Diquaternized Curarelike Myorelaxants: Structure and Biological Activity

N.F. Salakhutdinov* and G.A. Tolstikov

N.N. Vorozhtsov Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Novosibirsk, Russia

Abstract: This review discusses the most active natural and synthetic curarelike compounds demonstrating myorelaxants activity. The data are grouped according to chemical structures, namely, quinoline and isoquinoline myorelaxants, myorelaxants with saturated heterocyclic or alkylamine fragments, myorelaxants with a steroid framework, natural and synthetic alkaloid myorelaxants.

Keywords: Curarelike compounds, natural and synthetic myorelaxants, nondepolarizing and depolarizing substances, diquaternized myorelaxants.

INTRODUCTION

The paralyzing activity of curare, the concentrated extracts of South American plants of the species *Strychnos* and *Chondodendron*, has been known for centuries. In the mid-19th century, curare alkaloids were found to produce relaxant action on the skeletal muscles. Compounds with the same activity, including those of nonnatural origin, were called myorelaxants (curarelike compounds). Interest in these structures arised from their clinical use, primarily, in surgery. Myorelaxants include compounds from chemically diverse classes such as alkaloids containing one or more tertiary amino groups [1, 2], mono- [3-18] and diquaternized (at the nitrogen atom) compounds with different frameworks, and structures containing positively charged heteroatoms other than nitrogen [19]. The wide variety of synthesized and currently used myorelaxants is dictated by the demand for medical preparations with different action times (from minutes to hours) or selectivity with respect to different systems of organism (e.g., compounds with respiratory depressing or nondepressing activity while producing sufficient myorelaxant action on the required muscles).

This review is devoted to the structure and myorelaxant properties of the largest and most widely used group of curarelike structures, namely, compounds diquaternized at nitrogen atoms. The charged nitrogen atoms of these structures are connected by chains of different atoms and groups called linkers. Substances with this type of structure are extremely biologically active and possess antitumor [20-23], anti-HIV [24], antimalarial [25], hypotensive [26], and other activities in addition to the myorelaxant activity.

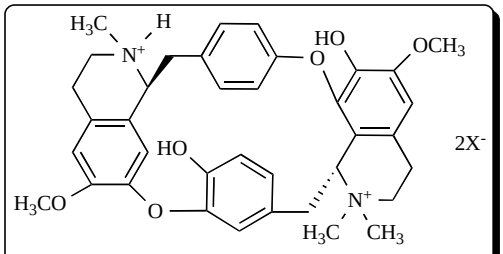
The compounds can be divided into three groups according to the mechanism of their activity:

- nondepolarizing substances. These compounds block cholinergic receptors without causing depolarization of the subsynaptic membrane;
- depolarizing substances, causing depolarization of the membrane of the muscle endplate. These are generally short-acting agents, relatively quickly hydrolyzed by choline esterase;
- substances with both mechanisms of action.

Compounds from the first group seem most promising because of fewer side effects and availability of antagonists for regulating the myorelaxant activity.

Quinoline and Isoquinoline Myorelaxants

(+)-Tubocurarine (**1**) (X = Cl, I) is the best known natural compound from this class. This isoquinoline alkaloid is contained in *Chondodendron tomentosum* from the family *Menispermaceae*. It was isolated in 1897 as an active compound of curare toxin and is now widely used in medicine as a nondepolarizing myorelaxant [27].



(1)

The tetrahydroisoquinoline fragment of natural tubocurarine was successfully used for the synthesis of a number of short-acting myorelaxants. Note that, according to the action time, myorelaxants are divided into ultrashort-acting (8 min and less), short-acting (up to 20 min), medium (up to 50 min), and long-acting (more than 50 min) [28].

Atracurium (**2**) is a synthetic compound structurally related to tubocurarine and also useful in clinical practice (action time – 15-35 min) [27].

The structural, electronic, and steric effects on the action time of symmetric bisquaternized esters of type (**3**), which are short-acting because of the lack of vagus nerve block, were studied and reported in [19-31].

*Address correspondence to this author at the N.N. Vorozhtsov Institute of Organic Chemistry, Siberian Branch, Russian Academy of Sciences, Novosibirsk, Russia; Tel/Fax: +7-383-330-97-33;
E-mail: anvar@nioch.nsc.ru

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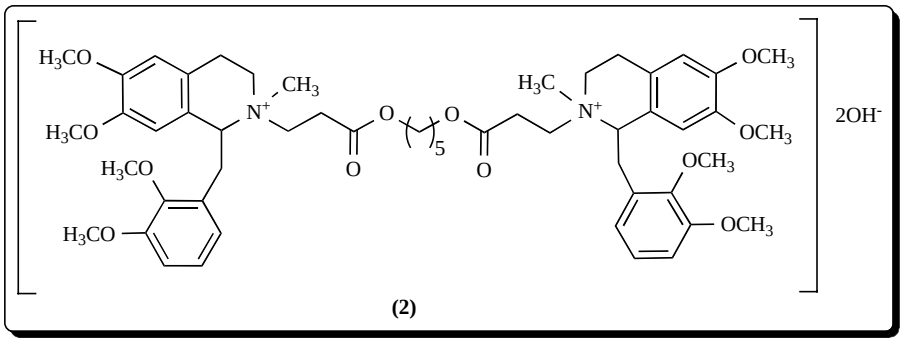

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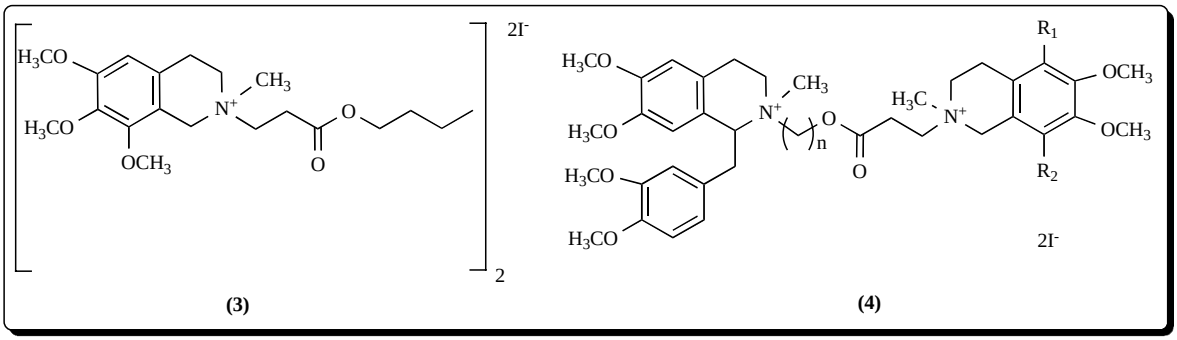
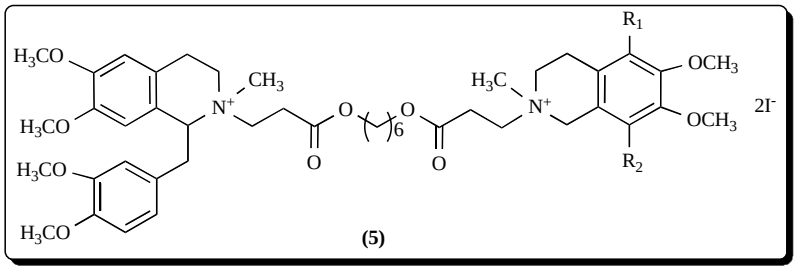


(3) **(4)**

The same research group obtained a number of asymmetric mono- (**4**) and diesters (**5**) and showed them to be more potent nerve blockers, capable of being inhibited by anticholine esterases [32]. Monoesters (**4**) were less effective than diesters (**5**). The action time was 8-15 min, and ED_{95} was 0.1-0.8 mg/kg for almost all of these compounds.

The diester fragment between the onium groups in these molecules originated from the structure of the ultrashort-acting myorelaxant succinyl choline (**6**), used for trachea intubation in clinical practice [33-35]. A number of serious side effects during its application (heart arrhythmia, acute muscle ache, etc.) have stimulated studies on the synthesis of the analogs of (**6**).

A number of bis- and mixed tetrahydroisoquinoline chlorofumarates have been synthesized, and their myorelaxant activity was tested on monkeys [36, 37]. Structure (**7**) proved



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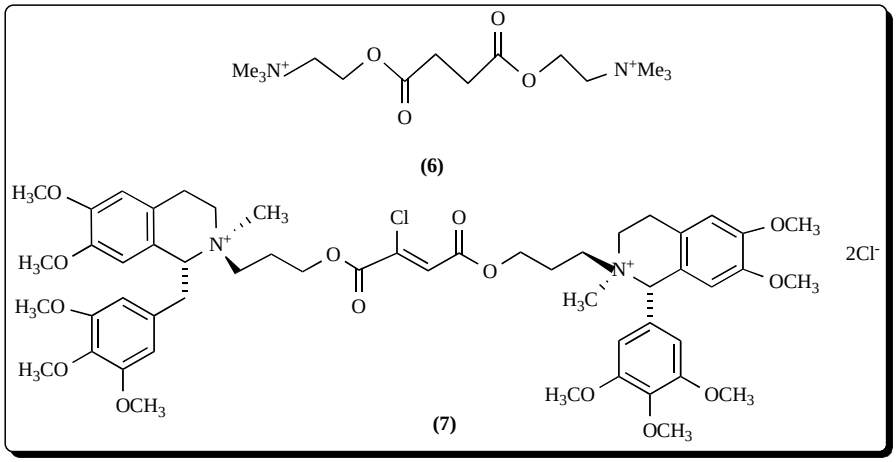
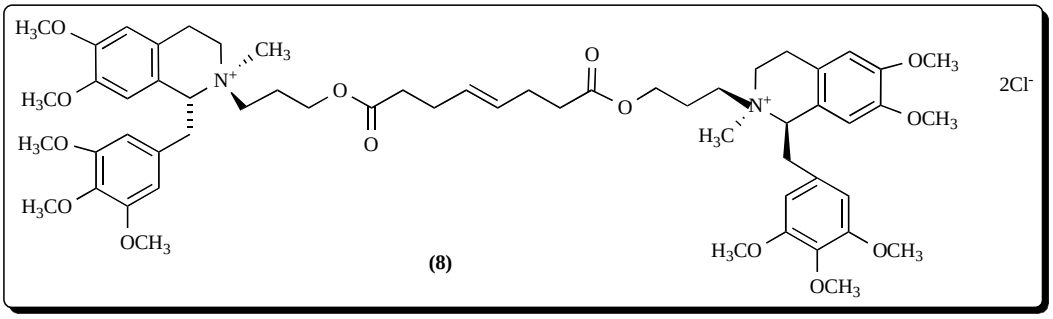


(6) **(7)**



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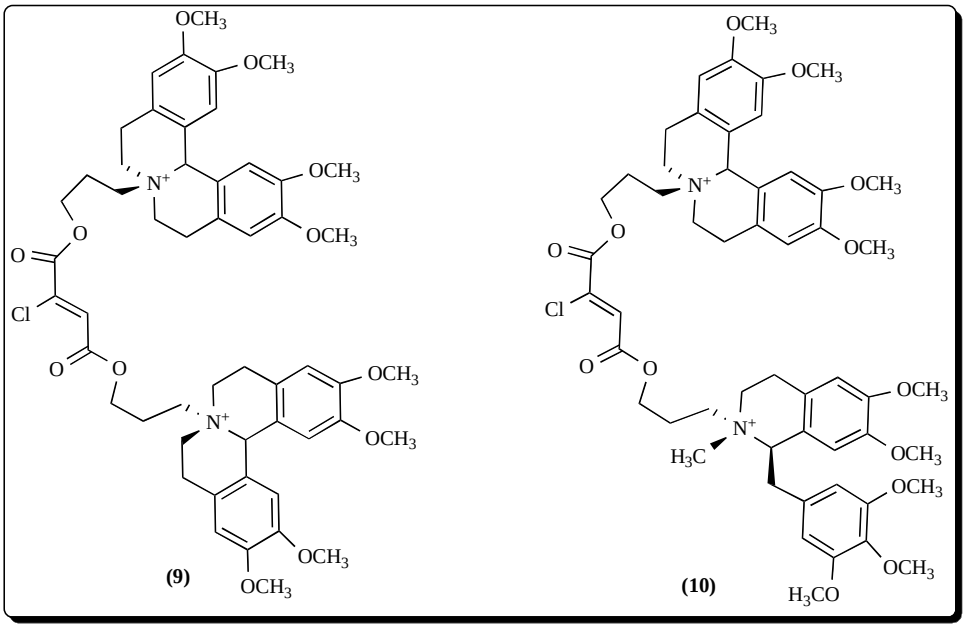


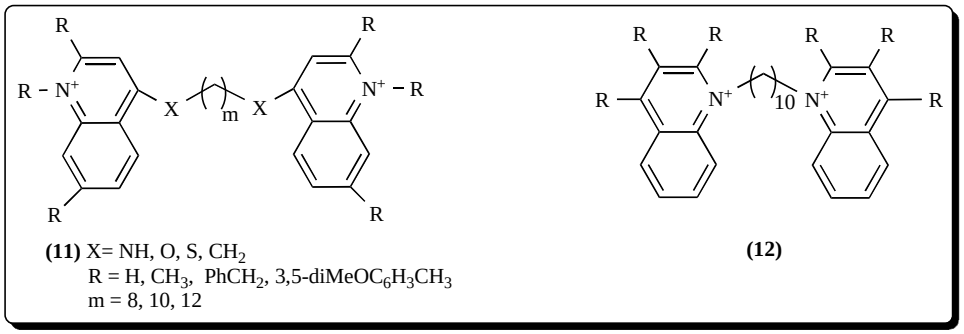
(9) **(10)**

to be most active. This is an ultrashort-acting nondepolarizing myorelaxant, having ED_{95} 0.063 mg/kg and no side effects inherent in succinyl choline (**6**). Its action time is twice as short as that of mivacurium (Mivacron) (**8**). In contrast to (**7**), the structure of (**8**) has no chlorine atom at the double bond, but contains additional methylene fragments in both the diester chain and the linker between the trimethoxyphenyl fragment and the right-hand tetrahydroisoquinoline part of the molecule.

Later, stereocontrolled synthesis afforded symmetric (**9**) and asymmetric (**10**) cis-dibenzoquinolizine chlorofumarates, which also proved to be ultrashort-acting myorelaxants [38].

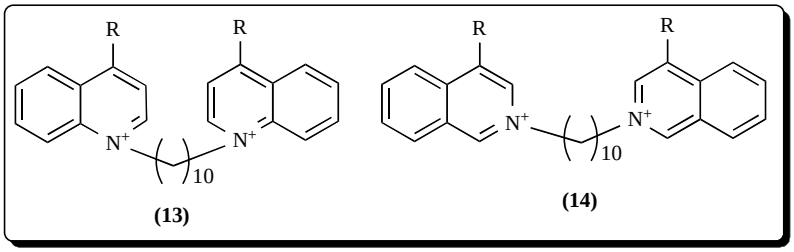
A number of compounds with two charged quinoline rings connected by one or two linkers were synthesized, and their effect on the conduction of neuron potassium channels was studied [39-46]. In compounds of type (**11**), the replacement of NH groups in a linker between the quinoline rings at the 4-position by O or S atoms or methylene groups decreased the activity of the compound. Quaternization of the ring nitrogen atoms was performed with methyl or benzyl groups; the best result was obtained in the latter case (IC_{50} = 400 nM). The activity of the compounds did not markedly depend on the number of methylene fragments (which varied from 8 to 12) in a linker.

The same activity was found for (**12**). In these compounds, the polymethylene linker connects the quaternized



(11) X= NH, O, S, CH_2
R = H, CH_3, $PhCH_2$, 3,5-di$MeOC_6H_3CH_3$
m = 8, 10, 12

(12)

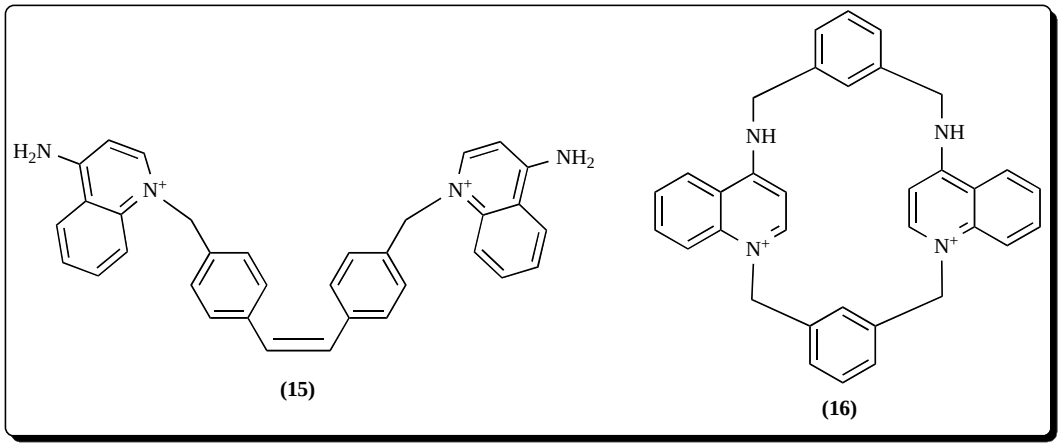


(13) **(14)**

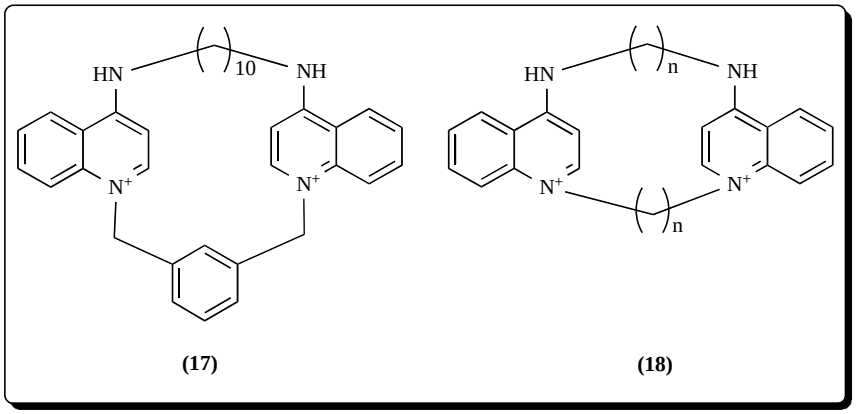
nitrogen atoms, while association of the charged quinoline rings at the 2 position (**13**) or the use of isoquinoline rings instead of quinoline ones (**14**) led to a sharp decrease in activity (IC_{50} = 4700-25,000 nM). For compounds (**12**), the role played by the nature of the quinoline ring [43] and the effect of the linker length [40], which varied from 3 to 12 methylene fragments, was studied. The best results were obtained for compounds with an unsubstituted amino group introduced at the 4 position, while the linker length played an insignificant role, at it did in (**11**).

The flexible polymethylene linker was replaced by a rigid or semirigid linker consisting of aromatic compounds (structures of type **15**) [39]. As a result, the activity of the compounds became two or more times higher than for the aliphatic linker. Variation of aromatic and fatty aromatic linkers led to the variation of activity by one order of magnitude within the series. The activity of compounds with *meta*-substituted biphenyl linkers (IC_{50} = 290 nM) was found to be similar to that of compounds with more rigid phenanthrene (IC_{50} = 200 nM) and *cis*-stilbene (IC_{50} = 190 nM) linkers. Separation of the two benzene rings of the *meta*-biphenyl linker by a polymethylene chain of one, two, three, or four units did not markedly affect the activity of the compounds (IC_{50} = 450, 410, 200, and 370 nM, respectively). However, rigid bridges such as the double (*trans*-stilbene) or triple bond or an additional benzene ring between the benzene rings reduced the activity (IC_{50} = 940, 1000, and 1900 nM, respectively). It is interesting to note the fivefold difference in activity between *cis*- and *trans*-stilbenes. The activity increased drastically when the distance between the onium groups was decreased by using the *meta*- instead of *para*-xylene linker (IC_{50} = 800 and 2800 nM, respectively).

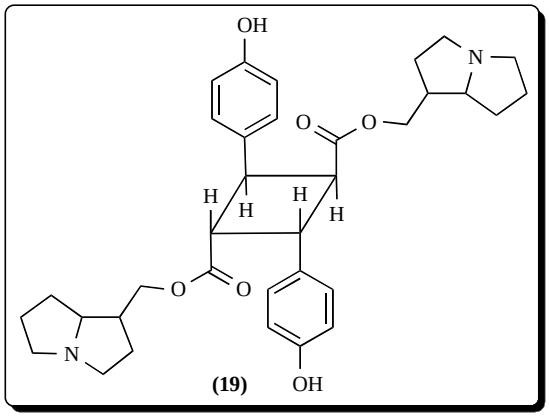
The creation of structures (**16**) with quinoline rings connected by two rigid linkers of phenyl or benzyl fragments led to a slight increase in the biological activity (IC_{50} = 70-570 nM). In the series in question, the activity changed by two orders of magnitude depends on the nature of the linkers. Structure (**16**) was the most active compound in this series;



(15) **(16)**



(17) **(18)**



(19)

its activity (IC_{50} = 3 nM) was approximately a hundred times higher than the activity of compounds with one rigid linker [41].

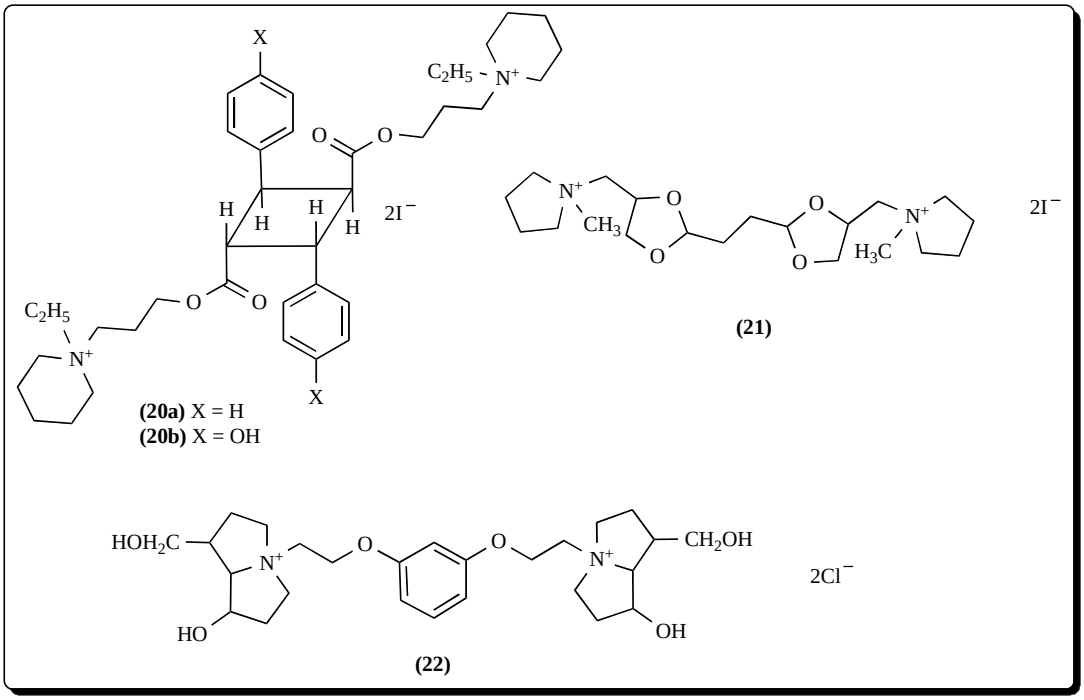
Combination of aliphatic and aromatic linkers (structures **17**) did not lead to any serious changes in the activity (IC_{50} = 60-600 nM) [42]. The use of two flexible aliphatic linkers (structures **18**) allowed researchers to detect the most active compound in the series (n = 5, IC_{50} = 2 nM) [45].

MYORELAXANTS WITH SATURATED HETEROCYCLIC FRAGMENTS

This section considers the structures of compounds with piperidine, morpholine, indolenine, or other saturated heterocyclic fragments in their frameworks.

A series of studies were undertaken after the discovery of curarelike properties in the alkaloid thesine (**19**) and its form diquaternized with methyl iodide [47, 48]. Diquaternized compounds with a central cyclobutane ring were synthesized. In the chemical transformations, the distances between the onium groups and the nature of the radicals at the quaternary nitrogen atoms changed. Thus, compound (**20a**) proved quite effective and led to a myoneural block in cats (dose 80-90 μg/kg). This compound was called anatruxonium and introduced in clinical practice in the USSR. Curiously, the replacement of phenyl by phenol fragments (compound **20b**) led to a twofold decrease in myorelaxant activity (myoneural block in cats, dose 150-180 μg/kg). The replacement of piperidine by morpholine rings was also ineffective because the products did not possess curarelike activities.

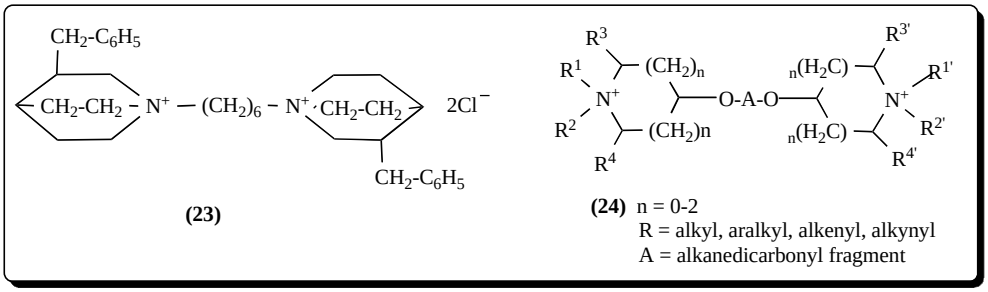
The synthesis and pharmacological studies of dioxonium (**21**) were described in [49]. This is a depolarization-noncompetitive drug, which is approximately 20 times more active than tubocurarine.



(20a) X = H
(20b) X = OH

(21)

(22)



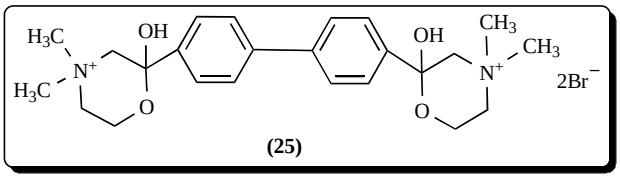
(23)

(24) n = 0-2
R = alkyl, aralkyl, alkenyl, alkynyl
A = alkanedicarbonyl fragment

Diplacin (**22**), a compound that is comparable to tubocurarine in the mechanism of its activity, is highly soluble in water due to four hydroxyl groups. This, together with myorelaxant activity that excludes respiratory standstill, makes it a very valuable myorelaxant, widely used in clinical practice.

Qualidyl (**23**) is a nondepolarizing drug, which has a short distance between the quaternized nitrogen atoms (six carbon atoms). It is characterized by high myorelaxant (causing head tilt in rabbits, dose 0.062 mg/kg) and moderate ganglioblocking activities [50]. This drug has successfully passed clinical tests and was approved for wide application.

A series of compounds of type (**24**) with an alkanedicarbonyl fragment between the saturated heterocyclic rings are described in patent [51]. The compounds are myorelaxants with moderate activity.



(25)

A number of compounds with a biphenyl linker between the charged fragments of molecules have been synthesized [52]. Compound (**25**) containing morpholine rings in its structure proved most active [53]. It has ED_{50} 4-40 μg/kg when applied to different muscles. The analogs of this compound were also synthesized and tested [54, 55]. The structural modifications involved changes in both the cation part of the molecule and the nature of the linker, which was replaced by diphenylmethane, diphenylester, or benzidine groups. All products showed lower activity than (**25**).

A group of asymmetric myorelaxants have a saturated heterocyclic fragment and an aliphatic chain with a quaternized nitrogen atom in their structure. Syntheses of a large series of compounds with a di- or tripeptide chain as a linker (structures of type **26**) were described in [56]. According to pharmacological tests, for compounds with a dipeptide linker the resulted in two or three orders of magnitude lower activity than reference compounds such as atracurium (2) both *in vitro* and *in vivo* (ED_{90} = 20-1000 μmol/kg). Those molecules, whose charged parts were linked by a tripeptide chain, showed different activities varying from nearly zero to high activities comparable to those of drugs currently in use in clinical practice. These are compounds (**27**) and (**28**), for which ED_{90} = 0.68 and 0.23 μmol/kg, respectively. In the same series of experiments on anasthetized cats and monkeys, the reference drug atracurium showed ED_{90} = 0.41 μmol/kg. The data obtained by the authors suggested that peptide linkers were very promising for creating synthetic diquaternized myorelaxants.

Several antagonists of acetylcholine, including diquaternized myorelaxants, possess a ganglioblocking activity.

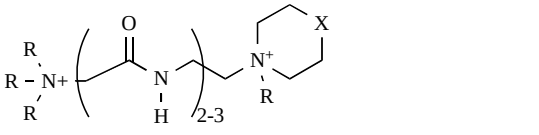
A group of asymmetric diquaternized compounds have been synthesized [57, 58], in which the charged heterocyclic and aliphatic parts of the molecule are linked *via* an ester group (**29**). It was noted that for n = 2, compounds with methyl substituents showed the greatest activity. Replacement of N-methyl by ethyl groups reduced the activity by a factor of 30 to 40; in the presence of a methylpiperazine fragment, the activity decreased hundredfold. The activity increased slightly (by a factor of 1.5-2) when the polymethylene chain became longer (n = 3), but decreased for n = 4.

Long-acting gangliolytics are camphonium (**30**), dimecoline (**31**), and chisindamon (**32**).

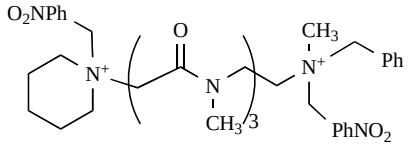
MYORELAXANTS CONTAINING ALKYLAMINE FRAGMENTS

This group of myorelaxants includes compounds in which the quaternary nitrogen atom is bonded to alkyl substituents. This is a wide group of compounds, many of which are currently in use in clinical practice.

One of the basic compounds from this group is the depolarizing myorelaxant dithylinum (**33**) also known as Suxamethonium. The dithylinum molecule can be regarded as a double acetylcholine molecule. This drug is widely used in medicine.



(26) R= Me, CH_2Ph, allyl, CH_2PhNO_2
X = O, N



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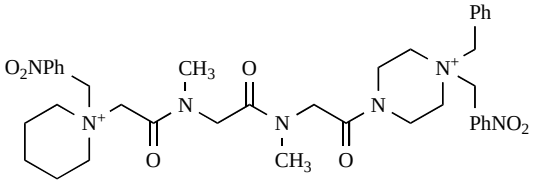

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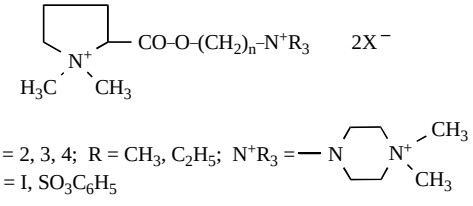
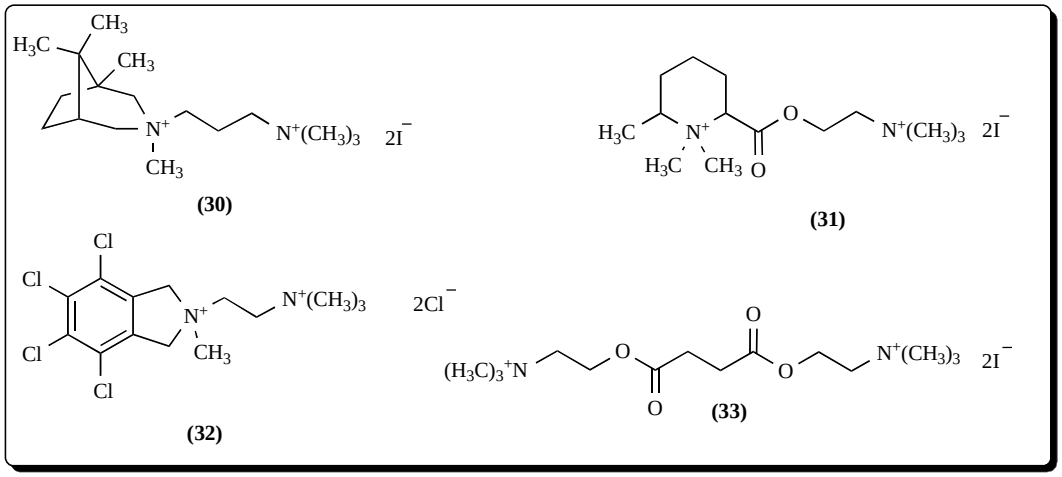
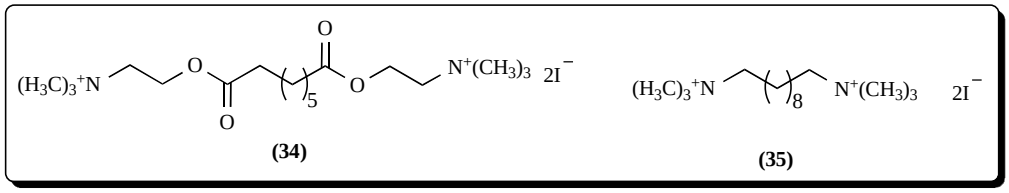


(29), n = 2, 3, 4; R = CH_3, C_2H_5; N^+R_3 =
X = I, $SO_3C_6H_5$



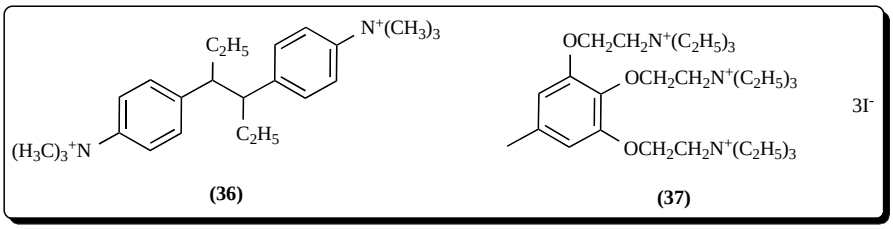


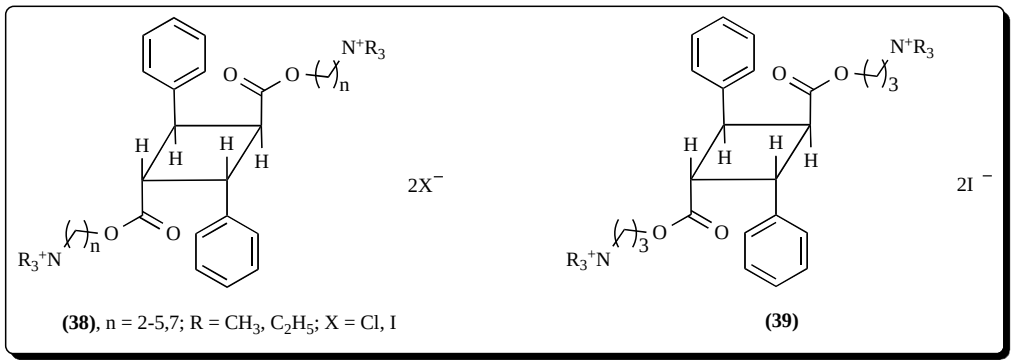
Imbretyl (**34**) differs from dithylinum in two amine fragments in the linker and a larger number of methylene units. The decamethonium molecule (**35**) does not contain any heteroatoms in the linker. Both compounds possess a high myorelaxant activity.

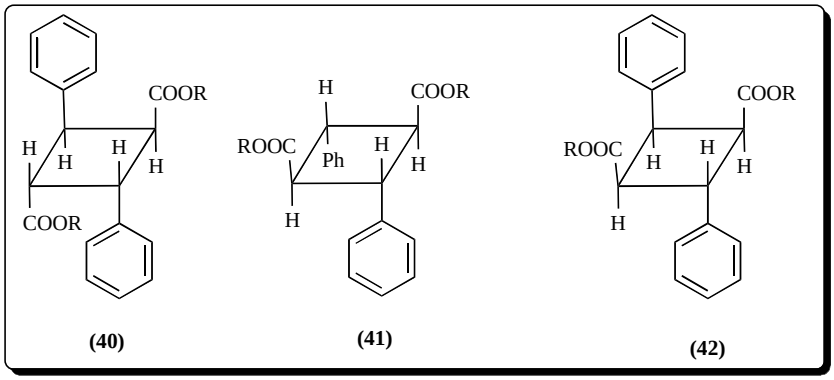
Paramyon (**36**) was widely used as a nondepolarizing myorelaxant in clinical practice in the 1960s and 1970s in the USSR, but was taken out of production later. Pyroxalon (**37**) is the only myorelaxant with three quaternized nitrogen atoms among myorelaxants that are currently in use.

Syntheses of compounds (**38**) with cyclobutane as the central fragment (as in (**19**) and (**20**)) were reported in a series of publications [59-63]. The attention was focused on studies of the structure-property relationship of the products. It was found that sequential replacement of methyl groups by ethyl ones increased the myorelaxant activity of the compound. The activity was also greatly affected by a change in the number of methylene fragments. The compound with n = 3 was most active. At n = 4 or 5, the activity slightly decreased and dropped drastically when the number of methylene units increased to 7 or decreased to 2. The most active compound in this series was called cyclobutonium (**39**) and introduced in clinical practice.

The same authors studied the spatial arrangement of substituents relative to the plane of the cyclobutane ring in the derivatives of α- (**40**), ε- (**41**), and γ- (**42**) truxillic acids. The

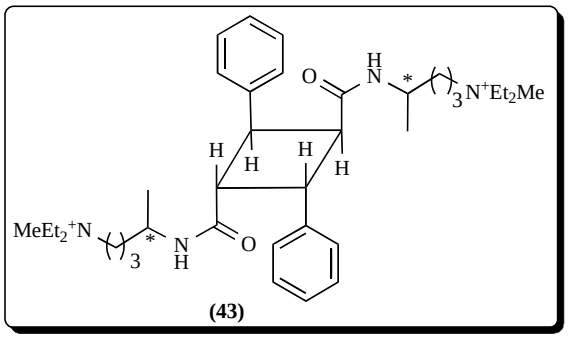






(40) **(41)** **(42)**

structure of α-truxillic acid was found to be optimum for interaction with cholino receptors. The derivatives of ε- and γ-truxillic acids were much (5- to 170-fold) less effective than the corresponding derivatives of α-truxillic acid.



(43)

The myorelaxant activity of the compounds also depends considerably on stereoisomerism due to the chiral carbon atoms (marked by asterisks) of the aliphatic chain. The myorelaxant activity of the optically active form of (**43**) is ten times higher than that of the racemate.

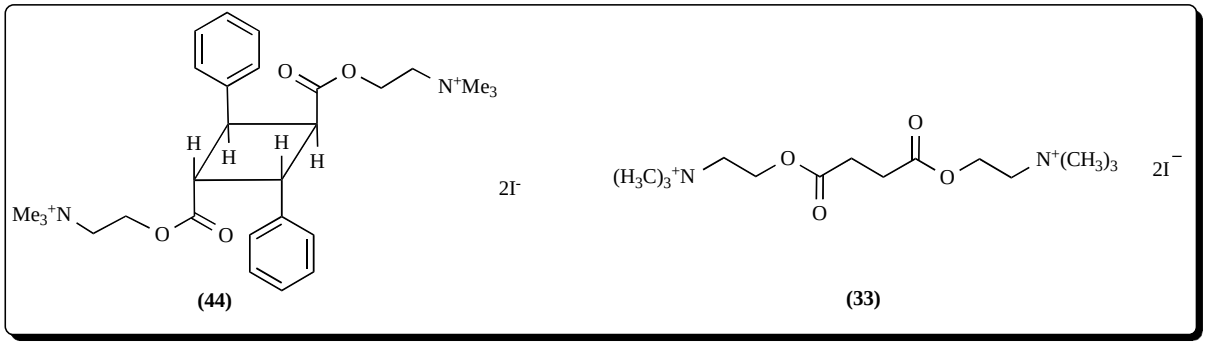
The activities of the series of compounds in question relative to the activity of tubocurarine reported in [2] are presented in Table **1**.

It is interesting to note that the substituted cyclobutane ring affects the mechanism of myorelaxation. If the two central methylene groups of the depolarizing myorelaxant dithylinum (**33**) are replaced by a substituted cyclobutane fragment, then product (**44**) will have a pronounced nondepolarizing activity.

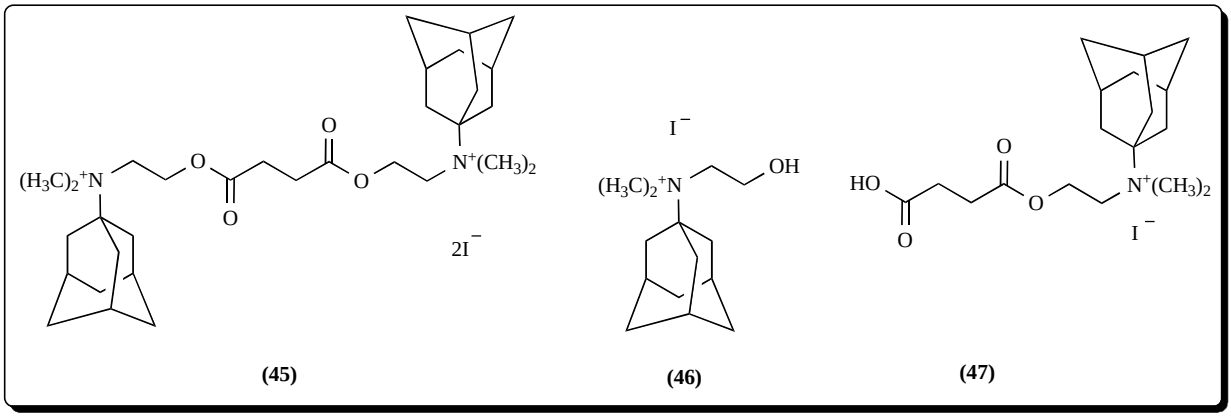
Another method for converting depolarizing drugs into nondeporalizing ones is replacing one methyl substituent at the charged nitrogen atom (e.g., in dithylinum) by the lypophilic 1-adamantyl radical. The product (**45**) called diadonium is a nondepolarizing myorelaxant, which causes

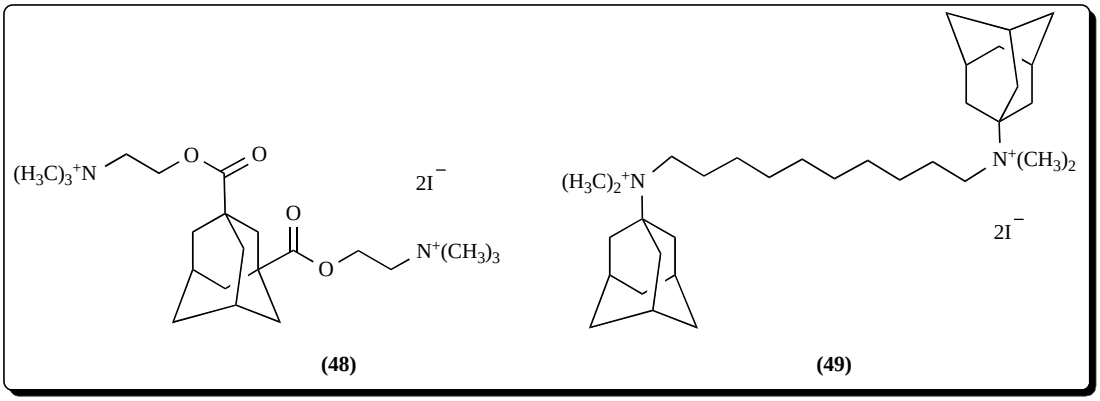
Table 1. Comparative Activities of Myorelaxants

Myorelaxant	Head tilt in rabbits (μg/kg, intravenously)	Blocking the excitation transfer from the sciatic nerve to the gastrocnemius muscle in cats (μg/kg, intravenously)
Tubocurarine (**1**)	120	125
Dithylinum (**34**)	120	60-80
Decamethonium (**35**)	78	30
Paramyon (**36**)	70	200-300
Pyroxalone (**37**)	200-250	850-900
Cyclobutonium (**39**)	32-43	130-180



(44) **(33)**

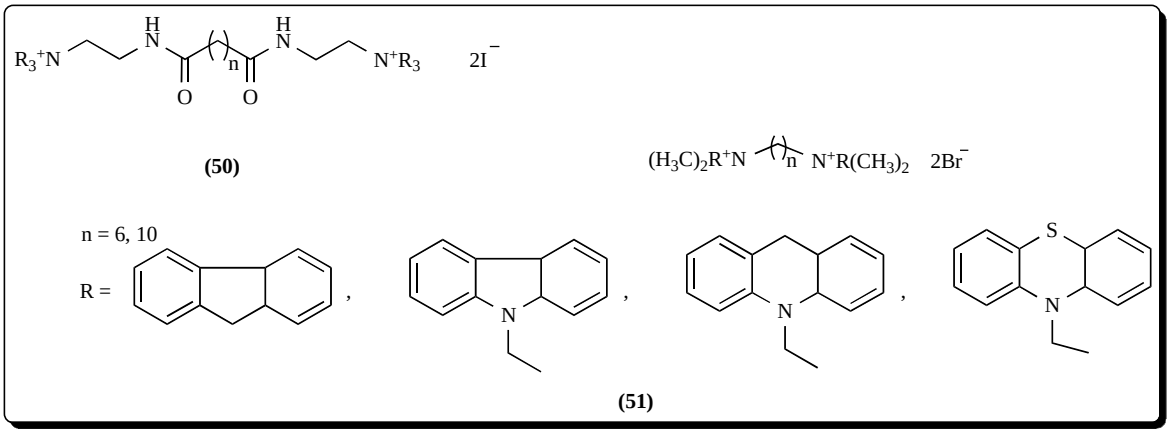


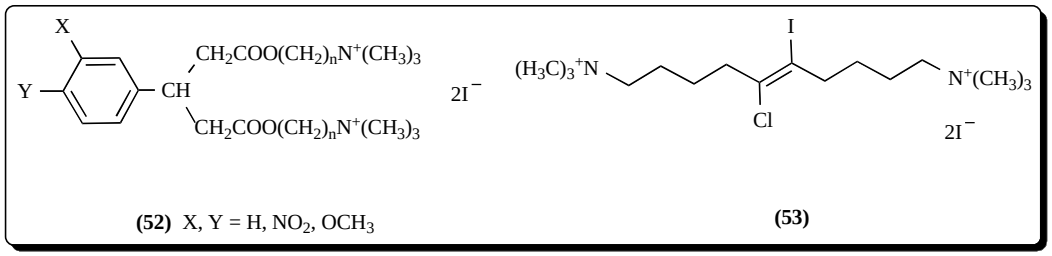


head tilt in rabbits in doses from 90 to 110 μg/kg. The hydrolysis products (**46**) and (**47**) of diadonium were also tested. Both also proved to be nondepolarizing myorelaxants, which were 20 to 40 times less active than diadonium. Curiously, the addition of adamantyl radicals to the linker's methylene groups adjacent to the nitrogen atoms, but not to the nitrogen atoms of dithylinum also changed the mechanism of myorelaxation to nondepolarizing, but the activity of the product was 50 to 60 times lower than that of (**45**) [64]. The activity of the product was still lower if the adamantyl radical was introduced at the center of the molecule (compound **48**). The replacement of methyl substituents by adamantyl radicals in decamethonium led to compound (**49**) called decadonium. This is an effective myorelaxant, blocking the transfer of excitation from the sciatic nerve to the gastrocnemius muscle in cats in doses from 250 to 300 μg/kg. The decadonium homologs with 9 to 11 methylene units in a linker exhibited lower activity.

In general, the following conclusions can be made for this group of compounds. The replacement of hydrogen atoms or methyl groups by adamantyl radicals in a number of depolarizing myorelaxants changes the mechanism of myorelaxant action to nondepolarizing irrespective of the site of the adamantyl residues. The most active myorelaxants are compounds with adamantyl radicals substituted for methyl groups at the quaternary nitrogen atoms.

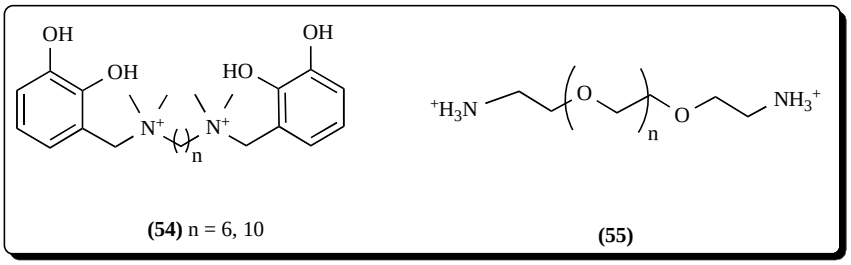
Syntheses of dicarboxylic acid amides were reported in [65, 66], and later, the corresponding bis-quaternary salts of type (**50**) were prepared from them. The number of methyl-





(52) X, Y = H, NO_2, OCH_3

(53)



(54) n = 6, 10

(55)

ene units in the linker was varied from 0 to 8; the methyl and benzyl radicals were used as substituents at the charged nitrogen atoms. It was shown that the compounds had moderate myorelaxant activity. The diquaternized compounds prepared from succinic acid were 1.5 times more active than the corresponding derivatives of adipic acid. Syntheses of compounds (**51**), which are analogs of decadonium containing aromatic fluorenyl, carbazyl ethyl, or phenothiazinyl substituents instead of the adamantyl radical, were described in [67]. It was noted that the mechanism of the activity of the products changed compared with the mechanism of decamethonium.

The electronic effects of substituents in the central phenyl ring of diquaternized structures (**52**) on the myorelaxant activity of the compounds were reported in [68]. It was found that both electron-acceptor (NO_2) and electron-donor (OCH_3) substituents in any combinations decreased the activity of the derivatives by a factor of 4 to 8 compared with the unsubstituted analogs. This suggests that steric effects on the properties of myorelaxants were stronger than the electronic ones. The introduction of a double bond flanked by two halogen atoms (structure **53**) in a linker of decamethonium did not cause any serious changes in the activity (ED_{50} = 0.43 and 0.37 mg/kg for 53 and decamethonium, respectively) [69].

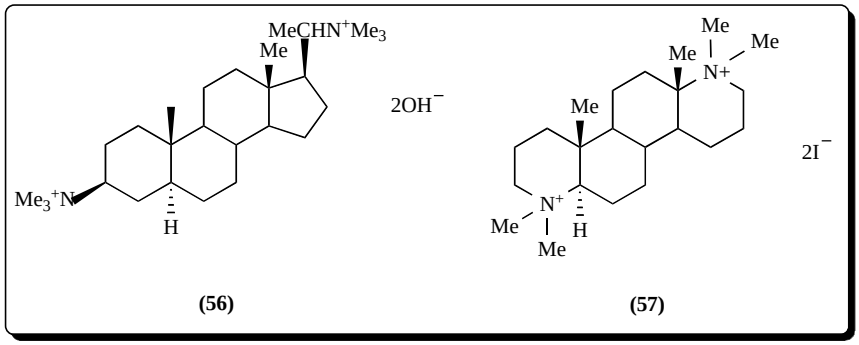
The binding of the synthesized analogs (**54**) of decamethonium (n = 10) or hexamethonium (n = 6) with the acetylcholine receptor was reported in [70]. It was found that the replacement of a methyl group by a catechol fragment did not result in cardinal changes in the binding constants with the receptor. Electrophysical experiments [71] showed that the association and dissociation constants of compounds (**55**) with the acetylcholine receptor depended on the length of the linker between two quaternized nitrogen atoms. The linker consisted of polyethyleneglycol units, whose number was easily varied. The binding constants decreased as the spacer length increased (n was varied from 2 to 20).

MYORELAXANTS WITH A STEROID FRAMEWORK

The discovery in the 1960s of the myorelaxant activity of the steroid malouetin (**56**), which was comparable to the activity of tubocurarine, has stimulated synthesis of diquaternized myorelaxants with a steroid framework as a nucleus. Compound (**57**) also had an activity comparable to that of tubocurarine, but longer action time and faster response of the organism to drug administration [73].

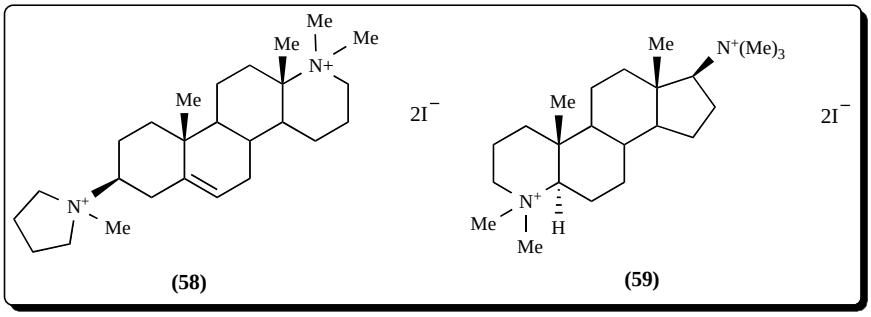
In the series of azasteroid myorelaxants, chandonium (**58**) is a powerful nondepolarizing short-acting drug with a short action time. Compound (**59**) was slightly less active [74].

Myorelaxants with a steroid framework do not possess hormonal activity because these are nondepolarizing blockers with a myorelaxant activity that is comparable to that of

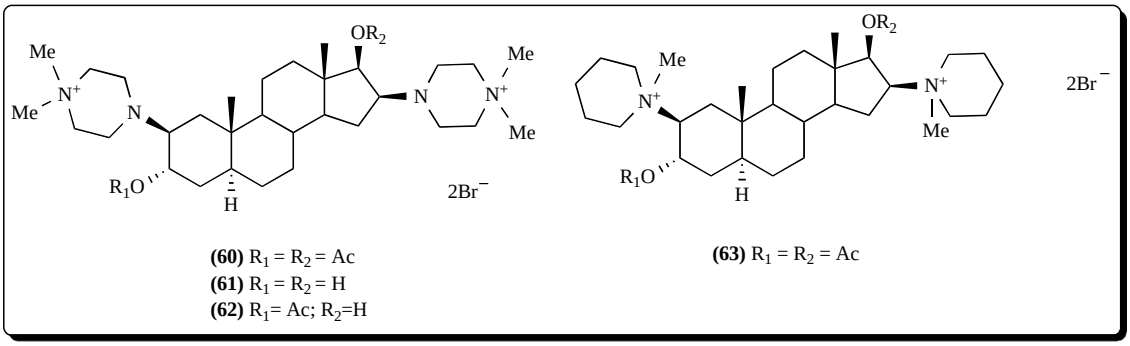


(56)

(57)



(58) **(59)**



(60) $R_1 = R_2 = Ac$
(61) $R_1 = R_2 = H$
(62) $R_1 = Ac$; $R_2 = H$

(63) $R_1 = R_2 = Ac$

tubocurarin. Some of these compounds, for example, arduan (**60**) and pancuronium (**63**), were introduced in clinical practice. A number of androstane derivatives with quaternized nitrogen atoms in the piperazine and piperidine rings were synthesized, as reported in [75]. Variation of substituents in the androstane framework affected the myorelaxant activity of the products.

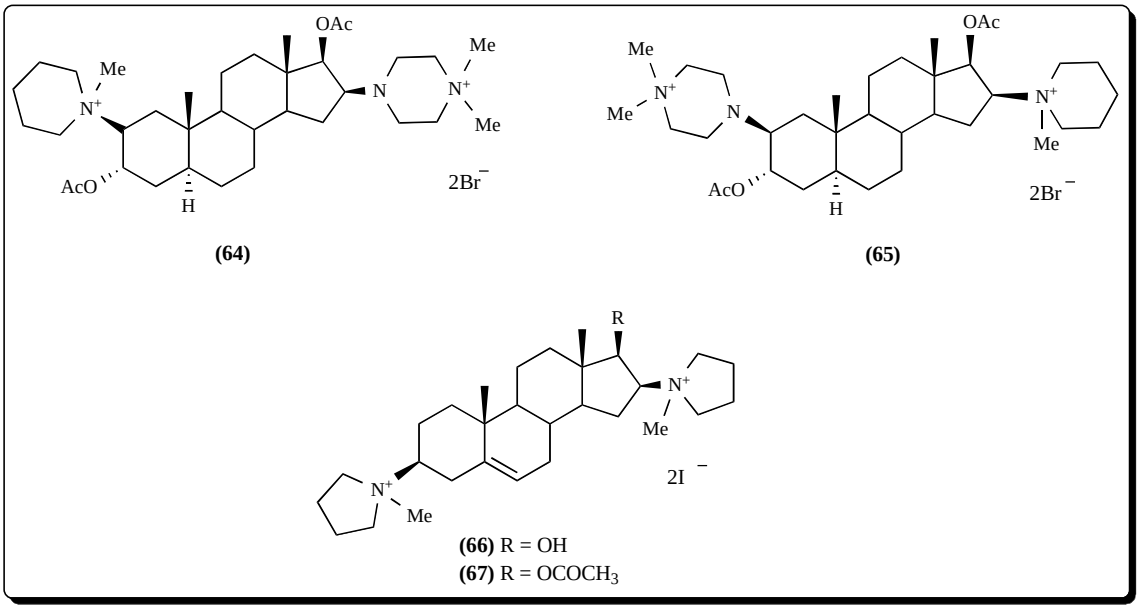
The most active compound is (**60**). The activity decreased dramatically when the ester groups were replaced by hydroxyl ones (compound **61**). Compound (**62**), having both these groups, showed intermediate activity.

Variation of the distance between the onium groups by synthesizing the asymmetric compounds (**64**) and (**65**) did not change the activity relative to the symmetric analogs, but the myorelaxant effect time decreased.

Working in this direction, the authors of [76] synthesized compounds (**66**) and (**67**) containing charged pyrrolidine fragments and various substituents in the androstane framework. Biological tests of the products revealed that hydroxyl-substituted derivative (**66**) had an activity comparable to that of tubocurarine, and myorelaxant (**67**) having an ester substituent exceeded tubocurarine by a factor of four in its activity.

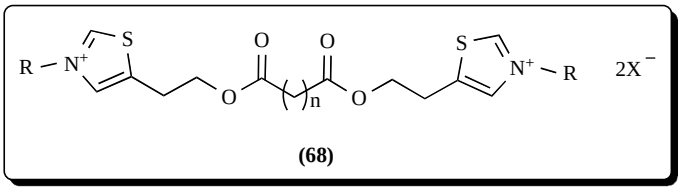
MYORELAXANTS WITH OTHER FRAMEWORKS

A number of short-acting myorelaxants (**68**, **69**) were synthesized by modifying dithylinum [77]. The quaternized

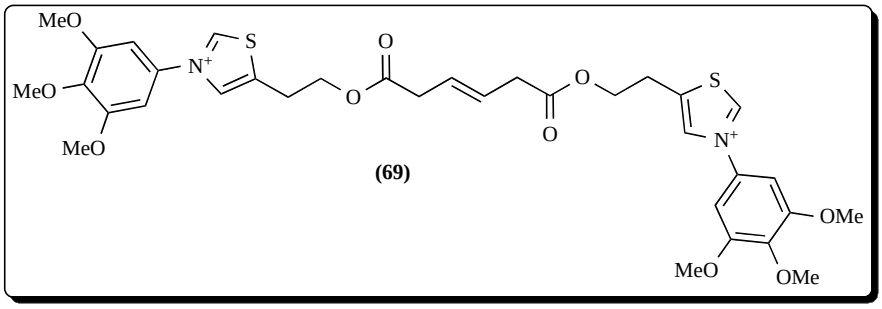


(64) **(65)**

(66) R = OH
(67) R = $OCOCH_3$



(68)

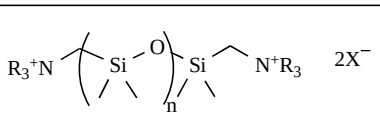


(69)

nitrogen atom was placed in the terminal thiazoline ring. In series (**68**), the nature of the substituent at the charged nitrogen atoms was varied; the number of methylene units n was varied from 2 to 6. As substituents, methyl, ethyl, and benzyl, as well as derivatives with substituted electron-donor and acceptor groups, were used. Compound (**69**) contained a central ethylene fragment and trimethoxybenzyl substituents at the quaternized nitrogen atoms. Biological tests were performed with an atracurium reference sample; the action time and efficiency of the compounds were tested. The activity of the compounds increased from alkyl to benzyl and substituted benzyl substituents; e.g., ED_{95} was 6-8 mg/kg for R = Me and 1 mg/kg for R = CH_2Ph. The compound with n = 3 and 3,4,5-trimethoxybenzyl groups as substituents was most active (ED_{95} = 0.2 mg/kg versus ED_{95} = 0.16 mg/kg for the atracurium reference). It is interesting to analyze the effect of the linker length on the action time and efficiency of the compounds with different R substituents. For methyl substituents, sequential lengthening of the linker (n = 2, 3, 4) changed the action time (14, 30, and 15 min, respectively), but not the efficiency of the compound (ED_{95} = 6-8 mg/kg). The case was similar with ethyl substituents. For 3,4,5-trimethoxybenzyl substituents, sequential lengthening of the linker (from n = 2 to n = 6) changed the efficiency (ED_{95} = 0.6, 0.2, 0.4, 1.0, and 1.5 mg/kg, respectively).

Compound (**69**) has ED_{95} = 0.75 mg/kg and action time 4 or 5 min.

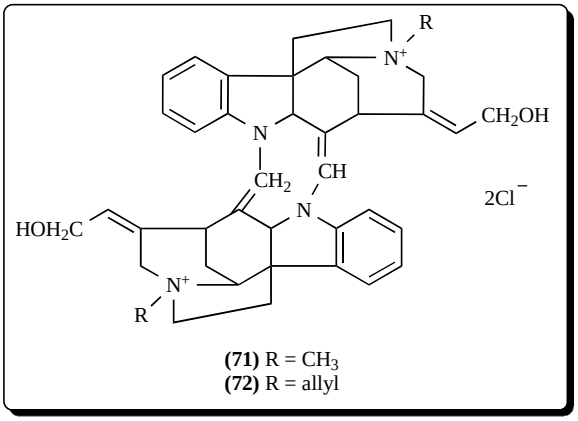
A new class of curarelike compounds - oligodimethylsiloxanes blocked by trialkylammoniomethyl groups (**70**) - were described in [78]. Compounds of this type are highly toxic (LD_{50} = 2-10 mg/kg, intraperitoneally) and suppressed the traction amplitude by 80% at a concentration of 10^{-4} g/ml.



(70) n = 1-3; R = Me, Et; X = I, Cl;

NATURAL AND SYNTHETIC ALKALOID MYORELAXANTS

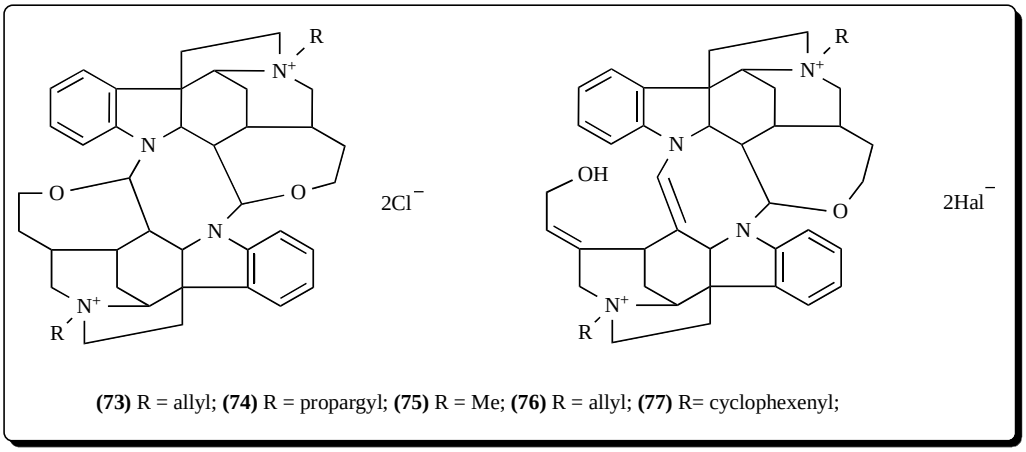
Tubocurarine (**1**) is the best known natural alkaloid myorelaxant. The diquaternized natural myorelaxants toxiferin (**71**) and alkuronium (**72**) were extracted from a plant of the family *Strychnos* and studied [79, 80].



(71) R = CH_3
(72) R = allyl

A wide range of diquaternized myorelaxants were isolated from the natural alkaloids caracurine and isocaracurine, which differ in the number of cyclic ester rings, for example, (**73**, **74**) and (**75-77**), respectively [80].

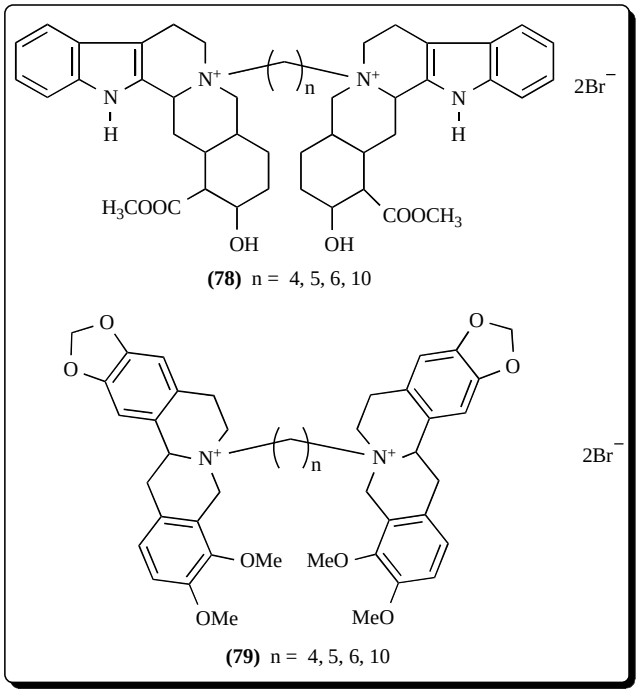
The authors addressed the important role of the nature of the varied substituent at the charged nitrogen atom. Thus, the substituents used in structures (**73**) and (**74**) included alkanes, alkenes, alkynes, cycloalkanes, and aromatic and heterocyclic substituents. The compounds with the allyl and propargyl substituents possessed the highest activity. The substituent at the charged nitrogen atom plays an important role if it is unsaturated. Thus, hydrogenation of the triple bond of the propargyl substituent led to an eightfold reduction in the myorelaxant activity. Replacement of the ethynyl group by an isosteric cyano group in the propargyl substituent led to a 50-fold decrease in activity. The lengthening of the allyl or propargyl substituents by introducing a terminal methylene unit also decreased the activity by a factor of 11 and 7, respectively. Finally, a comparison of the diaquater-



(73) R = allyl; **(74)** R = propargyl; **(75)** R = Me; **(76)** R = allyl; **(77)** R= cyclophexenyl;

nized compounds and the corresponding bases showed that quaternization increased the activity 50- to 100-fold.

Diquaternized compounds were also synthesized by bridging the charged yochimbine (**78**) and tetrahydroberberine (**79**) molecules *via* methylene units, and their myorelaxant activity was studied [81]. For bis-tetrahydroberberines, the compounds with linkers of 6 and 10 methylene units blocked the neuromuscular activity in dogs in doses of 0.5 and 0.3 mg/kg, respectively. The compound with a linker of four methylene units was inactive even in a dose of 5 mg/kg. For bis-yochimbine, the linker with four methylene units worked in the same way as when it had 10 units, blocking the neuromuscular activity in a dose of 1 mg/kg.



(78) n = 4, 5, 6, 10

(79) n = 4, 5, 6, 10

CONCLUSIONS

This review of the literature makes it possible to draw the following conclusions.

1. The compounds diquaternized at the nitrogen atom are the most active of all currently available myorelaxants and are mostly synthetic or semisynthetic products.
2. The activity, efficiency, and action time of these myorelaxants are affected by the nature of substituents at the charged nitrogen atoms and the length and character of the linker between the onium groups.
3. Synthetic procedures have been developed to control the mechanism of activity from depolarizing to nondepolarizing by introducing the lipophilic residues in the structure of the myorelaxant.
4. The character of the counterion does not affect the properties of the myorelaxant.

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