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# PREPARATION OF THE DIETHOCHLORIDES OF α- AND β-BELLADONNINES BY AN ION-EXCHANGE METHOD

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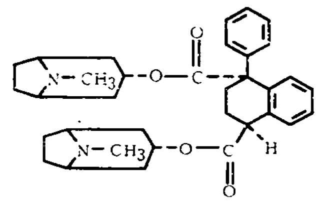
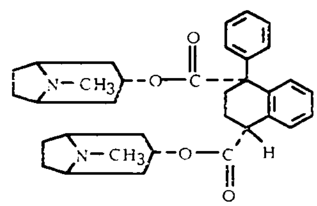
*The optimum conditions for the preparation of the new muscle relaxant belétonii have been found. It has been established that the most economically favorable and ecologically clean method is ion-exchange.*

Among drugs of plant origin, alkaloids of the tropane group (atropine, hyoscyamine, scopolamine), isolated from plants of the Solanaceae family, are widely used in medical practice. The tropane alkaloids α- and β-belladonnines are isolated from the plants *Physoclaina alaica* [1], *Datura innoxia* [2], and *Datura stramonium* [3].



α-Belladonnine



β-Belladonnine

Methods for the synthesis of these alkaloids have been described [4]. It is known that their quaternary derivatives possess a curaremimetic action. The diethochorides of α- and β-belladonnines (belétonii), obtained from hyoscyamine and atropine (*dl*-hyoscyamine) are effective muscle relaxants with a brief action, have an activity greater than that of *d*-tubocurarine, and are more than 50 times more active than the diodonii used in medical practice [5].

The essence of the method of obtaining belétonii consists in the conversion of the α- and β-belladonnines formed in the hydrolysis of hyoscyamine (atropine) into quaternary derivatives – diethiodides – which are then transformed into the corresponding α- and β-belladonnine diethochlorides by the action of silver chloride.

Recently, the wide development of theoretical and practical problems of ion-exchange technology in the field of medicine has led to the creation of sorption and chromatographic methods for the separation, fractionation, and purification of alkaloids and other biologically active compounds [6-8]. We have improved the final stage in the production of belétonii by using adsorption technology and eliminating the use of silver chloride.

As is known from the practice of ion-exchange technology, the selectivity factor of ion-exchangers from dilute solutions will be higher than from concentrated solutions [9-11], and it is therefore important to choose the optimum solvent for the desired product.

We established experimentally that the best solvent for the diethochlorides is methyl alcohol, and we used just this solvent for the subsequent experiments.

In order to select the anion-exchanger possessing the highest exchange capacity, we used anion-exchange resins of various types: AN-31, ÉDÉ-10P, AV-16gs, and ARA-8n in the Cl form. It can be seen from Table 1 that ARA-8n and AV-16gs possessed the highest exchange capacities.

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TABLE 1. Exchange Capacities of Ion-Exchange Resins with Respect to $\alpha$- and $\beta$-Belladonnine Diethochlorides

| Anion-exchanger | Concentration of the diethochlorides | Exchange capacity, m-eq./g |
|---|---|---|
| AN-31 | 0.25 | 0.26 |
| ÉDÉ-10P | 0.25 | 0.42 |
| AV-16gs | 0.25 | 1.52 |
| ARA-8n | 0.25 | 2.96 |

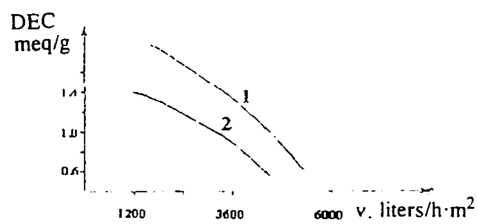


Fig. 1. Influence of the rate of flow of $\alpha$- and $\beta$-belladonnine diethochlorides on the DECs of ARA-8n (*1*) and AV-16gs (*2*).

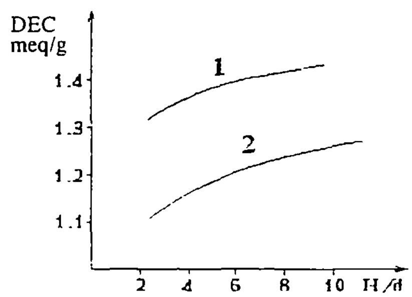


Fig. 2. Dependence of the DECs of ARA-8n (*1*) and AV-16gs (*2*) on the magnitude H:d.

During the ion-exchange process, the dynamic exchange capacity (DEC) of the exchange resin depends largely on the rate of flow of the solution under investigation. To study this relationship, we carried out the series of experiments the results of which are presented in Fig. 1.

It can be seen from Fig. 1 that with an increase in the rate of flow the DEC of an ion-exchanger falls. Under industrial conditions it is rational to perform this process at a rate of flow of 2400 liters/h·m$^2$.

One of the important factors affecting the exchange capacity of ion-exchangers is the shape characteristic of the column, i.e., the ratio of the height of the layer of resin to the internal diameter of the column, H:d. To study this relationship we performed the series of experiments the results of which are given in Fig. 2. As can be seen from Fig. 2, the optimum H:d ratio is 4-8.

Thus, the periodic process of converting the diethiodides of $\alpha$- and $\beta$-belladonnines into the ethochlorides has been replaced by a continuous ion-exchange method, and a technological scheme for obtaining the drug belétonii has been developed.

## EXPERIMENTAL

The study of the solubility of the diethiodides was carried out according to GF IX [USSR State Pharmacopeia, IXth edn.] (No. 1).

**Choice of Anion-Exchanger.** The anion-exchange resins studied, of types AN-31, ÉDÉ-10P, AV-16gs, and ARA-8n in the Cl form (2 g each), were placed in flasks and covered with 100 ml of a 0.25% solution of the diethiodides in methanol.

The contents of the flasks were stirred periodically and left for 48 h. Then the anion-exchangers were filtered off from the solutions. The amounts of diethiodides remaining in the filtrates were determined by a known procedure [2].

To determine the DEC of the anion-exchange resin ARA-8n, methanolic solutions of the diethiodides were passed through it at various rates of flow. The iodine that had not reacted – the "breakthrough" – was determined with the aid of a qualitative reaction for iodine using sodium nitrite as indicator. To determine the dependence of the DEC on the H:d ratio we took glass columns with different internal diameters, charged each with 2 g of ion-exchanger, and passed methanolic solutions of the diethiodides at the rate of 2400 liters/h·$m^2$. The residual amounts of diethiodides (after the breakthrough) were determined by the procedure mentioned above.

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