THE CHEMISTRY OF THE MUSCLE RELAXANTS

EDWIN J. DE BEER, PH.D.

THE following paper considers the chemical properties of the more common muscle relaxants. Some of the properties of the drugs are given, together with brief outlines of their synthesis and discussions of their structures. The drugs were selected on the basis of their present day clinical use or because of interesting structural details.

SUCCINYLCHOLINE

Succinylcholine (Anectine) is a white, odorless solid which melts at 160–164 C. It dissolves in water to the extent of 1 Gm. per ml. and in alcohol, 1 Gm. per 350 ml. It is slightly soluble in chloroform and almost insoluble in ether. The *p*H of the water solution as marketed ranges from 3.2 to 3.5.

Succinylcholine has been known for many years, but Bovet *et al.*[1] and Phillips[2] independently synthesized the drug specifically for the study of its myoneural blocking action. Phillips describes a synthesis which involves refluxing diethyl succinate with β-dimethylaminoethanol and forming bis-dimethylaminoethyl succinate. This is treated with methyl iodide to form succinylcholine.

Succinylcholine exhibits several structural details which are common to many muscle relaxants (fig. 1). The molecule contains two quaternary nitrogen atoms or onium groups which are separated by a chain of 10 interjacent atoms. The distance between the onium groups has been estimated at approximately 15 Å. The onium groups are sufficiently basic to form salts with strong acids which dissociate and react with water to yield acidic solutions.

Succinylcholine differs from the other relaxants described in this paper in its susceptibility to hydrolysis. This is due to the presence of two ester groups in the chain and is probably responsible for its brief action. The hydrolysis is appreciable at *p*H 7.4 if the solutions are warm and is rapid in the presence of strong alkalies. Ordinary aqueous solutions, however, have a *p*H of about 3.5 and will even withstand autoclaving for 10 minutes at 120 C. without serious decomposition.

Succinylcholine is also readily split by the plasma or pseudocholinesterase. This again is due to the presence of ester groups. The enzymatic hydrolysis probably takes place in two stages. The products of the first step are succinylmonocholine and choline. In the second stage the monocholine is split so that the final products are choline and succinic acid. It is noteworthy that succinylcholine is not broken down by the "true" or specific cholinesterase.

DECAMETHONIUM

Decamethonium (Syncurine) is a white, odorless, crystalline solid which is readily soluble in water and ethyl alcohol but insoluble in acetone. It decomposes at 252 C. The *p*H of its water solution is 5.5.

Paton and Zaimis[3] state that the compound may be synthesized by treating decamethylene-bis-diamine in methyl alcohol solution with methyl bromide and NaOH. The NaBr which is formed as a by product is removed by extraction with acetone.

Decamethonium is the simplest in structure of the commonly used blocking agents (fig. 1). It was the discovery by Paton and Zaimis[3] and Barlow and Ing[4] that maximal, myoneural blocking action, in this polymethylene series, occurred when 10 CH_2 groups were interposed between the two quaternary ammonium groups, which lent support to the hypothesis that a distance of 14 Å between the basic nitrogen groups was optimal for this class of drugs. The two quaternary ammonium groups form salts with acids and dissolve in water to give an acid solution. The decamethylene chain is relatively inert, and the drug is very stable in solution.

Dr. de Beer is Associate Director of Research, Burroughs Wellcome and Co. (U.S.A.) Inc., Tuckahoe 7, New York.

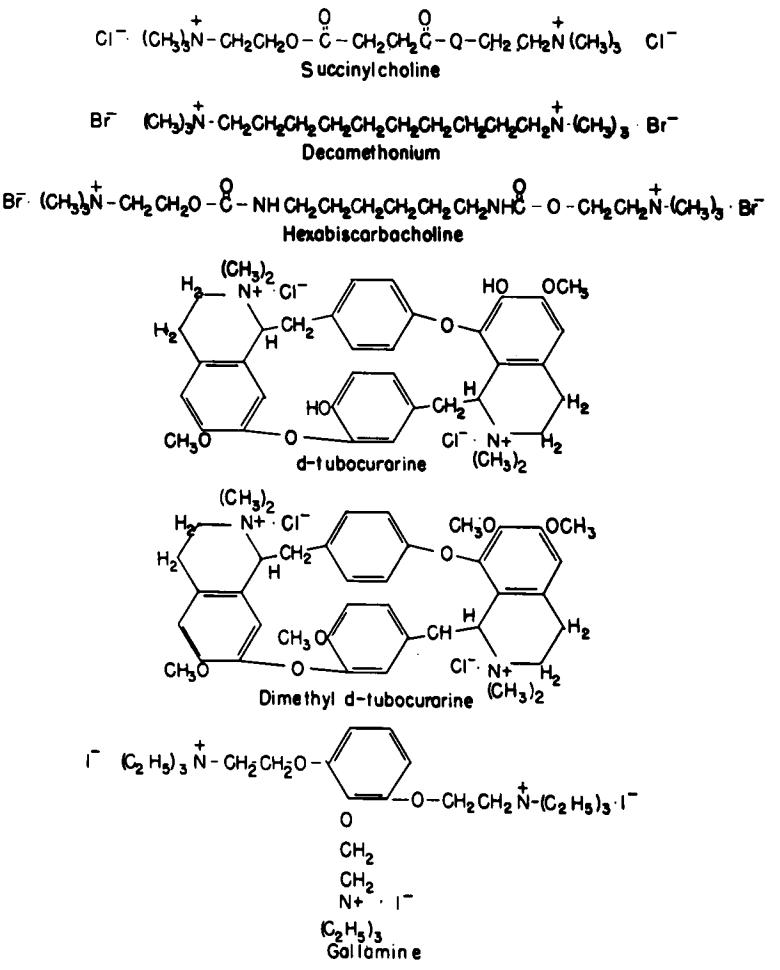

FIGURE 1.

HEXABISCARBACHOLINE

Hexabiscarbacholine (Imbretil) is a white, odorless, crystalline, solid which melts within a range of 172–176 C. It dissolves in water and ethyl alcohol; but is relatively insoluble in ether, chloroform, or benzene. Aqueous solutions as commercially issued have a *p*H of about 4.5.

An outline for a synthesis of the drug is given by Cheymol *et al.*[5] Hexamethylene bis (β-hydroxyethylcarbamate) is prepared by reacting glycol carbonate with hexamethylene diamine. The OH groups are then replaced with Cl by treating with $SOCl_2$. The Cl is changed to the iodide by NaI which in turn is treated with $(CH_3)_3N$ to form hexabiscarbaminoyl choline.

Figure 1 shows that the drug contains two quaternary ammonium groups separated by a chain which contains more than 10 atoms and hence seems to violate the hypothesis that the two quaternary nitrogen atoms should be 14 Å apart. Actually, however, the nitrogen atoms of the carbaminoyl groups may introduce bends in the chain so that it is possible for the two quaternary groups to be closer together than first seems apparent.

The two carbaminoyl linkages are remarkably stable, much more so than the plain ester linkages found in succinylcholine. Heating the drug with 0.1N NaOH for 2 hours on a steam bath failed to produce appreciable hydrolysis. The stability of the drug probably is due in

part to its long action. Unlike the ester groups, the carbaminoyl linkages are not split by the cholinesterases. In fact, the drug is reported to have some anticholinesterase activity.

The presence of a hexamethylene chain in the molecule does not endow the compound with any ganglionic blocking ability, since for this class of drugs the quaternary ammonium groups should be spaced at distances of about 7 or 8 Å, as is found in pentamethonium or hexamethonium.

Tubocurarine Chloride

This drug is a white or yellowish-white, crystalline solid which melts at about 270 C. The pentahydrate is relatively nonhygroscopic. One gram dissolves in 20 ml. of water and in 45 ml. of ethyl alcohol. The drug is relatively insoluble in diethyl ether, chloroform, pyridine, and acetone. The active isomer has a specific rotation of $[\alpha]_D^{22} = 215$ degrees. Aqueous solutions as commercially marketed have a *p*H of approximately 3. McIntyre [6] states that most of the *d*-tubocurarine is prepared from a tar-like concentrate obtained by boiling the vines or bushropes of *Chondodendron tomentosum*. Modern extraction-column chromatography is used to isolate the drug from the many other alkaloids which occur in the tar. Biological assay is generally used to insure the required amount of activity.

The structure of the drug is quite complicated (fig. 1). There are two onium groups as usual but these are spaced on the opposite sides of a large ring structure instead of at the end of a single chain. As usual, these basic groups form salts with acids and dissolve in water to give slightly acid solutions. The two free OH groups are evidently not very reactive, and the two ether and methylene linkages seem relatively inert. The molecule is quite stable, and aqueous solutions can be autoclaved or stored for long periods of time without serious decomposition.

Dimethyl Tubocurarine

The iodide of dimethyl tubocurarine is called Metubine; the chloride, Mecostrin. The iodide salt is an odorless, white or pale yellow, crystalline, powder which decomposes with the evolution of gas at 257 C. The specific rotation is $[\alpha]_D^{22} = 148–158$ degrees. The drug is slightly soluble in water, in dilute hydrochloric acid, and dilute sodium hydroxide. It is very slightly soluble in ethyl alcohol and practically insoluble in ether, benzene, or chloroform. The *p*H of its aqueous solution is about 6.1. The drug is prepared by replacing the two OH groups of *d*-tubocurarine with OCH_3 groups. This was performed by Wintersteiner and Dutcher.[7]

The drug is remarkable because the replacement of the OH groups by less reactive CH_3 groups in this complicated molecule leads to a pronounced increase in potency. The basic quaternary ammonium groups behave as they do in *d*-tubocurarine, and the rest of the molecule is not reactive. The drug is stable in solution. Its formula is given in figure 1.

Gallamine

Gallamine (Flaxedil) is a white, odorless, crystalline solid with a bitter taste. It melts between 145 and 150 C. It is soluble in water, alcohol, and dilute acetone. It is comparatively insoluble in anhydrous acetone, ether, benzene, and chloroform. The *p*H of the commercially available solution is about 3.2.

In the synthesis of gallamine advantage may be taken of the fact that the three OH groups of pyrogallol can be converted into ether linkages for the attachment of three choline residues to the benezene ring.[8]

This compound bears several interesting structural differences from the other myoneural blocking agents discussed in this paper. It contains three quaternary ammonium groups. By writing the formula as in figure 1, one can introduce a considerable distance between the nitrogen atoms of the 1 and 3 substituents and thus satisfy to some extent the hypothesis that for optimum activity the two onium groups should be 14 Å apart. The presence of a third onium group apparently also contributes to the potency of the drug for the 1,2,3 derivative is stronger than either the 1,3 compound or the 1,2 derivative. The 1,3 derivative in turn, in which the two nitrogen groups are farthest apart, is stronger than the 1,2 derivative in which the two choline residues are adjacent. As usual, the basic ammonium groups form salts with acids and dissolve to produce weak acid solutions. It is also interesting that this highly potent drug has ethyl instead of methyl groups attached to the quaternary nitrogen since it has

been accepted as a general rule that the ethyl derivatives are less potent muscle relaxants than the methyl compounds. Gallamine is generally nonreactive and is stable in solution.

Incompatabilities

Occasionally in clinical anesthesia a muscle relaxant and a barbiturate are mixed and injected simultaneously. Not all muscle relaxants however, are compatible with the barbiturates, and the proper proportions of the drugs may be critical.

The sodium salts of the barbituric acids when dissolved in water have a basic reaction while, as mentioned earlier, the muscle relaxants produce acid solutions. Preservatives may increase the acidity still more. The stability of the various mixtures will depend upon the nature of the ingredients and whether an acid or an alkaline *p*H predominates. Succinylcholine, for example, is unstable in alkaline solutions and will decompose if added to an excess of thiopental sodium.

The sodium salts of the barbituric acids are generally soluble while the corresponding free acid is not. Consequently, if a sufficient amount of acid muscle-relaxant solution is added to the mildly alkaline barbiturate salt so that the *p*H is converted to an acid reaction, the free barbiturate acid may precipitate. The permanence of the precipitate will depend on just how acid the solution may have become.

For example, compatible proportions of thiopental sodium to *d*-tubocurarine are 33 mg. of the former to 1 mg. of the latter; for decamethonium and thiopental sodium solutions 13 mg. to 1 mg.

Discussion

The drugs discussed in this paper share several common features. All of them have at least two quaternary ammonium groups which are sufficiently basic to form salts. The presence of one or more of such groups seems to be a common property of drugs which act at the myoneural junction. Perhaps this group enables the drug to interfere with the normal action of acetylcholine.

One of the best known hypotheses in the structural-activity relationships of the myoneural blocking agents postulates that maximal activity is obtained when the molecule contains two quaternary ammonium groups spaced 14 Å apart. Somewhat Procrustean efforts are needed, however, to fit all of the drugs listed above into this hypothesis. Two dimensional, conventionalized, structural formulas give at best inadequate representations of three dimensional molecules. This is without taking into account the influence of electrical charges. Loewe and Harvey [9] show that it is possible to construct a Fisher-Hirschfelder model of *d*-tubocurarine which indicates a distance of only 6.5 Å between the two quaternary nitrogens but other forms can be arranged in which the distance is about 12 Å. Finally, McIntyre [6] points out that β-erythroidine, an extremely potent myoneural blocking agent, has only one quaternary nitrogen atom and that the toxiferines, some of which are many times more potent than *d*-tubocurarine, contain the two nitrogens separated by an interjacence of only 2 carbon atoms. Also one of the nitrogen atoms appears to be quaternary, the other tertiary. In spite of these criticisms, however, the hypothesis has been most fruitful in designing new myoneural blocking agents.

Finally, it is interesting that the myoneural blocking agents tend to be hydrophyllic rather than hydrophobic in their solubilities. This may be important in enabling the drugs to reach their proper site of action and in aiding in their elimination.

Summary

The following muscle relaxants have been considered from a chemical point of view: succinylcholine, decamethonium, hexabiscarbacholine, tubocurarine chloride, dimethyl tubocurarine, and gallamine.

All of these drugs share the common properties of possessing two or more quaternary ammonium groups spaced widely apart by a long chain of 10 or more atoms and of being more hydrophyllic than hydrophobic.

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