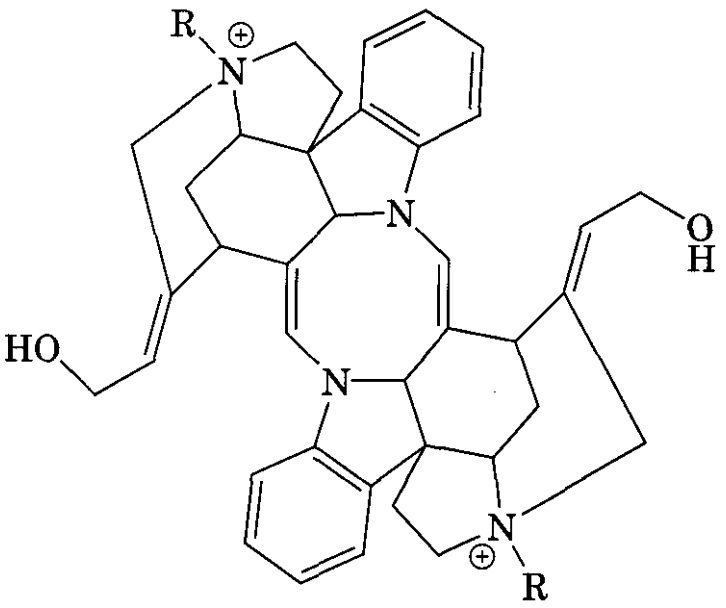
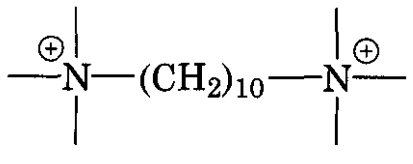


(31) C-toxiferine **1** R = CH_3
(30) alcuronium R = $CH_2CH{=}CH_2$

drugs that have made a major impact on survival rates during surgery.

At the time of King's work in the 1930s there were no spectroscopic aids to structure elucidation, and it is not surprising that he made a small error in the structure assigned to D-tubocurarine, believing it to have two quaternary nitrogens, a mistake that was not corrected (49) until 1970. The methylation product of D-tubocurarine, known as **metocurine** (32) is a more potent muscle relaxant. It was known for a long time as **dimethyltubocurarine** because of the error in the structure allocated to compound (29). King's error, in assigning a bisquaternary structure to a molecule with one quaternary and one protonated tertiary nitrogen, led to a large number of highly active synthetic bisquaternaries. The simplest of these was decamethonium (**33**), which was nothing more than two **trimethylammonium** end groups connected with a decamethylene chain. **As** one of a series with different chain lengths (50), decamethonium became the prototype for many more complex structures with 10 atoms between the quaternary centers, which appeared to be optimal for



(33) decamethonium

binding to the acetylcholine receptor at the neuromuscular junction.

Unlike tubocurarine, decamethonium depolarizes the muscle endplate, rendering the membrane insensitive to acetylcholine (48). The action of tubocurarine is competitive and can be overcome with increased concentrations of acetylcholine, brought about by administration of an anticholinesterase: the latter is thus an antidote to tubocurarine, but not to decamethonium. Despite the lack of an antidote, decamethonium was used very widely for over two decades. One of its disadvantages is an overlong duration of action, during which time the patient has to be maintained on artificial respiration, because the muscle of the diaphragm is also susceptible to the actions of the drug. An early and highly successful attempt (51) to shorten the action of decamethonium gave suxamethonium (**34**), a diester formed between succinic acid and two molecules of choline, which hydrolyzes rapidly in the presence of pseudocholinesterase.

Tubocurarine suffers from cardiovascular side effects induced by direct interactions with ganglionic acetylcholine receptors and from stimulation of histamine release, so analogs have been well worth pursuing. The **macrocyclic** structure of tubocurarine is a difficult synthetic target, but fortunately ring-opened analogs, such as laudexium (**35**), have high potency and relatively few side effects (52). The main problem with (35) is the duration of action, which at about 40 min is too long for many operations. Two approaches have been used to shorten the duration of action. The concept of pH-controlled Hofmann elimination was employed successfully (53) in the design of atracurium (**36**), which in clinical use **(54)** has the big advantage that the drug disappears at a constant rate, irrespective of liver or kidney function. Some ester hydrolysis contributes to the destruction of atracurium in *vivo*, as might be expected. **A** slightly later development (55) centered on an empirical search for structures that would undergo ester hydrolysis more rapidly, resulting in **mivacurium** (**37**), which has a slightly shorter duration of action than that of atracurium, the latter being about 15–20 min.