange columns (sulphonic acid type and carboxylic acid type in the H and NH_4 form), on to which they had been sorbed. Street and Niyogi (28) separated a mixture of acetophenetidine, sulphacetamide, promacyine and quinine by a combination of chromatography and ionophoresis on cellulosic ion-exchange sheets. Detection was accomplished by examination in ultra-violet light. Similarly (29) separation of a mixture of tablet fragments containing amobarbital, acetylsalicyclic acid, acetophenetidine, caffine, codeine and quinine into its constituent parts was accomplished by chromatography on modified cellulose ion exchange papers using both horizontal circular and ascending cylindrical paper chromatography. Street (30) has described a rapid method using ion exchange paper for the preliminary separation and detection of a mixture of quinine, strychnine and nicotine in whole blood. Proteins were precipitated and the acid filtrate was extracted with ether. The aqueous phase was made alkaline with ammonium hydroxide and shaken with ether to extract basic compounds. The ether extract was evaporated to dryness and the residue was taken up in the chloroform. This solution was spotted on a cellulose cation exchange paper and subjected to chromatography in an

aqueous solvent at pH 4.5. The separated compounds were detected by their fluorescence or absorbance in ultra-violet light at 254 mμ. Quinine showed a bright blue fluorescent spot and strychnine and nicotine as dark purple absorbing areas.

Saunders and Srivastav (31) studied the rates of sorption on, and elution from a carboxylic acid cation exchange resin for quinine. The factors which influenced the rate of sorption of quinine on Amberlite IRC-50 were found to be (a) the initial concentration of the solute ('a' milimoles / 100 cc.) (b) the nature of solvent, sorption from 50 % ethanol solution being more repid than that from pure ethanol for a given value of 'a' (c) the method by which the resin was converted to the hydrogen form, aqueous 2 N acid producing a less effective absorbent than alcoholic 2 N acid (d) the amount of base already sorbed on the resin (x milimoles) (e) the stirring condition (f) the particle size of the resin and (g) the initial pH of the solution. An empirical relation $dx / dt = Ka (a - x) / x^2$ (where K = constant ; a = initial solution concentration in milimoles / 100 cc.; x = milimoles sorbed by 5 gnams of resin and t = time in hours), represented the rate of sorption quite closely for values upto 24 hours. The interaction of quinine with the resin was considered to be mainly a molecular sorption process. The sorption process has been visualised as a diffusion of base into the resin particle under chemical potential difference enhanced by the acid-base interaction

with the resin and by the van der Waal's forces between the base molecule and gel structure of the resin ; the effect of viscous flow into spherical particles and the swelling of the resin caused the rate of sorption to fall off rapidly as the resin became saturated with base. Saunders and Srivastav (32) also examined the sorption of a number of organic bases from aqueous, water ethanol or ethanolic solutions by various carboxylic acid ion exchange resins and described the results of studies of the equilibrium distributions of some bases between the solutions and the resins. This, in the case of quinine has been demonstrated by showing that the distribution was independent of resin particle size and also that it was reversible. The systems studied have been classified into two groups. The first consisted of very weak bases which followed a simple distribution law, concentration of base in resin / concentration in equilibrium solution = constant. The second group, consisted of strong bases, the distributions mostly followed a logarithmic law $Y = A \log C + B$ where C = concentration of base in the equilibrium solution in moles per litre of total phase volume and Y = corresponding base concentration in the resin phase in moles of base per litre of total resin phase volume. Observations have also been made of the swelling of the resins caused by saturating them with the different bases and it was found that swelling was a function of base sorbed.

Segal, Miller and Morton (33) have described the quinine form of a weak cation exchanger as in indicator for the determination of the presence of free hydrochloric acid in gastric juice without intubation. If a special cation (quinine) is combined with a cation exchange resin (Amberlite IRC-50 or XE-96) and the cation is displaceable only or mainly by hydrogen ion, is readily sorbed from the stomach and detectable in the urine or blood, the presence of free hydrochloric acid in gastric juice can be detected if quinine appears in the urine within 2 hours, after introduction of the complex, without subjecting the patient to intubation. Shay and others (34) found that the results of studies in patients after subtotal gastric resection indicated that the tubeless method for detection of the presence of free hydrochloric acid in the remaining gastric pouch was not suitable in these patients because of the rapid emptying of the quininium resin from the pouch. In such patients the determination of pH of gastric contents during fractional gastric analysis was the best method for studying gastric acidity.

1.3.c. EPHEDRA ALKALOIDS :

Huyck (35) attempted sorption and liberation of ephedrine from ion exchange resins and found that Amberlite IRC-50 was a good sorbing medium for the weak base while Dowex-50 was unsatisfactory. Blajot and Toribio (36) recovered ephedrine from plant sources using a sulphonic acid cation exchange resin (phenolic). The plant material

was macerated with 0.1 N sulphuric acid and the extract was passed through the ion exchange columns. The columns were then treated with 0.5 N sodium hydroxide, followed by a limited washing with distilled water to remove excess alkali. Ephedrine was then displaced from the resin column by washing with alcohol. The alcohol was evaporated to leave a deposit of ephedrine which was then purified. The yield which was 81 % of the ephedrine content, was 99.8 % pure. Tsi-Chem Fan (37) prepared ephedrine from chinese ephedra by using sodium form of Ku-2 resin. The plant material after drying and grinding was steam distilled. The distilate was passed through the resin column and concentrated by sorption desorption operations. To separate the ephedrine from pseudoephedrine a saturated solution of oxalic acid was added to the eluate (acid to methyl red). The precipitate was filtered and the filtrate evaporated.

Jindra (21) carried out work using Amberlite IR-4B (aweakly basic anion exchanger) for the determination of ephedrine sulphate and several other alkaloidal salts. Vincent and Krupski (38) found that Amberlite IR-45 was suitable for the quantitative separation of many sympathomimetric amines including L-ephedrine sulphate, racephedrine sulphate, propadrine hydrochloride and paredrine hydrobromide. Gundersen and others (39) used a strongly basic anion exchange resin, Dowex-2, for the assay of tablets containing ephedrine, codeine etc. The results were comparable with those obtained by official assay methods. Sanders and others (25) confirmed the

accuracy of this method for estimating the alkaloid content of ephedrine hydrochloride and a number of other alkaloid salts. The method gave results within 0.5 %. Kelly (40) separated and colorimetrically determined phenyl-ephedrine in pharmaceutical products. Ling and others (41) described an economic separation of ephedrine hydrochloride and pseudoephedrine hydrochloride from ephedra by sulphonated coal. A 0.5 % hydrochloric acid extract of ephedra was passed through a column filled with 40 grams of resin at a rate of 40-50 drops/min. ; the resin was washed with water and alcohol and then eluted with 4 N hydrochloric acid. The first litre of the eluate gave ephedrine in 70 % yield and the second litre of the eluate gave pseudoephedrine. Elution with dilute hydrochloric acid (less than 4 N) or alkali solution (caustic soda or ammonium hydroxide) failed to give the alkaloids in good yields. The sulphonated coal could be regenerated by washing with caustic soda and hydrochloric acid alternately and reused ten times without loss of efficiency. Sadayushi and others (41 A) quantitatively separated L-ephedrine and D-pseudo ephedrine by salting out chromotography. A column (26 x 500 mm.) of Dowex 50 x 2 (200-400 mesh) carrying the sample was developed with 0.1 M potassium phosphate to separate the two alkaloids and each alkaloid was determined by non-aqueous titration after extraction with chloroform.

Larsen (42) used ion exchange resin to prolong the therapeutic effect of ephedrine in allergic disorders.

Ephedrine and ephedra combined in ratio from 1 : 10 to 1 : 3 have a synergistic action eliminating many undesirable side effects produced by each drug alone. To prolong the effect, ion exchangers added to the combinations were useful as medications for allergic disorders. R.J. Strasenburgh Co. (43 and 44) has taken a patent for using sulphonic acid cation exchanger with therapentic amines (alkaloid) sorbed on it and giving slow release in the body. The amine was sorbed on the ion exchanger and when eluted with artificial gastric juice, it released the amine continuously, in a therapentically effective amount, for at least three hours. The compositions were particularly applicable to adrenergic amines such as amphetamine and ephedrine. Lundgren and Wallen (45) prepared cigarettes with nicotine free tobaco and ephedrine. The smoke was collected with a cottrel electro filter, dissolved in ethanol, chromatographed on Dowex-2 and Amberlite IRC-50 and the ephedrine determined photometrically. The ephedrine in the main stream of smoke amounted to about 16 % . Nash and Crabetree (46) combined, randomly labeled d-deoxyephedrine-H^3 with a sulphonic acid type and a carboxylic acid type ion exchange resin. Both forms showed sustained release but the rate of release from the carboxylic acid type resin was greatly influenced by the acidity of the medium. Barucha and Hamied (47) studied the release of ephedrine and chloroephedrine from their respective resin complexes (sulphonic acid cation exchange resin) in artificial gastric and stimulated intenstinal juice. The results showed that under the experimental

conditions, nearly 75 % of ephedrine and 73 % of chloroephedrine were released in a total time of six hours.

1.3.d. OPIUM ALKALOIDS :

Applezweig (15) used ion exchange resins for the sorption of morphine, atropine, cinchona etc. Morphine was isolated by elution with ammonical alcohol. Stolman and Steward (48) used synthetic magnesium silicate (Florisil) for the isolation of morphine, codeine and heroin in miligram quantity in ethanol and trichloroacetic acid extracts of tissue, blood and urine. The elution was complete with methanol. The preparation of radioactive morphine and related alkaloids by biosynthesis, using an ion exchanger was given by Mc Intosh and others (49). Tomko (50) could increase the purity of morphine from 82.5 % to 93.4 % from the water extracts of dry poppy seeds by ion exchange. Viguera, Lobo and others (51) used Zeo-karb (sulphonated coal) to extract morphine from the stems and leaves of the poppy plant. 1 miligram of morphine could be sorbed by 1.2 gram of the exchanger and was best eluted with 2 % potassium hydroxide (elution with sodium hydroxide or ammonium hydroxide was poorer). Achor and Geiling (52) recovered morphine in high purity from plant material, animal tissue and the pharamaceutical preparations by using Dowex-2 and Amberlite IRC-50. Mehltretter and Weakley (53) and Mc Guire and Van Etten (54) found that morphine is rapidly and completely extracted from aqueous

alcoholic ammonia extract of poppy capsules by Duolite C-10 and Zeo-karb (H). The recovery was about 94 % when the sodium form of resin was used and 89 % for the ammonium form. Zeo-karb had appearently a 55 % greater sorption capacity for morphine in comparison to Duolite C-10. Mushinskaya and others (55) have compared the sorption of morphine on the H, NH_4, Na and Ca form of espatit. Dalev and Illieve (56) used ion exchangers to isolate morphine from dry capsules of the poppy heads. Brekke and others (57) showed that with Duolite A-7 about 16 % greater yei yield was obtained from 2-butanol extract of poppy meal than the distillation method. Romancsuk (58) used Ku-1 (Ph-OH-CH_2O resin containing SO_3H and phenolic OH groups) and Ku-2 (sulphonated copolymer of styrene and divinyl benzene) exchangers for recovering morphine from neutralized dilute mother liquors. The Ku-2 resin was more useful, being stable in alkaline solution. The sodium form of Ku-2 was more useful than the ammonium or hydrogen form. The yield of morphine was 76 % of the morphine content in the mother liquor, the concentration of morphine in the eluate was 0.6-0.7 % . Romanchuk and others (59) have used Ku-2 resin for the recovery of morphine from waste liquors in the production of codeine, containing 0.07 - 0.01 % of morphine and about 17 % of mineral impurities. The eluate contained 0.6 to 0.7 % morphine. The alkaline eluate was treated with dilute (1 : 1) sulphuric acid to pH 4-5, filtered,evaporated and morphine precipitated with ammonia. Resins were used without

deterioration for three years. Lee (60) proposed a general method for the isolation of alkaloids in relatively pure form, from plant materials. This consisted in precipitating the alkaloids as insoluble reineckates, from which the free alkaloids could be recovered by passing an acetone solution of reineckates through ion exchange column. The method was adopted for isolation and quantitative estimation of papaverine from opium and strychnine from nuxvomica.

Oberst (61) used synthetic Zeolite to free morphine from substances which interfere with its colorimetric determination in the urine of morphine addicts. Morphine was extracted by the procedure of Pierce and Plant and the final residue was dissolved in water and sorbed on exchanger which was washed three times to remove soluble impurities. The concentration of morphine in the exchanger was determined colorimetrically. Jindra (21) sorbed the alkaloidal salt dissolved in alcohol by passing through a column of Amberlite IR-4B synthetic resin. The elution was done with a little alcohol at 50^{0}C and the effluent was titrated with 0.1 N hydrochloric acid using a mixture of methyl red and methyl blue as indicator. The method was applied to opium, nux vomica tinctures and a number of other alkaloids. Jindra and Pohorsky (62) described the determination of alkaloids depending on ion exchange chromatography with Amberlite IR-4B. Determination of codeine phosphate, morphine hydrochloride and a number of other alkaloidal salts have been described. Baggesgaard

and others (63) carried out determination of alkaloids in their salts by use of strongly basic resin Amberlite IRA-400. The eluted base was titrated with 0.1 N hydrochloric acid in 50 % ethanol medium with bromophenol blue indicator. However, unsatisfactory results were obtained for morphine and homoatropine-methyl-bromide. Levi and Farmilo (64) used Amberlite IR-4B in the free base form for the estimation of a considerable number of narcotic salts and tablets made from them. The precision of these estimations was within 1.6 % by ion exchange method. The method was applicable to the narcotics as purchased from the manufacturer or in pharmaceutical preparations. Jindra and Motl (65) separated and evaluated morphine and other alkaloids from tablets and drugs. Codeine and morphine were extracted with 50 % ethanol and were separated on Amberlite IRA-400 and titrated with 0.1 N hydrochloric acid potentiometrically. Gundersen and others (39) used Dowex-2 (strongly basic anion exchange resins) for the assay of tablets containing alkaloids. They tabulated results for atropine sulphate, cocaine hydrochloride , codeine phosphate, ephedrine hydrochloride, lobeline hydrochloride and a comparison has been made with those obtained by official assay methods. Grant and Hilty (66) separated morphine from codeine by strongly basic quaternary ammonium type anion exchanger. Because of the phenolic character of morphine, it exchanged with the resin while codeine was washed through the column and determined by titration. Morphine was then removed with dilute acid and determined spectrophotometrically. Hamlow and others (67)

studied the behaviour of morphine on Amberlite IR-120 and IRA-400. These two resins showed promising prospects for the exact determination of morphine in opium. Blaug (68) separated morphine from atropine by ion exchange chromatography. Morphine sulphate and atropine sulphate could not be separated on a weakly basic resin. Amberlite IRA- 410 did sorb all anions but did not sorb morphine sulphate quantitatively, but by using a two bed column including Amberlite IR-4B, a quantitative separation was effected. Morphine sulphate could be determined spectrophotometrically in the presence of atropine sulphate without elution of column. Morphine could be recovered quantitatively by elution of the column with 1 N sulphuric acid. Mariari and Vicari (69) investigated the use of several types of ion exchange resins for the separation of morphine from opium. Amberlite IRA-400 H^+ and IR-4B OH^- showed no sorption while it was completely sorbed by IRC-50 Na^+, from which it was eluted with 0.1 N hydrochloric acid or 1 N acetic acid. Morphine was determined colorimetrically at 520 mμ. Separation of morphine from codeine and the determination of the former by ion exchange was carried out by Shemyakin and Karpore (70). 0.02 N aqueous solution of morphine and codeine was chromatographed on the hydrogen form of an ion exchanger. Morphine sorbed on the column was eluted by 0.74 N ammonium hydroxide and determined colorimetrically by condensation with diazosulphanilic acid and by refractometric analysis. Out of the different solvents tried for the elution of codeine,

only trichloroethylene gave a positive test for codeine in the eluant. Asahina and Ono (71) determined meconic acid and morphine in opium, based on selective sorption of meconic acid on an ion exchange resin. Methanolic (75 %) solution of opium was passed through an Amberlite IRA-411 (chloride form) column (mobile phase 75 % methanol). The meconic acid free effluent was then poured on to a column of Amberlite IRA-411 (OH^- form) and morphine eluted with 0.5 N hydrochloric acid (recovery 98.1 %) and determined spectrophotometrically at 765 mμ. Meconic acid was eluted from the resin with 4 N hydrochloric acid (recovery 97.9 %) and determined colorimetrically at 765 mμ. Niyogi and others (72) used Dowex-50X8 to separate codeine and strychnine in the extracts of dog liver. The 1 x 7 cm. column was washed with 4 N, then with 1 N hydrochloric acid and the extracts applied to the column as a 1 N hydrochloric acid solution. After washing the column with 1 N hydrochloric acid, codeine was eluted with 250 cc. 4 N hydrochloric acid and strychnine with 400 cc. Recovery of the two alkaloids from the mixed liver was 62 % and 38 % and from liver extract 92 and 95 % respectively. Morphine was also retained by the column and eluted with hydrochloric acid of the appropriate normality. Tompsett (73) used Dowex 50 X 12 (200-400 mesh) for the separation of alkaloids from extracts of animal tissue. Liver tissue (100 grams) was macerated in 500 cc. of water and 100 cc.of 10 N hydrochloric acid was added. The mixture was heated to boiling and held in a boiling water bath for one hour. Then the mixture was diluted to one litre with water and filtered.

The filtrate was passed through a column of Dowex-50 X 12 (200-400 mesh) cation exchange resin. The column was eluted with 300 cc. of 6 N ammonium hydroxide solution ; morphine was recovered in this fraction. The column was then washed with 200 cc. of water and 200 cc. of 1 N hydrochloric acid ; codeine, brucine or strychnine were then eluted with 8 N hydrochloric acid. Morphine was extracted from the aqueous ammonia eluate with chloroform / isopropanol and then quantitatively determined by colorimetric method. Eluates of codeine, brucine and strychnine were neutralised by sodium bicarbonate before its quantitative determination by colorimetry . Romanchuk and Demina (74) showed that codeine could be sorbed from a solution containing 5-10 grams/litre and upto 15 times as much of mineral salts by sulphonic acid resin in the sodium form, optimal pH 7. Codeine was eluted with 1 N ammonia in 75-80 % isopropanol. After removal of ammonia by heating in vaccuoto 50°C the residue was acidified with sulphuric acid (1 : 1) and evaporated to obtain 80 % codeine sulphate. Carboxylic acid resins were not effective. Clair (75) has described the separation and determination of morphine and thebaine by passing the solution through a column containing a basic ion exchange resin. Morphine was quantitatively removed and was eluted from the column with 0.1 N hydrochloric acid and determined colorimetrically. The absorbance read at 450 mμ conformed to Beer's law.

Dvorakova and Tonko (76) used Catex for the sorption of morphine and found that with smaller particle

size the sorption was better. Van Elten (77) studied the effects of degree of crosslinkage of the resin and of the pH and ionic strength of the eluant on the elution of morphine from strongly acidic and strongly basic ion exchangers (Dowex-50 and Dowex-1). Dowex-50 containing 1,2,4,8 and 16 per cent of divinyl benzene were used. Columns, 8 mm. in diameter, were filled to a depth of 4 cm. with 0.2 to 0.6 gram of ion exchange resins. 10 cc. of solution containing morphine sulphate were pipetted on these columns. After morphine was exchanged on the column, it was washed with 5 to 10 cc. of water. The column was eluted with 50 cc. of eluant (caustic soda solution or ammonium hydroxide), collected in a volumetric flask and morphine determined in suitable aliquots by colorimetric method. Complete elution was obtained from the 1,2 and 4 percent crosslinked cation exchange resins with either ammonium or sodium hydroxide but incomplete elution was obtained from the 8 and 16 per cent crosslinked resins. Conditions for complete elution from the anion exchange resins were more restricted. Only for the 1 % crosslinked resin, with acetic acid as the elutriant, was quantitative elution always obtained. Results showed that as the degree of crosslinking of the exchange resin increased above a certain minimum (4 % with Dowex-50 and 1 % with Dowex-1) morphine was not completely eluted. The results indicated that the following factors were critical in determining conditions for complete elution of organic ions from ion exchange resins : (a) degree of crosslinkage of the resin, and the size of the ion (b) pH of the eluant and

(c) effect of ionic concentration of the eluant on volume changes of the exchange resin.

1.3.e. STRYCHNOS ALKALOIDS :

Lloyd (12) observed that strychnine, cocaine and other alkaloids were purified by mixing with hydrous magnesium silicate in water, filtering and removing the alkaloids from silicate by dissolving the former in chloroform or alcohol made alkaline. The solution after filtration and removal of the volatile solvent left the alkaloid in crystalline or colloidal form. Smith (78) studied the reaction between bentonite and salts of organic bases such as strychnine, nicotine and piperidine and concluded that bentonite entered into base exchange in chemical equivalence.

Jindra (21,62) used Amberlite IR-4B a weakly basic anion exchanger for the determination of alkaloids such as strychnine nitrate, brucine and ipecac, opium and nux vomica tinctures. Larger quantities of active constituent in galenical preparations used in a semimicro method, enabled a more accurate result. Yoshino and Sugihara (79) separated nicotine, strychnine and brucine by (ion exchange chromato--graphy) sorbing them on a column of weakly acidic exchange resin (ammonium form of Duolite CS-101) and eluting fractionally with 0.1 - 1 M ammonium chloride in steps. With H - R form of the resin the separation of strychnine and brucine was incomplete. With Na - R form these two hardly eluted. With K - R form the alkaloids were not retained

quantitatively by the column. Same way, Yohimbine and strychnine were separated (80) chromatographically with a weakly acidic cation(NH_4-R) exchanger (Duolite CS-101) and eluting with 0.1 M and 1 M ammonium chloride respectively. Na-Rresin could be used (0.1 M sodium chloride for elution) tosseparate strychnine from yohimbine. Hydrogen form and potassium form of the resins were not suitable for this separation. Yoshino and Suguhara (26) separated quinine and strychnine by sorption on weakly acidic cation exchange (NH_4-R) resinssuch as Duolite CS-101 or Amberlite IRC-50 and the subsequent elution with 0.2, 0.3 or 0.1 N ammonium chloride respectively. H-R exchangers could also be used but then a large amount of eluting solvent was required to separate strychnine. Kum Tatt Leo (60) described the isolation and quantitative estimation of strychnine from nux vomica and of papaverine from opium. A general method proposed for the isolation of alkaloids in relatively pure form, from plantmaterials, consisted in precipitating alkaloids as insoluble reineckates, from which the free alkaloids could be recovered by passing an acetone solution of reineckates through an ion exchange column. Watanabe (81) used weakly acidic cation exchanger in the ammonium form to separate berberine and strychnine. The elution was done with 1 N ammonium chloride for strychnine and 0.5 M sodium carbonate for berberine. Kamp and Post (82) used ion exchange method for the determination of strychnine in seeds of strychnos nuxvomica, strychnine extracts and in tincture of strychnine . Brucine and strychnine in 10 cc. of 2 N hydrochloric acid were washed on to a column containing anion exchanger,

Dowex 1 X 2 (100-200 mesh) (ferrocyanide form). The column was left standing over-night and brucine was eluted with 300 cc. of ammonium chloride. Strychnine was eluted with 300 cc. of 1 N ammonium hydroxide in 96 % ethanol and was thenextracted with chloroform and determined titrimetrically.

Yoshino and Sugihara (83) studied the influence of ionic size upon the elution curve. They observed that alkaloids sorbed by a weakly acidic cation exchange resin (Amberlite IRC-50) were eluted less with higher concentrations of hydrochloric acid because of the shrinkage of the resin retarding the diffusion of alkaloids through the network structure of the resin. Low molecular weight alkaloids (nicotine, caffeine and ephedrine) were easily eluted by 6 N hydrochloric acid but high molecular weight alkaloids (strychnine, brucine and berberine) were eluted only slightly. The intermediate molecular weight alkaloids (cinchonine, cinchonidine and quinine) were eluted about 50-80 %. Yoshino, Nagara and Sugihara (84) observed that the weak acid type exchangers ($R-CO_2M$) took up strychnine nitrate depending upon the kind of cation in the order, Li, Na, NH_4, K, Mg, Ca, Ag and Cu. The ease with which the alkaloid was eluted from the exchanger in water was not proportional to its exchange capacity but was probably governed by pH of the effluent and the degree of dissociation of the base at the particular pH. The specificity of the resin was a determining factor.

1.3.f. TOBACCO ALKALOIDS :

Smith (78) studied the exchange between bentonite and the salts of organic bases such as nicotine and strychnine and observed that equivalent amounts of organic bases were exchanged, when saturation could be reached. Higgins (85) took a patent for the preparation of horticultural poisons by absorbing nicotine from the solution of base salt on a carbonaceous exchanger. Mannelli (86) treated nicotine and its hydrochloride and sulphate with natural and activated bentonite, which did not lose the base on dispersion in water, if the nicotine absorbed was less than about 4 %. These materials were proposed as agricultural insecticides. Riley (87) patented a process for sorbing nicotine in insoluble and non-volatile form on a carbonaceous exchanger. Tiger and Dean (88) described the use of ion exchangers for the recovery of nicotine from tobacco waste extracts. The solution was passed on a carbonaceous exchanger and normal hydrochloric acid was used to elute the nicotine as a salt.

Kingsbury, Mindler and Gilwood (89) used carbona--ceous ion exchanger for the recovery of nicotine from the gases evolved from tobacco driers. The drier gases were passed through a scrubbing tower, the water being recirculated to build up the concentration of nicotine. The solution was then passed through the hydrogen form of the cation exchanger. The nicotine was eluted from the exchanger by one s tep recovery process or used directly as insecticide. Almost

100 % of the nicotine was removed from the drier waste gases. Nagasawa and Sakurai (90) patented a method for sorbing nicotine on cation exchange materials. Niwa (91) took a patent for the use of ion exchangers containing nicotine directly as insecticides. The nicotine could also be liberated with an alkali and extracted with a solvent.

Romanchuk and Demina (92) have given a method for extracting anabasine, spherophysine and methyl caffeine from vegetable raw materials and from other solutions by ion exchange. An aqueous extract, from anabasis aphylla, brought to a pH of 8.4 by adding alkali, was sorbed on a series of columns, filled with the hydrogen form of Ku-1 resin. All the columns, when saturated with anabasine, were eluted with 5 % ammonia in 20 % isopropanol. Evaporation of the solvent left concentrated solution of anabasine base. Similarly spherophysine was extracted from aqueous extracts of sphaerophysa salsula by ion exchange on the hydrogen form of Ku-2 resin, using a number of columns. Elution was achieved with a mixture of 3 % sodium carbonate, 1 % sodium hydroxide and 30 % isopropanol.

Kawabe and others (93) have studied the sorption rate of nicotine by sodium form of cation exchangers (two of sulphonic acid type and four of carboxylic acid type) for 0.2 M solution of nicotine hydrochloride and have discussed the results in relation to the structure of the resin.

1.3. g. TROPANE ALKALOIDS

Applezweig (15) employed a sulphonated coal type cation exchanger for the isolation of atropine from the acid extracts of raw material. To liberate the alkaloid from the column, ammonical alcohol was used as the regenerant and elution solvent. This technique was also applicable for the isolation of scopolamine and morphine. Sussman and others (16) tried the use of non-aqueous solvents such as ethanol, acetone or chloroform for the removal of liberated alkaloid base from the column. Recoveries of scopolamine from datura plants and totaquine from cinchona barks could be effected. Vota and Yufera (94,95) studied the extraction of belladona alkaloids from the plants using a cation exchanger. Alkaloids were taken up by the exchanger at low pH, and were displaced with 0.5 N sodium hydroxide solution in 96 % ethanol and purified after distilling the solvent. The recovery of alkaloid was reported as 80-85 % . Applezweig and Nachod (96) have studied the interaction of atropine sulphate from datura stramonium plant with cation exchanger. Sullivan and Martin (97) demonstrated the sorption of atropine by anion and cation exchange resins and discussed the basic mechanisms involved. In vivo studies with atropine sulphate, demonstrated the removal of compounds of this type from gastric and intestinal content. This reduces the accute toxicity. Kuznetsov and Ioffe (98) studied the sorption capacities for atropine and acetyl choline in their mixtures, by using exchanger from $CH_2=C(Me).COOH$, $CH_2=C(Me).CO.NH.CH_2.COOH$ and $CH_2=C(Me).CO.NH.CH_2-CO.NH-CH_2.COOH$.

Atropine despite its higher molecular weight, had a higher affinity and sorption capacity of the ionites increased as amide groups were introduced. Stucin (99) has described the application of ion exchange resins to the isolation of L-hyoscyamine from the folium belladonna extracts. Bozhko (100) obtained scopolamine by sorption on ion exchange resins. Seeds of datura innoxia containing 0.15 % of scopolamine were ground and extracted with 0.25 % sulphuric acid and was sorbed (95 %) on cationite Ku-1 at pH 5.0 to 6.0 by passing the extract over the resin. Complete desorption was attained by mixing the resin with 1.5 % of ammonia in ethylenedichloride ethanol (4 : 1), three times for 12-16 hours. Scopolamine was obtained as hydrobromide salt in 65 % yield.

Jindra and Pohorsky (21,22,62) described the methods depending on ion exchange chromatography with Amberlite IR-4B (weakly basic anion exchanger) for the determination of atropine sulphate, scopolamine hydrobromide and a number of other alkaloidal salts. Detailed descriptions of apparatus, reagents, preparation of t he ion-exchange columns and general micro and semi-micro methods of assay were given. The methods were applied to belladona herb, hyoscyamus herb, nux vomica seeds, cinchona bark etc. and their preparations. Baggesgaard and others (63) did not get satisfactory results with homo-atropine-methyl bromide and other alkaloids by using a strongly basic anion exchanger Amberlite IRA-400 for the direct determination of alkaloids in their salts. Bjorling and Berggren (101) made use of

synthetic sodium alluminium silicate, Decalso, in the analysis of tropa alkaloids in their salts, tablets or extracts. Tropa alkaloids were sorbed quantitatively by activated Decalso-F from wate r and some organic solvents. They were completely desorbed by moderately strong solutions of acids (0.2 N hydrochloric acid) or salts (25 % potassium chloride). This applied to tertiary and quaternary alkaloids. Sjostrom and Randella (102) separated atropine and scopolamine from morphine on a column of Dowex-1 and determined colorimetrically. They found that when solutions of relatively high methanol concentrations were used, the tropane alkaloids were not hydrolysed by the strongly basic resin. Yoshino and Sugihara (103) attempted the separatory determination of scopolamine, homoatropine and atropine by ion exchange chromatography using a weakly acidic cation exchange resin. A buffer solution prepared from boric acid, lithium chloride and lithium hydroxide was added to the hydrogen form of the weakly acidic exchanger. Separation was best achieved when the swelling of the exchanger became about 1.17 times by addition of the buffer solution to the exchanger. The alkaloids were eluted from the exchanger with 0.2 M lithium chloride (scopolamine) and 1 M potassium chloride or sodium acetate (atropine). Strongly acidic cation exchange resin was not suitable for this purpose. Jung and Petrikova (104) studied the determination of N-(p-benzyl) atropine bromide and its administration forms. N-(p-benzyl) atropine bromide in 70 % methanol was passed through a column of Dowex 50 X 2. Neutral and acid substances present

in the administration forms were eluted with 70 % methanol. N-(p-benzyl) atropine bromide was eluted with 0.1 N hydrochloric acid in 70 % methanol at 50° and determined spectrophotometrically at 275 mμ. Khanna and others (105) reported the occurance of tropine and pseudotropine in withania somnifera. An ethanol extract of the root was purified by passing through a column of Amberlite IRC-50 (Na form). The alkaloid fractions were combined and chromatographed on a column of powdered cellulose and the upper fractions were chromatographed on basic alumina. Tropine and pseudotropine were isolated and identified by their infrared spectra. Watanabe (106) attempted the separation of berberine, atropine and scopolamine. An aqueous solution containing the hydrochloride, sulphate and hydrobromide of the three alkaloids, respectively, was passed through a column of Duolite CS-101 (NH_4 form) for sorption of the alkaloids. A portion of the scopolamine was eluted un-sorbed and the residual portion of the same, in the column was removed by washing with water. Atropine was then liberated by treating the column with 0.2 N ammonium chloride and finally with 1 N sodium carbonate for liberating the berberine. Each alkaloid thus liberated was determined by amperometric titration. The recovery was over 85 % for berberine and atropine and over 95 % for scopolamine. Staub (107) obtained hyocyamine, scopolamine and atropine from the alkaloid fraction isolated from Mandragora root, by partition and paper chromatography. Amberlite IRA-400 (Cl form) was used for further purification of the alkaloids.

1.3. h. MISCELLANEOUS ALKALOIDS :

Lloyd (12) purified cocaine with magnesium silicate. Jindra and Pohorsky (62) estimated arecoline, cocaine ; and pilocarpine with ion exchangers. A patent was taken by establishments Roques (108) for the extraction and purification of alkaloids by ion exchangers. Alkaloids were extracted and purified in an aqueous medium by means of cation exchangers such as sulphonated coal or synthetic resin containing sulphonic or carboxylic groups. The leaves of the drug plant were macerated in an acid bath, the liquid obtained was passed through an exchange column and the effluent acid was recycled. The complete extraction required a few hours. Finally the alkaloids were eluted. Thus 5 kilograms crushed coca leaves were macerated for 1-3 hours in 30-50 litres of 0.1 N hydrochloric acid. The liquid obtained was freed from suspended and colloidal matter and passed at a rate of 20-30 litres / hour through a column. The alkaloid free effluent (pH 1) was recycled untill complete extraction of the drug took place. The resin was washed with water and the alkaloids eluted with two litres of 10 % ammonium hydroxide. The ammonia solution was extracted with benzene and the solvent was recirculated several times until saturated. This operation was repeated until complete removal of the alkaloids from the column was obtained. The benzene solution was extracted with sulphuric acid and the extract was purified to give pure alkaloid in 89-93 % yield (based on the alkaloid content of the plant). A number of alkaloids could be eluted with 10 % aqueous calcium

chloride giving the corresponding hydrochloride salts. Florea and Demetrescu (108 A , 108 B) applied the ion exchange methods for the analysis of alkaloids. The hydrochlorides of procaine, cocaine, etracaine and dionine were studied by using the micro and macro ion exchange method with Amberlite IR-4B, anionic resin and with various types of alluminium oxides. By passing the solution of an alkaloid salt through an anionic column, the anion was retained by the resin and in the effluent the liberated base could be titrated. The indicator was a mixture of equal amounts of an alcoholic solution of methyl red and an aqueous solution of methylene blue, producing a more exact colouring than that cited in the literature. The principle of work with alluminium oxides was the same. The method gave reproducible, accurate results.

Bashour (109) used the anion exchanger (Amberlite IR-4) to remove excess hydrochloric acid from the mother liquors for the crystallisation of d-tubocurarine chloride.

Sugihara and Yoshino (110) separated caffeine (with a relatively small dissociation constant) from strychnine, brucine and quinine (with relatively large dissociation constant) by passing through a resin layer of Amberlite IRC-50 (sodium form), at pH above 6.2, which sorbed all the alkaloids except caffeine.

Edwards (111) fractionated an amorphous commercial preparation of mixed veratrum alkaloids. The commercial preparation was freed of non-tertiary bases and placed on Dowex-50 ion exchange column in acetic acid solution. The

elution was done with ammonium acetate - acetic acid buffer solution. Activity approaching that of neogermitrine or germitrine was observed in some fractions at pH 5.0 - 5.2 but in none at pH 4.5.

Okamoto and others (112) reported that bases of aconite roots could be obtained in good yield, in a short time by continuous extraction with Amberlite IRC-50. Ochiai and Okamato (113) used Amberlite IR-120 to convert the potassium salt to acid in the synthesis of ignavine, an aconite alkaloid.

Romanchuk and Demina (92) extracted spherophysine from the aqueous extract of sphacrophysa salsula. The latter was chromatographed on hydrogen form of Ku-2 resin, several columns being used. These were eluted with a mixture of 3 % sodium carbonate, 1 % sodium hydroxide and 3 % isopropanol.

Berlage and others (114,115,116 and 117) have used anion exchangers to convert the iodide salt to the chloride salt in connection with calabsch alkaloids and to deionise the solution.

Robertson (118) used Amberlite IR-4B resin to prepare L (-) pipecolic acid from L(-) pipecolic acid (-) bitartarate while establishing an absolute configuration of (-) homostachydrine, a new alkaloid, isolated from alfalfa.

Lewandowski and Witkowski (119) described a method for determining total alkaloids in yellow lupine (lupinus luteus) by cation exchange paper. Ten grams of yellow lupine powder (obtained by drying seeds at 60^{o}) was treated with 10 cc. of 10 % potassium hydroxide and left for

twenty minutes. Twenty grams of kieselguhr was added batch wise and the mixture was powdered. Twenty grams of chloroform were then added and left for twelve hours, with shaking after every half an hour. This was filtered and washed with chloroform and 0.1 N perchloric acid in four-fold excess with respect to alkaloids. Chloroform was then evaporated and the aqueous acid solution was concentrated upto 1 cc., neutralised with potassium hydroxide solution to slightly yellow in the presence of dinitrophenol. 1 cc. of ethanol was added and left in the cold for half an hour. This was filtered, washed with 80 % ethanol and diluted to 5 cc. 0.5 cc. of this solution and standard solutions (0.2, 0.4, 0.6 and 0.8 cc.) were placed on a strip of chromatographic paper. This was washed with 0.1 cc. of distilled water after sorption and the chromatogram was treated with Dragendorff reagent.

Patt and Winkler (120) prepared and determined solamine by ion exchange. Alcoholic extract of the powdered drug was treated with Duolite C-10 resin, washed with alcohol till the eluates were colourless and the alkaloid recovered with 10 % ammonia in alcohol. The eluate was evaporated to dryness,solamine was then estimated from this, by paper chromatography.

Zewisza and Kuczynski (121) isolated ergot alkaloids by cation exchanger. Ergot alkaloid acetates are soluble in trichloroethylene and this solvent, when acidified with acetic acid, could be used for extracting the ergot from crude material. 20 kilograms of ground dry

ergot (0.04 % alkaloid content) were subjected to eight percolations, each time with 20 litres of the solvent (acetic acid added). The combined extracts were stirred for two hours with 400 grams of cation exchanger and two litres of water and filtered. Sorbed ergot alkaloid was converted into the free base by stirring with 10 % sodium chloride and eluted with organic solvent, preferably acetone, to yield, after the usual working up, 8 grams of ergot of 90 % purity.

Yoshino and Suguhara (26) extracted lycorine by ion exchange. Lycoris radiate bulbs were chopped to pieces, then extracted with M-acetic acid and freed from tannin and other impurities with lead acetate. After removing the excess lead acetate with dilute sulphuric acid, the purified extract was passed through a column of hydrogen form of exchange resin (Dowex-50). The sorbed alkaloids were eluted with ammonical ethanol (1 : 1) and the eluate was passed through a column of strongly basic anion exchanger (Dowex-1). From the column the colouring matter, sekisamoline, was eluted with 0.1 M ammonium chloride. The residual eluate was passed through a column of weakly acidic (hydrogen form) exchanger (Duolite CS-101) and lycorine was eluted with 0.05 M tartaric acid and sekiamine, lycaromine (pseudohomolycorine) and lycorenine with ammonical ethanol. Kori and others(122) treated the aqueous extract of corn of lycoris radiata with Amberlite IRC-50 to sorb the alkaloids and to separate from non-alkaloid substances. The alkaloids were liberated with ammonical ethanol, the ethanol was removed

and the residue was passed through double columns of Celite, with phosphate buffer of pH 7 as the stationary phase. The column was eluted with chloroform to separate lycorine. The later was determined spectrophotometrically.

Shostenko and Simon (123) purified lobeline, by passing the aqueous acid extract of the plant (at pH 1.9) through an ion exchanger which retained the alkaloid. This was washed with an acid or alkali combined with a 1 : 9 mixture of alcohol and chloroform. Simon and others (124) investigated the effect of pH, granules of phenolsulphonic acid cation exchange resin, esparite-1 and contents of total extracted substances on sorption of lobeline from its extracts. Under optimim conditions, the degree of saturation of the resin with the lobeline was 1.2 - 2.2 %. After desorption with 1.5 % solution of ammonia in a 9 : 1 chloroform-ethanol mixture, the concentration of the extract in the eluate was increased by 20 times. From the lobelia inflata, lobeline was isolated in 60 % yield.

Mattocks and others (125,126) used Dowex-50 (H form) for the extraction of indicine alkaloid from H. Indicum at room temperature with ethanol. Elution was done with 0.8 N aqueous ammonia, only by this method of extraction, indicine could be readily obtained in crystalline form, from Heliotropium Indicine.

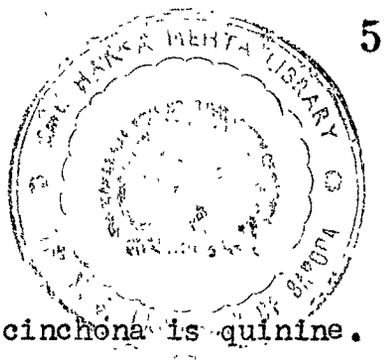
Watanabe (127) determined berberine sulphate with weakly acidic cation exchange resin. 5-25 cc. of 0.3 % berberine sulphate solution was passed through a column of Amberlite IRC-50 or Duolite CS-101 (Na or NH_4 form

100-200 mesh) at 0.5 - 1.0 cc./min., washed with water, the filtrate and the washings were collected and acidified with 1-2 cc. of 0.1 N HCl. Barium chloride solution was added after heating on steam bath and further heated for 20-30 minutes more. This was then cooled and 2.5 cc. of 1 : 1 methanol and concentrated ammonium hydroxide was added and 5 drops of phthalin complexone and titrated with 0.01 M EDTA until violet colour had disappeared. Barium chloride alone was titrated with 0.01 M EDTA for blank. Watanabe (81) used weakly acidic cation exchanger in the ammonium form to separate berberine and strychnine. The elution was done with one M-NH_4Cl for strychine and 0.5 M Na_2CO_3 for berberine. Watanabe (128) studied the behaviour of berberine on cation exchange resins. Berberine and hydrochloric acid were shaken with Amberlite IRC-50 and Duolite CS-101 and the amount sorbed berberine was determined. Weakly acidic resins sorbed berberine more readily and the amount was maximum with ammonium form of resins. Monovalent cation resins were more effective than the bivalent cation resins. Elution from a strongly acidic resin was difficult. Elution from weakly acidic resins could be done by using hydrochloric acid, sodium sulphate, sodium acetate, sodium carbonate, sodium hydroxide, alcoholic ammonia or magnesium sulphate according to the type of resin. Sodium carbonate was found to be the best eluant when the resin was of sodium form. Watanabe and Zasshi (129) separated and determined berberine in Phellodendron alkaloids. The alkaloids were extracted by shaking the Phellodendron powder with a weakly acidic cation

exchange resin (Duolite CS-101, NH_4 form) in 50 % methanol with heating. After separating the powder and the resin by back-wash technique, berberine was separated from the alkaloids in such a manner that when N NH_4OH, N NH_4Cl and N Na_2CO_3 were passed through the resin in this order, the last effluent contained the berberine. After acidifying this effluent with sulphuric acid, berberine was determined by amperometric titration. The yield was about twice than that obtained by conventional techniques.

Briggs and others (130) partially purified the basic fraction of the flowers of sophora by absorption on Amberlite IRC-50 resin and displacement by 0.1 N ammonia to give a mixture of 8 grams of crude alkaloids. Le gall (131) isolated a new alkaloid, raugalline from rauwolfia serpentina. Two litres of alkaloid sulphate solution (containing 11.48 grams of total alkaloids) were passed through 300 grams of column of cation exchange resin (at pH 6.5) with a speed of 5 volumes/hour. The column was eluted with aqueous ammonia and then with chloroform to obtain 5.4 grams of alkaloid. Yield of raugalline was 600 mg. Robinson and others (132) purified the crude salt with Amberlite IRA-400 (chloride form) for the preparation of non hypertensive sedatives derived from methyl resperate (Rauwolfa Alkaloids).

Oletta (133) extracted funtumidine and funtamine in a combined form with latex or chlorophyll from the whole plant and after purification, was chromatographed on alumina. The two compounds were separated and purified on an ion exchange resin.



1.4 CINCHONA ALKALOIDS : (134)

1.4.a. Introduction :

The most important alkaloid of cinchona is quinine. In addition about 20 other alkaloids have been isolated from cinchona (Table 1.3) of which cinchonidine, quinidine and cinchonine are important. The alkaloids chiefly exist as salts of quinic and cinchotannic acids and their relative concentrations vary in different species. The bark which is known to the trade as druggist's bark has a quinine content of 1.8 to 2.0 %.

In the early years of planting, the total alkaloids were used for medicinal pumposes under the name of quinetum. In India quinetum was gradually replaced by cinchona febrifuge consisting of the residual alkaloids left after the removal of quinine. The Malaria Commission of the league of Nations redefined quinetum as a mixture of equal parts of quinine, cinchonidine and cinchonine and introduced a new product called totaquine or totaquina which is defined in the B.P. as containing not less than 70 % of crystallisable cinchona alkaloids-quinine, cinchonidine, cinchonine and quinidine of which not less than one fifth is quinine. Cinchona febrifuge varies greatly in physical character and composition, for use as an antimalarial drug. It should be of the same standard as totaquine.

1.4.b. Extraction :

The greater part of the world's production of cinchona barks is employed in the manufacture of quinine.

Table 1.3

Cinchona Alkaloids

Name of the alkaloid.	Formula	m.p. ^{o}C	Dextro(D) or Laevo(L) Rotatory.
Quinine	$C_{20}H_{24}O_2N_2$	175	L
Quinidine	$C_{20}H_{24}O_2N_2$	173.5	D
Cinchonine	$C_{19}H_{22}ON_2$	264	D
Cinchonidine	$C_{19}H_{22}ON_2$	204.5	L
Quinicine	$C_{20}H_{24}O_2N_2$	Vicous Liquid	D
epiQuinine	$C_{20}H_{24}O_2N_2$	011	D
epiQuinidine	$C_{20}H_{24}O_2N_2$	113	D
Cinchotine	$C_{19}H_{24}ON_2$	267	D
Hydrocinchonidine	$C_{19}H_{24}ON_2$	232	L
Hydroquinine	$C_{20}H_{26}O_2N_2.2H_2O$	173.5	L
Hydroquinidine	$C_{20}H_{26}O_2N_2.2\frac{1}{2}H_2O$	169.5	D
Quinamine	$C_{19}H_{24}O_2N_2$	185.6	D
Conquinamine	$C_{19}H_{24}O_2N_2$	121	D
Paricine	$C_{16}H_{18}ON_2.\frac{1}{2}H_2O$	136	-
Dicinchonine	$C_{38}H_{44}O_2N_4$	40	D
Diconquinine	$C_{40}H_{46}O_3N_4$	-	D
Javanine	-	-	-
Aricine	$C_{23}H_{26}O_4N_2$	188	L
Cusconine	$C_{23}H_{26}O_4N_2.2H_2O$	110	L
Cusconidine	-	-	-
Cuscamine	-	218	-
Cuscamidine	-	-	-

For this purpose finely powdered bark is mixed with about one third of its weight of sifted slaked lime and a 5 % aqueous solution of caustic soda. The mixture is extracted under stirring in steam jacketed vassels, with high boiling kerosene. Three successive extractions are made. The mixed extracts are shaken with sufficient hot, dilute sulphuric acid to convert the alkaloids into sulphates. The oil is separated while hot and then neutral aqueous solution cooled when quinine sulphate separates out and is subsequently purified by recrystallisation from aqueous solutions after decolorising with animal charcoal. The mother liquor containing the other alkaloids is treated with caustic soda and the precipitate of quinidine,cinchonidine and cinchonine extracted with dilute alcohol which dissolves the first two,leaving cinchonine behind ; the former two can then be separated by means of their neutral tartarates, that of quinidine being considerably more soluble.

The method adopted by the Bureau of Science, Philippines, is to percolate to exhaustion with alcohol, a mixture of finely powdered bark, lime and water. The percolate is distilled to recover the alcohol, and the gummy residue treated with sulphuric acid to dissolve the alkaloids. The solution is decolourised with charcoal, filtered and the mixed alkaloids precipitated by the addition of sodium hydroxide.

An ion exchange process for the separation of alkaloids from cinchona barks poor in alkaloids has been developed and was successfully employed in the U.S.A. during the war period. This sorption procedure has been

recommended for adoption in India for the recovery of alkaloids from the waste material left after the separation of barks. On the basis of figures for quinine manufactured in 1944-45, it is computed that the wastage of cinchona alkaloids from Indian plantations is about 69,679 lbs. a good part of which is recoverable by the application of the sorption process.

The estimation of individual alkaloids in mixtures has assumed importance since the therapeutical recognition of totaquina. A number of methods based on differences in the solubilities of salts and polarimetric, colorimetric, turbidimetric, fluorometric and chromatographic methods have been developed.

1.4.c. Uses :

The oldest and the most important use of quinine is for the treatment of malarial fevers. Quinine continues to be effective in spite of its prolonged used. Quinine possesses marked bactericidal action and until the advent of sulphanilamide derivatives, quinine and certain of its derivatives were being employed in the treatment of baterial infections. Thus β-hydroxy-ethyl apoquinine and sulphapyridine give equal procetection to mice against virulent pneumococci and the drug has been successfully used in large number of cases of human pneumonia. Quinine has been used as a sclerosing agent in the treatment of internal haemorrhoids and vericose veins.

Quinine added to aquaphor, protects the skin against sun burn.

Quinine sulphate is the most important salt of quinine used in therapy. Other salts of quinine such as acetyl salicylate, arsenate, benzoate, citrate, dihydrobromide, dihydrochloride, disalicylo-salicylate, ethyl carbonate, glycerophosphate, lactate, phosphate, salicylate, tannate and valerianate are recognised by the B.P.C. Quinine ethyl carbonate and tannate are almost tasteless and are sepecially useful for children. Quinine with urea hydrochloride is used as a local anaesthetic. Practically tasteless compounds are obtained by combining quinine with an acid mixture derived from camphoric acid and an aromatic alcohol or a terpene alcohol or a phenol.

In addition to their use in pharmacy, quinine and quinidine and their derivatives are utilised in insecticide compositions for the preservation of fur, feathers, wool felts and textiles. They are also ingredients of moth repelling preparations. Quinine stearate is used in hair lotions and pomades. The residual bark of quinine factories after the extraction of the alkaloids is a tanning material. Debarked cinchona poles are durable and resistant to termites.

New and effective antimalarial drugs, specially, paludrine have certain advantages over quinine in the treatment of malaria. These new developments have no doubt affected cinchona expansion schemes in India. However, from a strategic point of view, cinchona alkaloids are still of importance as indigenous materials particularly in war time, when imports may not be feasible.

1.4.d. Physical properties of the important cinchona alkaloids and their salts : (135)

These are white, odourless but intensely bitter, high-melting,crystalline solids. The bases are almost insoluble in water or aqueous solutions of salts and alkalies but dissolve in general, in dilute mineral acids and in a variety of organic solvents. Quinine and quinidine which contain a methoxy group when dissolved in dilute oxy acids, exhibit a blue fluorescence which is particularly intense when viewed in ultraviolet light.

These are optically active. They fall into two groups, the dextro and laevo-rotatory series respectively. To the former belong chinchonine, quinidine and their dihydro derivatives ; cinchonidine, quinine and their dihydro derivatives are laevoratory. In general, the rotations of the bases in alcohol are of the same order of magnitude as those of the salts (B.HA) in water. The rotations of the salts,however, progressively increase in arithmetic value with addition of acid. A maximum is reached at about the stage at which the amount of acid added suffices to convert the salt (B.HA) into (B.2HA) ; with further additions of acid the rotation falls slowly.

The cinchona alkaloids are diacidic bases, and form two series of salts, viz. neutral salts, B.HA, and acid salts, B.2HA . B.4HA is also occasionally met with. The neutral salts are neutral or faintly alkaline to litmus ; the acid salts are acid to litmus but neutral to methyl orange or congo red.

Cinchonidine :

It crystallises in anhydrous, large trimetric prisms or thin plates. Its melting point has been given variously, ranging from 202° to 210.5°. Cinchonidine is almost insoluble in water (1 in over 5000) ; it dissolves in 300 parts of cold alcohol (sp.gr. 0.935). It is readily soluble in chloroform.

Cinchonine :

It crystallises from alcohol or from ether in prisms, the recorded melting point is variable (depends on the rate of heating), ranging from 254° to 268.8°. Cinchonine is soluble in 3670 parts of water ; it dissolves in 115 parts of alcohol at 17°.

Quinidine :

It crystallises from dilute alcohol in prisms containing 2.5 H_2O (losing 0.5 H_2O on exposure). The quinidine in British Pharmaceutical Codex 1934,872, contains $2H_2O$ and melts at about 168°. Anhydrous quinidine has a melting point 174.5°. Quinidine is not very readily soluble in any one organic solvent ; it dissolves best in alcohol, but is soluble also in ether, chloroform or benzene. It is almost insoluble in cold water but dissolves in 750 parts of boiling water.

Quinine :

It is precipitated from aqueous acid solutions of its salts at first as a white, anhydrous, amorphous powder. To avoid precipitating the sparingly soluble neutral salts, particularly the sulphate : $2(B.H_2SO_4)+2\ NaOH = B_2.H_2SO_4 + Na_2SO_4 + 2\ H_2O$: this operation is best performed by

introducing the alkaloidal solution very slowly into a large excess of the well stirred solution of the alkali. The commercial material is usually $B.2H_2O$; the two water molecules are removed over concentrated sulphuric acid or on drying in an oven at 125°. Anhydrous quinine base has a melting point 173.5°. One part of quinine requires for solution nearly 2000 parts of cold water. Quinine dissolves in less than its own volume of alcohol.

Cinchonidine sulphate :

$B_2.H_2SO_4$ crystallises from cold water in needles containing $6H_2O$, from hot water in needles containing 3 H_2O and from alcohol with 2 H_2O. The salt becomes anhydrous at 100° (m.p. 205°, decomp.) and reabsorbs 2 H_2O on exposure. At 25°, the salt is soluble in 63 parts of H_2O or 72 parts of alcohol. The solubility in H_2O at 80° is about threefold of that at 25°.

Cinchonidine acid sulphate :

$B. H_2SO_4$, 5 H_2O is readily soluble in water. The tetra sulphate, $B.2 H_2SO_4$, H_2O is slowly soluble in water.

Cinchonine sulphate :

$B_2.H_2SO_4$, 2 H_2O crystallises from water in the form of hard, transparent prisms which become anhydrous at 100°, and then have m.p. 200° (decomp.). It is readily soluble in alcohol, less so in water (70 parts cold, 13 parts at 100°) and dissolves in chloroform to about the same extent as in water (distinction from quinine and cinchonidine).

Cinchonine acid sulphate :

B. H_2SO_4, 4 H_2O forms large colourless prisms, is difficult to crystallise, being very soluble in water and in alcohol.

Quinidine sulphate :

B_2. H_2SO_4 crystallises from hot water in prisms or needles with 2 H_2O. The anhydrous salt reabsorbs 2 H_2O on exposure and is light sensitive. It is soluble in about 100 parts of cold water, 7 parts of boiling water, 10 parts of alcohol or 20 parts of chloroform.

Quinidine acid sulphate :

B. H_2SO_4 is readily soluble in water.

Quinine sulphate :

B_2. H_2SO_4 crystallises from boiling water probably with 8 H_2O. However, it is difficult to determine the water content with accuracy and is often given as 7 or 7.5 H_2O. The latter hydrate is official in B.P. The salt forms a light mass of colourless,odourless, glistening silky needles. They rapidly effloresce on exposure or on warming at 50° with the formation of lusterless crystals B_2. H_2SO_4, 2 H_2O (m.p. 205°) which constitutes the stable form and is formed also from the anhydrous salt on exposure. The anhydrous salt can be obtained by drying at 100° (m.p. 235°). The quinine sulphate is faintly alkaline to litmus and on exposure to light slowly turns yellow. The salt with 7.5 H_2O requires for solution nearly 800 parts of cold water but dissolves in 30 parts of boiling water. It is soluble in 65 parts of cold 90 % alcohol.

Quinine acid sulphate :

B. H_2SO_4, 7 H_2O crystallises from water in small colourless, odourless, transparent or opaque, acicular crystals. The salt is efflorescent and light sensitive. Aqueous solutions are fluorescent and acid to litmus but not to congo red. The anhydrous salt has m.p. 160°. It is soluble in about 10 parts of cold water.

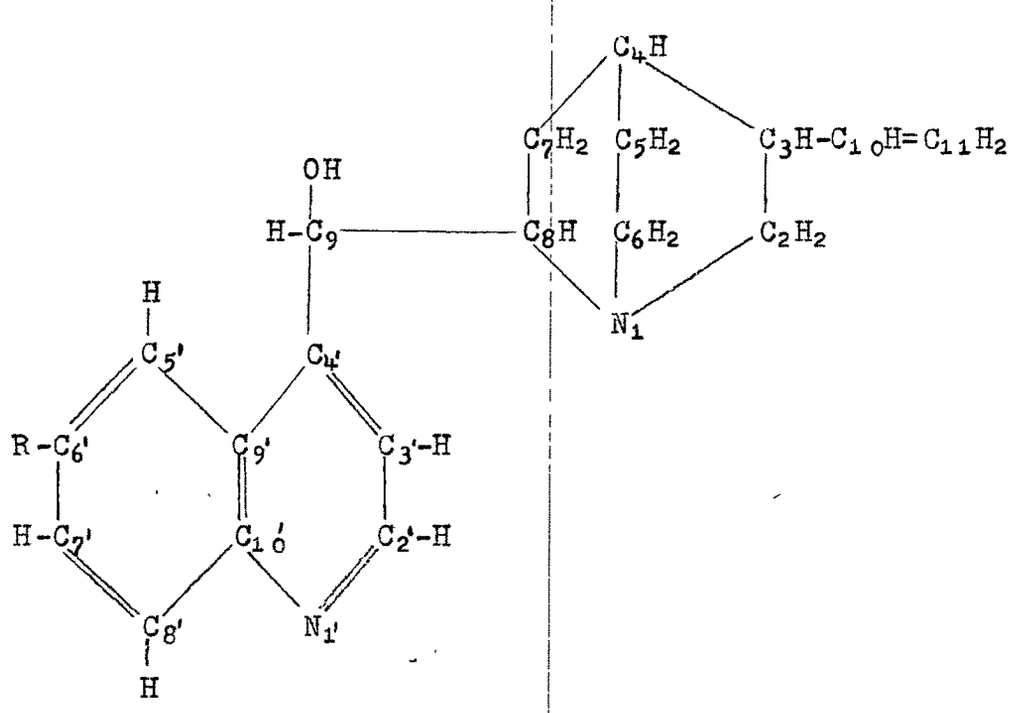
Quinine tetra sulphate :

B. 2 H_2SO_4 crystallises from water with 7 H_2O. It is very soluble in water.

Structural formulae of :

(a) Quinine and Quinidine (R = $-OCH_3$)

(b) Cinchonine and Cinchonidine (R = H)



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