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A New Method of Purification of Raw Mixtures of Alkaloids

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Summary

In this paper a new method of purification of raw mixtures of alkaloids by dialysis of aqueous solutions of their salts through a semipermeable membrane is described. The results obtained by using this method of purification of raw mixtures of alkaloids from plant extracts and mother liquors after crystallization of the major alkaloid have been given. In all cases under investigation this method of purification gave crystalline substances.

One of the problems of isolation of alkaloids from plant extracts is how to separate the dark polymeric substances from solutions of mixtures of alkaloids. These substances frequently prevent or more or less inhibit the crystallization of alkaloids from mixtures.

In general, these polymeric substances are removed by adsorption to hydrophilic or hydrophobic adsorbents according to whether an aqueous solution or a solution in an organic solvent is used. Other well-known methods are purification by means of ionexes, countercurrent distribution, and repeated extraction or precipitation in water-insoluble alkaloids.

The principle of our method is the dialysis of an aqueous solution of salts of alkaloids through a semipermeable membrane. The semipermeable membrane (cellophane, collodion membrane, different dialyzing tubes, etc.) is permeable to salts of alkaloids but not to polymeric substances having a large molecule.

The general procedure is as follows: The raw mixture of alkaloids (from plant extracts or from mother liquors after crystalliza-

tion of the major alkaloid) is converted into an aqueous solution of the corresponding salts by treatment with organic or inorganic acids (according to the stability and solubility of the concerned salts). This solution is dialyzed through a semipermeable membrane against pure water. The latter is exchanged several times and the alkaloids are then recovered from the dialyzate in the usual manner according to their properties.

We have applied this method of purification to three mixtures of alkaloids of various types which could not be brought to crystallization. In all these cases crystalline substances were obtained. After dialysis, the mother liquors remaining after crystallization of the alkaloids contained therein were also much purer than before application of this procedure. They could be easily separated by chromatography and the column of the adsorbent did not become contaminated with ballast substances.

EXPERIMENTAL

Alkaloids of the Cinchona Bark

The evaporated and desiccated mother liquors (30 g) after isolation of quinine from the cinchona bark were obtained under the designation quinoidine (*1,2*) from the N.V. Amsterdamsche Chininefabriek. They were suspended in 150 ml of water, made acidic with concentrated hydrochloric acid, and filtered through a sintered glass. The filtrate (200 ml) was then dialyzed against 3000 ml of distilled water at laboratory temperature through a dialyzing tube ϕ 46 mm (manufacturer: Koch-Light Laboratories Ltd., England). At intervals of 24 hr the dialyzate was exchanged for the same volume of distilled water. The procedure was repeated five times on the whole and the dialyzed portions were made alkaline with ammonia and were extracted five times with 200-ml portions of chloroform. The chloroform extracts were dried over anhydrous sodium sulfate. The solvent was removed by distillation to afford a pure mixture of alkaloids (Table 1). The single fractions were diluted with benzene, combined, and then filtered through a layer (ϕ 2.5 cm) of alumina 5 cm thick. The filtrate was concentrated to yield 2.3 g of a crystalline substance whose infrared spectrum was identical with that of cinchonine (3). The layer of alumina was then washed with chloroform, and the filtrate was evaporated to dryness to afford 0.4 g of crystalline cinchonine. The total

TABLE 1

Dialysis of Raw Mixtures of Alkaloids

Material	Weight, g	Weight of the purified mixture, g						Pure alkaloids after crystallization, g and (%)
		1	2	3	4	5	Total (%)	
Chinoidine (*1,2*)	30.0	12.1	6.8	1.5	0.2	0.03	14.90 (49.7)	Cinchonine, 2.7 (9.0)
Senecio erraticus (*4*)	173.0	36.4	17.8	2.1	0.3	0.05	56.65 (32.7)	Senecionine, 25.6 (14.8)
Ligularia clivorum (*5*)	33.5	14.5	6.6	2.2	0.6	0.10	24.00 (71.7)	Clivorine, 8.5 (25.4)

amount of both portions of mother liquors obtained after crystallization of cinchonine amounted to 12.2 g.

Alkaloids from *Senecio erraticus* Bert., ssp. *barbaraeifolius* Krock

After crystallization of the alkaloid senecionine (*4*), the strongly contaminated mother liquors (173 g) were acidified with a concentrated solution of citric acid of pH 3.5 and then diluted with water $\overline{aa}$. The insoluble portion was filtered off and the dark-colored filtrate was concentrated in vacuo to a volume of 150 ml and dialyzed through a dialyzing tube ϕ 26 mm (manufacturer: Kalle Aktiengesellschaft, Wiesbaden, GDR). The rest of the procedure was the same as that adopted in the case of the mixture of alkaloids obtained from cinchona bark. Table 1 shows the yields of purified mixtures of alkaloids obtained after dialysis. These mixtures of alkaloids (56.65 g) were crystallized from ethyl acetate to yield pure senecionine (25.6 g). The mother liquors (31.05 g), which did not contain any polymeric substances, were separated by column chromatography on alumina.

Alkaloids from *Ligularia clivorum* Maxim

The raw mixture of alkaloids (33.5 g), obtained (*5*) from the methanolic extract of the plant *L. clivorum* Maxim, was dissolved in the smallest possible volume of a saturated solution of citric acid, diluted with water to a volume of 180 ml, and dialyzed through a dialyzing tube ϕ 26 mm (manufacturer: Kalle Aktiengesellschaft) at 4°C against 800 ml of distilled water. At intervals of 8 hr the dialyzate was exchanged for distilled water, which was repeated on the whole five times. The rest of the procedure was the same as that adopted in the case of the alkaloids of the cinchona bark. Table

1 shows the obtained yields. The purified mixture of alkaloids (24 g) crystallized from ethyl acetate; yield was 8.5 g of pure clivorine (5,6). The mother liquors (15.5 g), which did not contain any polymeric substances, were separated by column chromatography on alumina.

RESULTS AND DISCUSSION

The results obtained in the three cases under investigation after application of our new technique of purification of raw mixtures of alkaloids are listed in Table I. This tabulation shows that after a fivefold dialysis practically the whole content of alkaloids passes into the dialyzate and the loss is insignificant. Raw mixtures of alkaloids containing up to 65% of ballast substances can be purified by one application of the procedure, which is not so easy when other methods of purification are employed. It is well known, for example, that, on using organic solvents, adsorption of these substances contained in solutions of alkaloids is effective only when nonpolar solvents are applied, which is not always possible since the solubility of the purified substances has to be taken into consideration. One of the most efficient methods of purification of raw mixtures of alkaloids is adsorption of impurities from aqueous solutions of their salts to charcoal. This, however, sometimes results in a considerable loss of the purified substances due to adsorption to the purifying means.

The application of the procedure described above can be carried out very easily. The utilization of a rapidly operating dialyzer in connection with adsorption of alkaloids to ionexes would accelerate the whole procedure. Moreover, it would automatize the procedure, which could be of great importance, particularly in industrial production. By working up the so-far discarded mother liquors having a low content of alkaloids, the production process could be rendered more efficient from the viewpoint of economy.

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