SYNTHESIS OF MEDICINAL SUBSTANCES WITH CONTROLLABLE LENGTH OF ACTION (IN THE CASE OF CURARE-LIKE COMPOUNDS)

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Control of the length of action of medicinal substances is an important pharmacological problem. From the chemical standpoint, its successful solution would be possible with the aid of inactivators which act selectively on the medicinal substances and convert them into inactive compounds. Such substances, introduced at the right moment, would stop the action of the medicinal agent.

If one searches for analogies with nature, it is possible to point out the inactivation of ditilin by cholinesterase [1]

\[
\begin{align*}
&\text{Ch}_2\text{CO}-\text{O}-\text{CH}_2\text{CH}_2\text{NMe}_3 \xrightarrow{\text{Cholinesterase}} \text{CH}_2\text{COOH} \\
&\text{CH}_2\text{CO}-\text{O}-\text{CH}_2\text{CH}_2\text{NMe}_3 + \text{H}_2\text{O} \xrightarrow{\text{H}_2\text{O}} \text{CH}_2\text{CO}-\text{O}-\text{CH}_2\text{CH}_2\text{NMe}_3 \\
&+ \text{HOCH}_2\text{CH}_2\text{NMe}_3
\end{align*}
\]

A characteristic feature of ditilin is the presence of two weak bonds (the ester bonds). Cholinesterase acts on them selectively. The decomposition products II and III are practically free of the curare-like activity of I. In this case, the inactivator is not introduced from without, but is present in the neuromuscular synapse. The result is shortness of action of ditilin.

We have synthesized a medicinal substance which contains a specific link in its molecule that may be broken up under the action of inactivators introduced from without. To do this, we took compounds from the myorelaxant class. As a specific link we selected the disulfide bond, which possesses suitable lability.

The structure of the myorelaxant was chosen on the basis of the following considerations: It should contain two quaternary ammonium groups; the spacing between the quaternary nitrogen atoms should be 14-15 Å; and there should be a S-S bond between the ammonium groups.

These conditions were satisfied by a diphenyl disulfide structure with two quaternary ammonium groups in the 4,4'-positions (compound III), which was taken as a model:

\[
\begin{align*}
\text{R}^\oplus\text{R}^\ominus\text{S-S}\text{S-S}\text{R}^\ominus\text{R}^\oplus
\end{align*}
\]

The disulfide bond in this compound possesses enhanced lability, since it connects two aromatic nuclei which contain electroacceptor ammonium groups in the para position. It might be hoped that a suitable chemical reagent could break the S-S bond, which would lead to removal of the neuro-muscular blockade.

Starting from dimethylaniline, we prepared 4,4'-bis-(dimethylanilino) disulfide and a number of its mono- and diquaternary derivatives, by the following scheme:
The tertiary diamine (IV) was prepared by the method of Merz [2]. Alkylation of product IV leads to formation of both the mono- and also the diquaternary product (compounds V and VI), wherein the ratio of these depends on the character of the solvent, the reaction temperature, and the form of alkylating agent. Thus, with dimethyl sulfate or methyl iodide in benzene at 15-20°, IV forms practically pure V; from the same reagents, but in acetone at 15-20°, VI is formed; and in acetone at 55-60°, a mixture of V and VI in approximately equal amounts by weight is formed.

By selecting reaction conditions we also prepared mono- and diquaternary compounds of IV with benzyl or p-nitrobenzyl radicals. In connection with the low reactivity of ethyl iodide, the corresponding ethiodide from product IV was prepared by the action of ethyl benzenesulfonate on IV, with subsequent replacement of the benzenesulfonate anion by the iodide anion.

The results obtained are presented in Table 1.

The diquaternary derivatives can be prepared not only from the tertiary amine but also from the corresponding monoquaternary compounds. For example, upon action of dimethyl sulfate on the monoquaternary product (V), \( R = CH_3, X = CH_3SO_4 \), the diquaternary derivative (VI) is formed (\( R = CH_3, X = CH_3SO_4 \)). Thus, it is possible to prepare unsymmetrical diquaternary derivatives.

Pharmacological investigation of the preparations made showed that the original model was correctly chosen [3]. For example, the diquaternary product, VI, \( R = CH_3, X = CH_3SO_4 \) (KhGM-1) proved to be a typical curare-like compound of mixed type of action. It possesses characteristic cholinomimetic activity, which was studied in experiments on isolated straight frog stomach muscle. This compound causes a contraction amounting to 50% of the maximum possible, in a concentration of 2.9 \( \times \) 10^{-5} M. This same preparation causes blockade of neuro-muscular transfer in experiments on isolated rat phrenic diaphragm preparation in a concentration of 3 \( \times \) 10^{-5} M.

Further work consisted in the choice of such a chemical agent that, possessing sufficient selectivity, it could get, unchanged, to the myorelaxant molecule present in the neuro-muscular synapse, and, along with this, would possess enough activity to cleave the myorelaxant at the S-S bond.

As is known, the mechanism of heterolytic cleavage of the S-S bond is similar to the mechanism of nucleophilic substitution at a carbon atom, with this sole difference, that the so-called S-nucleophilic agent is not attacking a carbon atom, but a sulfur atom, adding to it and dislodging the appropriate mercaptide;

\[
R-S-S-R + \overset{y}{\text{S}} \rightarrow R-S-y + S-R
\]

One of the active S-nucleophilic agents is the sulfite anion, \( SO_3^- \). Experimentation showed that the reaction of sodium sulfite with KhGM-1 actually leads to breakdown of the KhGM-1 at the point of the disulfide bond, with formation of the zwitterion (VII) and the mercaptan (VIII); the reaction takes place in water at room temperature:

\[
\begin{align*}
\text{Me}_3N \overset{\text{MeSO}_4}{\text{S-S}} \overset{\text{Na}_2\text{SO}_3}{\text{H}_2\text{O}} & \rightarrow \text{Me}_3N \overset{\text{MeSO}_4}{\text{S-S}} \overset{\text{SO}_3^-}{\text{H}_2\text{O}} + \\
& + \text{HS} \overset{\text{NMe}_3}{\text{S-S}} \overset{\text{MeSO}_4}{\text{H}_2\text{O}}
\end{align*}
\]