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Azasteroids as Promising Neuromuscular Blockers: A Review

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ABSTRACT

Neuromuscular blockers are used during surgery with anesthesia to cause relaxation of muscles and control muscle movements. The purpose of this review is to focus on the synthesis and pharmacological activity of the neuromuscular blockers, to compare the main differences between the available polarizing and non-depolarizing neuromuscular blockers. Continuous improvement of knowledge about neuromuscular blockers in respect to synthesis, their pharmacology, adverse effects, and toxic effects were unanswered questions about neuromuscular junction and neuromuscular blockade in children is essential for the correct use of these drugs. In this review article, structure-activity relationships within polarizing and non-depolarizing neuromuscular blockers have been reviewed.

INTRODUCTION

This review article deals with a comprehensive survey of the progress in chemical, pharmacological, and some respects of clinical studies of neuromuscular blocking agents used in clinical practice and under development, including the synthesis, structure elucidation pharmacological actions and structure activity relationship of steroidal and non-steroidal derivatives. Quaternary ammonium muscle relaxants are quaternary ammonium salts used as drugs for muscle relaxation, most commonly in anesthesia. It is necessary to prevent spontaneous movement of muscle during surgical operations. Muscle relaxants inhibit neuron transmission to muscle by blocking the nicotinic acetylcholine receptor. What they have in common, and is necessary for their effect, is the structural presence of quaternary ammonium groups, usually two. Some of them are found in nature and others are synthesized molecules (Raghavendra, 2002; Bowman, 2002). Curare is a crude extract from South American plants. It was known in the 19th century to have a paralysing effect. *d*-tubocurarine a *mono*-quaternary alkaloid was isolated from *Chondodendron tomentosum* in 1942, and it was shown to be the active chemical in curare that had the paralysing effect. At that time it was known that curare and therefore d-tubocurarine worked at the neuromuscular junction. The isolation of tubocurarine and its marketing as the drug Intocostrin led to more research in the field of neuromuscular blocking drugs. Scientists figured out that the potency of tubocurarine was related to the separation distance between the two quaternary ammonium heads (Raghavendra, 2002; Nedegard, 2003).

Further research led to the development of synthesized molecules with different curariform effects, depending on the distance between the quaternary ammonium groups. One of the synthesized *bis*-quaternaries was decamethonium a 10-carbon *bis*-quaternary compound. Following research with decamethonium, scientists developed suxamethonium, which is a double acetylcholine molecule that was connected at the acetyl end. The discovery and development of suxamethonium lead to a Nobel Prize in medicine in 1957. Suxamethonium showed different blocking effect in that its effect was achieved more quickly and augmented a response in the muscle before block.

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Also, tubocurarine effects were known to be reversible by acetylcholinesterase inhibitors, whereas decamethonium and suxamethonium blockers were not reversible (Raghavendra, 2002; Bowman, 2002).

Another compound malouétine that was a *bis*-quaternary steroid was isolated from the plant *Malouetia bequaertiana* and showed curariform activity. This led to the synthetic drug pancuronium a *bis*-quaternary steroid and subsequently other chemicals that had better pharmacological properties as drugs (McKenzie, 2000).

Classification of Neuromuscular blockers

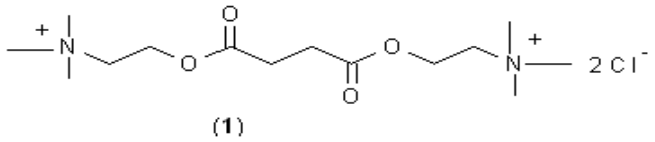
Most widely neuromuscular blockers are classified into two classes: depolarizing and non-depolarizing neuromuscular blockers (Joao *et al.*, 2000).

- Depolarizing neuromuscular blockers: There is only one depolarizing agent, succinylcholine, which mimics Ach but stays at the neuromuscular junction for a longer period of time. At first, succinylcholine stimulates the muscles, causing transient twitching and can cause painful fasciculation.
- Non-depolarizing neuromuscular blockers: They act by blocking the binding of Ach to the receptor. All of the agents except succinylcholine are non-depolarizing, which means that they work by binding to the Ach receptors on the muscle side of the junction. With these receptors blocked, Ach cannot transmit the nerve impulse, so the muscle cannot depolarize and contract.

Neuromuscular blockers are also classified on the basis of the chemical structure:

Succinylcholine and Decamethonium

Succinylcholine **(2)** was synthesized by connecting two acetylcholine **(1)** molecules and has the same number of heavy atoms between methonium heads as decamethonium **(3)**. Just like acetylcholine, succinylcholine, decamethonium and other polymethylene chains, of the appropriate length and with two methonium, heads have small trimethyl onium heads and flexible links. They all exhibit a depolarizing block (Katz *et al.*, 1966).



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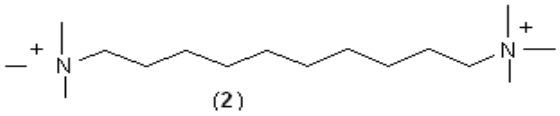

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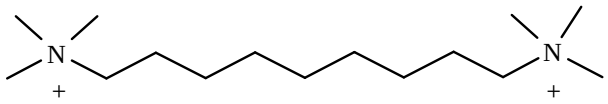

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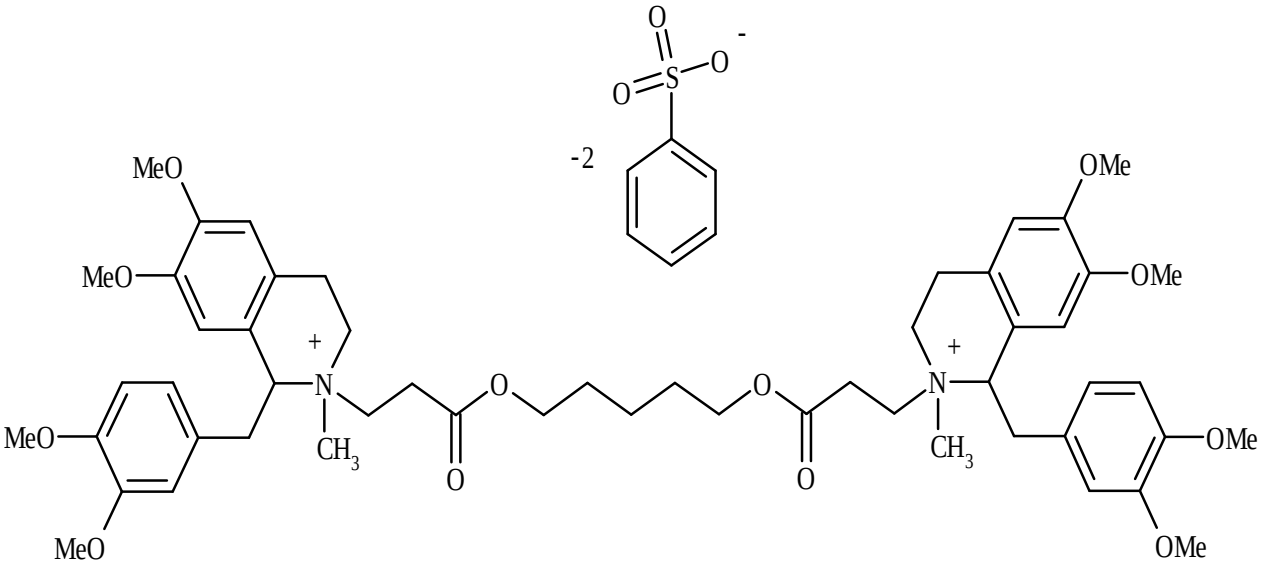
Tetrahydroisoquinoline Derivatives

Compounds based on the tetrahydroisoquinoline moiety such as **Atracurium (4),** mivacurium (Basta, 1992) **(5)** and doxacurium (Basta *et al.*, 1988) **(6)** would fall in this category. They have a long and flexible chain between the onium heads, except for the double bond of mivacurium. D-tubocurarine and dimethyltubocurarine are also in this category. Most of the agents in this category would be classified as non-depolarizing.



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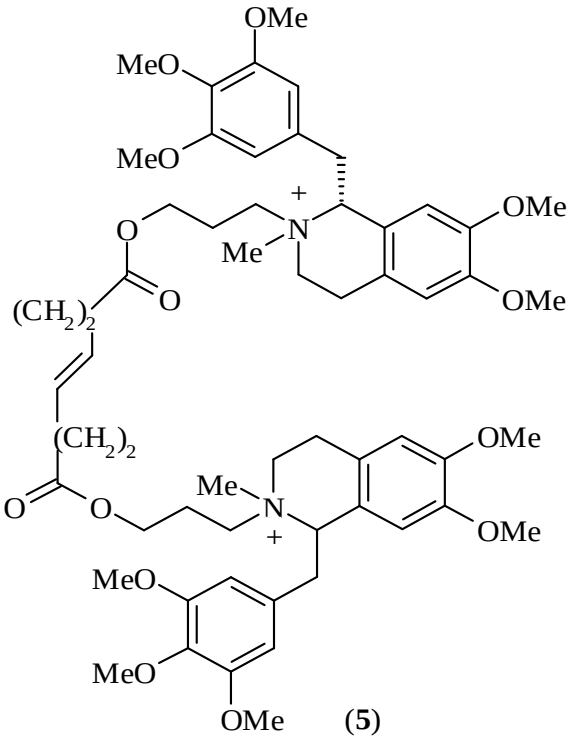

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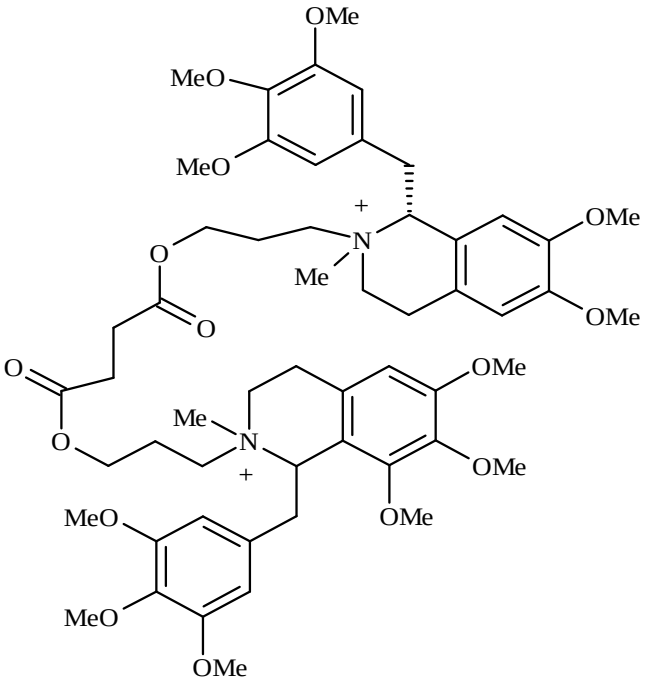

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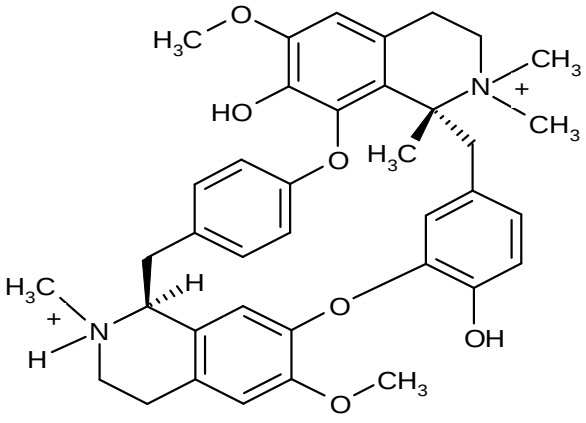
A neuromuscular non-depolarizing agent is a form of neuromuscular blocker which do not depolarize the motor end plate. The quaternary ammonium muscle relaxants belong to this class. Below are some of the more common agents that act as competitive antagonists against acetylcholine at the site of postsynaptic acetylcholine receptors. Tubocurarine **(7)**, found in curare of the South American plant Pareira, *Chonodendron tomentosum*, is the prototypical non-depolarizing neuromuscular blocker. It has a slow onset (>5 min) and a long duration of action (1–2 hours). Side effects include hypotension, which is partially explained by its effect of increasing histamine release, a vasodilator (Inada *et al.,* 1986) as well as its effect of blocking autonomic ganglia.



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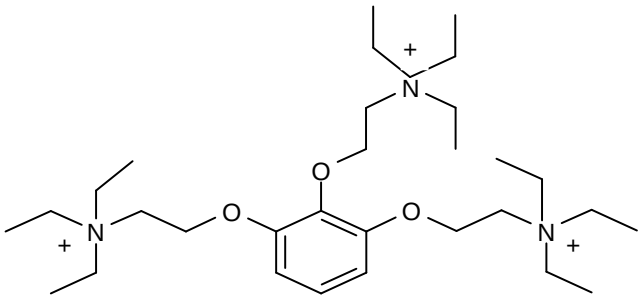
Gallamine and Other Chemical Classes

Gallamine (Ostergaard *et al.,* 1989) **(8)** is a trisquaternary ether with three ethonium heads attached to a phenyl ring through an ether linkage. Many other different structures have been used for their muscle relaxant effect such as stercuronium iodide.



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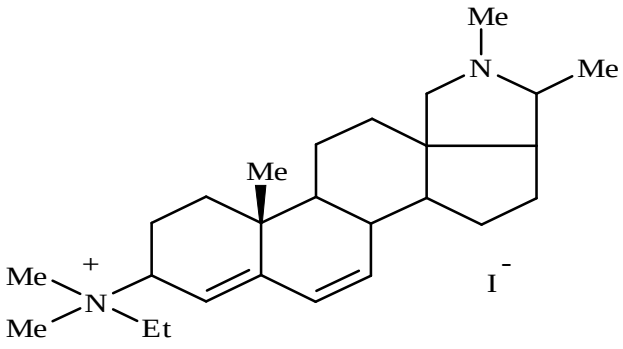
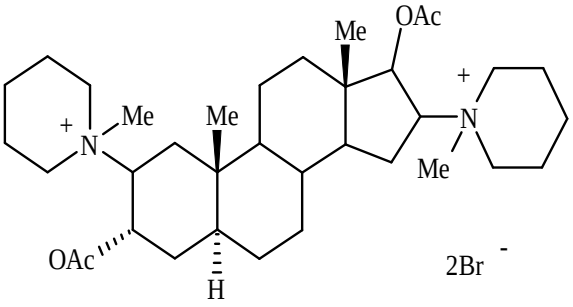


(**9**)

Aminosteroids

Pancuronium (Bowman *et al.,* 1988; Norman *et al.,* 1971) (**10**), vecuronium (Bowman *et al.,* 1988; Foldes *et al.,* 1983) (**11**), rapacuronium (Bevan, 2000) (**12**), rocuronium(England *et al.,*1996) (**13**), malouetine (Janot *et al.,* 1960, Quevauviller *et al.,* 1960) (**14**), dipyrandium (William *et al.,* 1964) (**15**), pipecuronium (Denman *et al.,* 1996; Diefenbach *et al.,* 1993) (**16**), chandonium (Singh *et al.,* 1974; Gandhia *et al.,* 1974) (**17**), and other bisquaternary ammonium compounds are aminosteroidal agents.

These agents constitute the majority of the clinically-relevant neuromuscular blockers. They act by competitively blocking the binding of Ach to its receptors, and in some cases, they also directly block the ionotropic activity of the Ach receptors (Bufler *et al.,* 1996).



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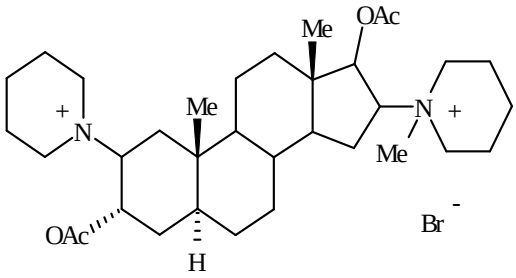

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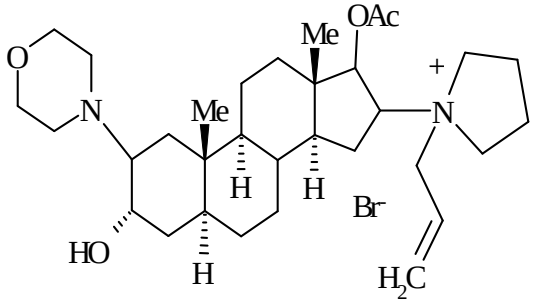

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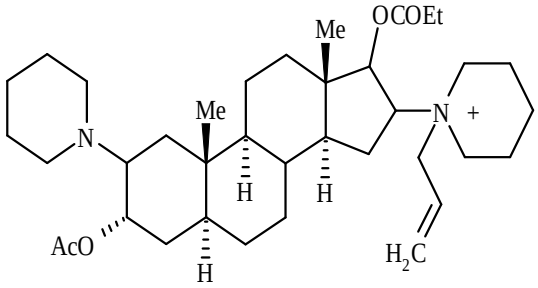

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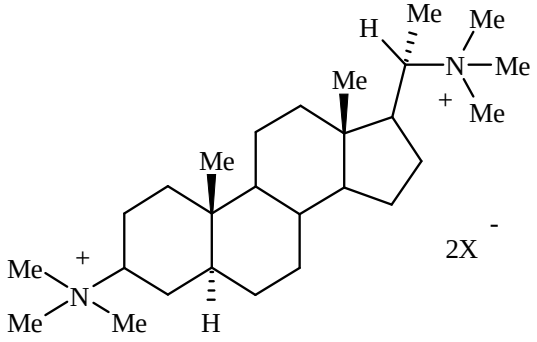

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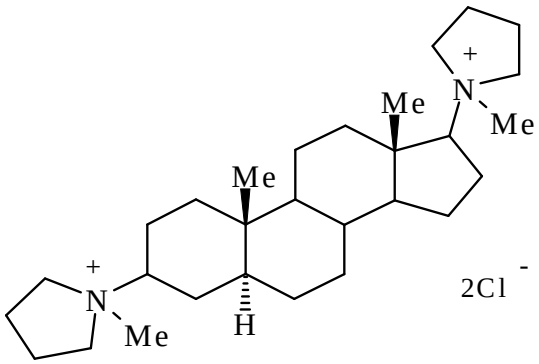

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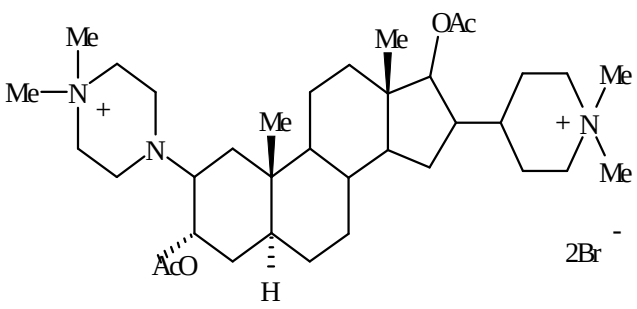

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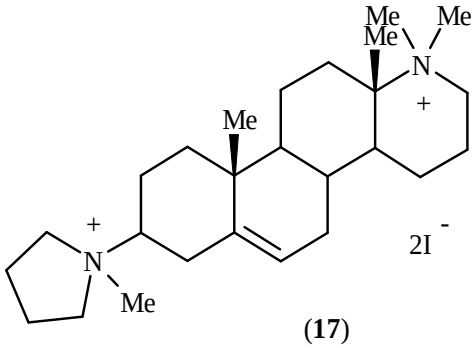


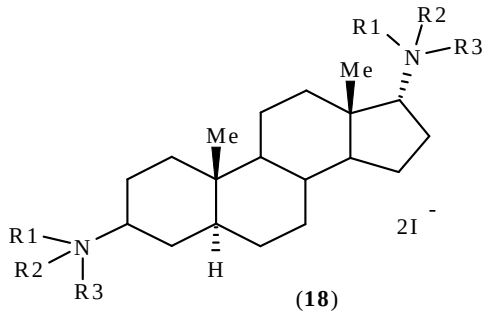
(**17**)

Aminosteroids are Non-depolarizing neuromuscular blockers having a common the steroidal structure with quaternary nitrogen which provides a rigid and bulky body (Lee, 2001).[24]

Due to flexibility in steroidal molecule various researchers synthesized aminosteroids with promising neuromuscular blocking activity will be discussed separately.

The neuromuscular blocking agents available are nonsteroidal and azasteroidal. Advances in both these areas have been reviewed (Rang, 2003; Singh *et al*., 1984; Booij *et al*., 1984; Singh *et al*., 1979; Buckett, 1972; Buckett, 1975). The work on azasteroidal neuromuscular blocking agents has been reviewed by different workers. The findings of the work are discussed here;

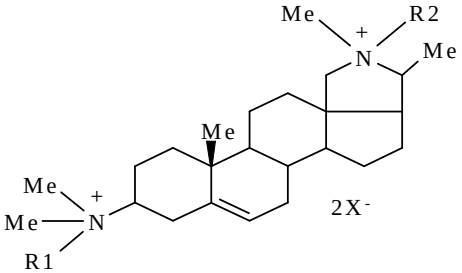
Janot *et al*, synthesized steroidal alkaloid malouetine (Janot *et al.*, 1960) **(14)** and its C-3 and C-20 configurational isomers (Alauddin *et al.,* 1962; Strange *et al.*,1997). Due to free rotation of the side chain, and as such study of bisonium azasteroids having both the quarternary ammonium groups directly attached to the nucleus was considered worthwhile.



(**18**)

Alauddin *et al*, synthesized a series of 3α,17α-*bis*(quaternary ammonium)-5α- androstanes (Alauddin *et al.*, 1965) **(18)**, in which the interonium distance (0.92- 1.06nm) was near the favourable range and steric hindrance to post junctional binding by β- face angular methyl groups on C- 10 and C- 13 was excluded. These compounds showed pharmacological activity, though less than that of (+)- tubocurarine.

Davis *et al* reviewed on dipyrandium chloride (William *et al.*, 1964; Rosemarie *et al.*, 1964) **(15)** and its eight isomers (Bamford *et al.*, 1967; Davis *et al.*, 1967) which involved *in vivo* test on cat and monkey sciatic nerve tibialis muscle preparation it was found that 3β- isomers were in general more potent than the corresponding 3α- compounds and there was no general relationship between potency and interonium distances.



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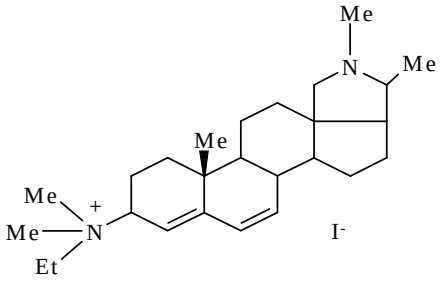
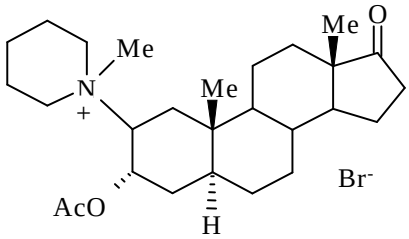


(**20**)

Clarke *et al* at Glaxo Laboratories (UK) showed quarternary salts (Busfield *et al.*, 1968) **(19)** derived from alkaloid derivatives. The bisquarternary compounds reported possess the interonium distance of 1.01nm. Seven of the eight 3- monoquarternary compounds tested were also potent neuromuscular blocking agents; this observation may not be taken as a convincing evidence for the one point attachment, since the second nitrogen could get protonated in the system and thus provide second cationic head. N, N- dimethylconessine (4; R^1, R^2 = Me) had potency comparable to that of (+)- tubocurarine; its duration of action was comparable to that of suxamethonium in the cat. The rate of recovery was slower in monkey and man (Verner, 1968). The related drug stercuronium iodide **(20)** is a monoquarternary compound. Wieriks *et al* reported non-depolarizing type, has no histamine release property and has the duration of action lying between those of gallamine and suxamethonium (Hespe *et al.*, 1971).

Pancuronium bromide (Pavulon^R) (Baird *et al.*, 1967; McDowell *et al*., 1969; Dick *et al.*, 1970) **(10)** is a successful drug discovered at the Organon Laboratories Limited (UK). Rapacuronium **(12)** and rocuronium **(13)** are pancuronium analogues.



(**21**)

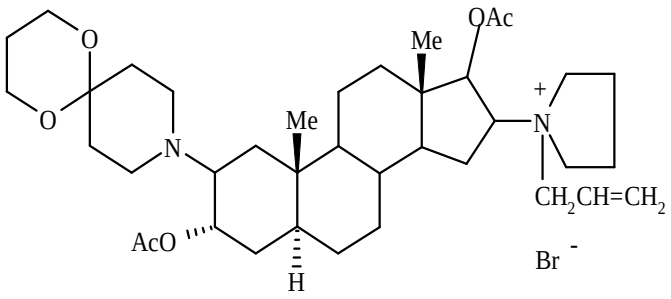
Buckett *et* a (Speight *et al.*, 1972; Buckett *et al.*, 1973, Savage *et al.*, 1968, Lewis *et al.*, 1967) study on 2β-amino-3α-hydroxyl-5α-androstanes and derivatives and the corresponding 3α- amino-2β- hydroxyl isomers, A substituent in specific molecular conformation akin to the neurotransmitter acetylcholine **(1)** and thus most potent of series 3α-acetoxy-2β-piperidino-5α-androstan-17-one-methyl bromide **(21)** may be expected to occupy the transmitter of action and neuromuscular transmission. As the monoquarternary analogue **(21)** had only a low activity, it was thought that a bisquarternary azasteroid may be potent and pancuronium bromide **(10)** was ultimately synthesized (Buckett *et*

al., 1973) and tested. Even here the 16- and 17- substituents are pseudoequatorial.

A notable discovery after pancuronium from the Organon Laboratories, is one of the potent non- depolarizing neuromuscular blocking agent vecuronium bromide (Org NC 45; Nouran) **(11)** (Buckett *et al.,* 1973; Durant *et al.,* 1983; Durant *et al.,* 1980; Booij *et al.,* 1983), which has short duration and rapid onset of action and little accumulative effect.It is suggested that quarternary ring D acetylcholine fragment is intrinsically suited to skeletal muscle nicotine receptors and is relatively unsuited to cardiac muscarinic receptors.

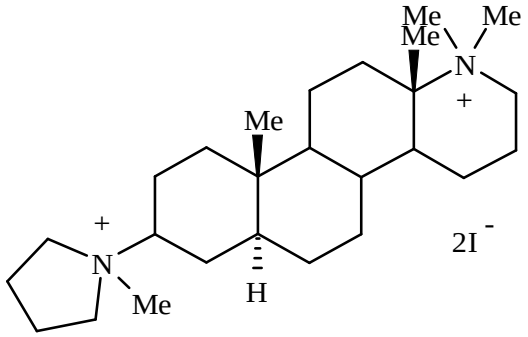
Pipecuronium bromide (RGH-1106, Asduan) **(16)** (Tuba, 1980), an analogue of pancuronium **(10)**, was discovered at the laboratories of Gadeon Richer Ltd,. (Budapest, Hungary). Pipecuronium is a non- depolarizing blocker and in animal experiments (Karpati *et al.,* 1980; Alyautdin *et al.,* 1980), it has shown activity 2-4 times than that of pancuronium and duration of action is twice as long as that of pancuronium in equiactive doses.

Tuba *et al* synthesised certain analogues of **(22)** have been prepared as neuromuscular blocking agents (Tuba *et al.,* 2003).



(**22**)

Singh *et al*, synthesized compound which proved to be of particular interest was 17α- methyl-3β-pyrrolidino- 17α-aza-D-homo-5-androstene dimethiodide (Chandonium Iodide) (Singh *et al.,* 1974) **(17)** (now candocuronium). The X- Ray diffraction studies showed the interonium distance to be 1.029nm (Gandhia *et al.,* 1974). Taking chandonium **(17)** as a model several structural modifications been carried out. Certain interesting structure activity relationships are evident.



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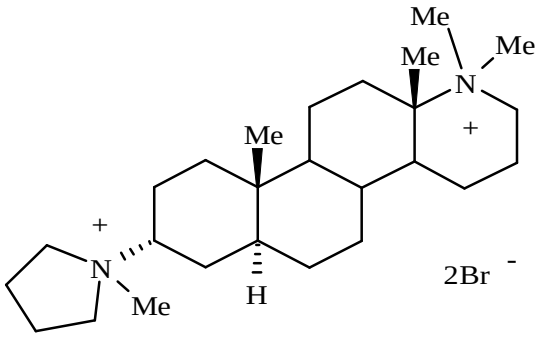
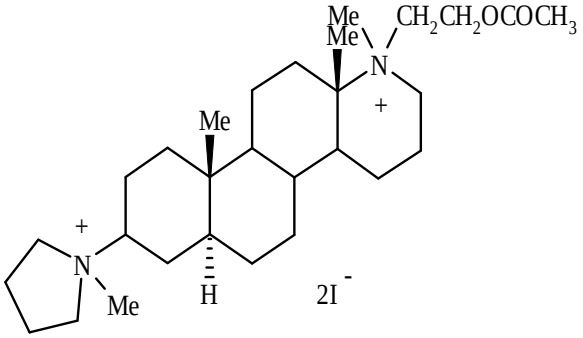


(**24**)

The saturated congener dihydrochandonium iodide **(23)** and the analogues possessing bulkier cationic heads have been synthesized (Gandhia *et al.,* 1974). Saturation of 5,6- double bond in chandonium and increase in onium bulk in **(17)** and **(24)** diminish the potency (Apon *et al.,* 1979). Dihydrochandonium iodide has half the potency of chandonium. It is again short acting but has lesser vagolytic action as noted in anaesthetized cat.



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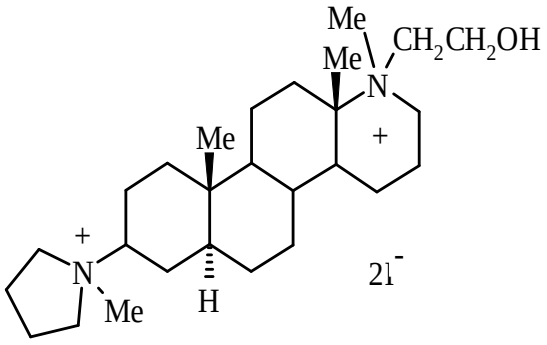
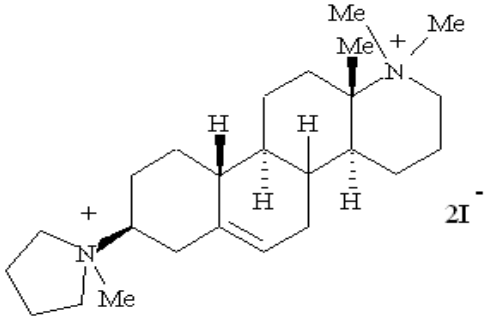


(**26**)

The Gadeon Richter scientists have designed RGH-4201 **(25)**, 3α-isomer of dihydrochandonium **(24)**, and showed it to be equipotent to chandonium in conscious dog, but 2-3 times less active in anaesthetized cat (Biro *et al.,* 1981). Notwithstanding the observation that there is a decrease in potency with increase in the onium bulk in chandonium iodide **(17)**, HS-627 **(26)**, which contains acetylcholine-like moiety was prepared (Foldes *et al.,* 1983) by Singh *et al* since, pancuronium bromide has bulky

quarternary groups and contains acetylcholine like fragments HS-627 **(26)** and HS-626 **(27)** to be 1.033nm. The synthesis of 19-norchandonium iodide **(28)** by Organon group has been reported (Singh *et al.*, 1979).



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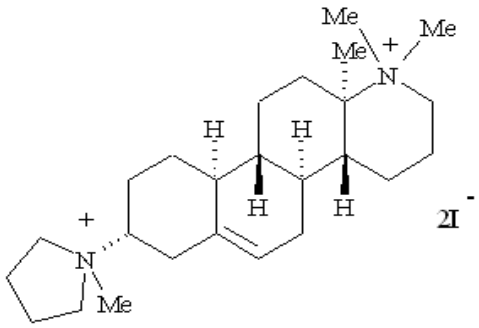
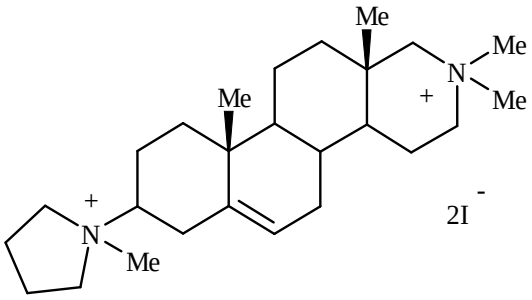


(**28**)

The 19-nor analogue **(28)** was 3-4 times less active than chandonium iodide **(17)**. Interestingly, the enantiomer **(29)** (Marshall *et al.*,1984) has virtually the same potency as **(28)**. It appears that the effect of complete change in steric configuration is insignificant compared to that resulting from the change in lipophilicity caused by the removal of the 10-methyl group of chandonium iodide.

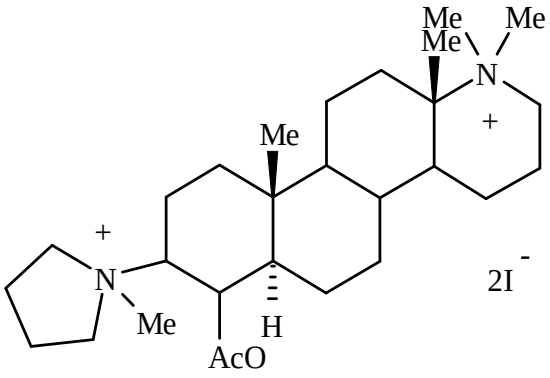


(**29**)

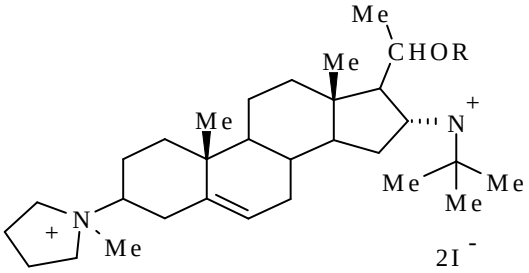
Jindal *et al* has synthesized new analogue **(30)** of chandonium and evaluated for neuromuscular blocking activity (Verma *et al.*, 1994; Yadav, 1993).

Yadav *et al*, synthesized a new azasteroidal neuromuscular blocker having acetylcholine like moiety in ring A, was found to be half as active as chandonium **(30).** (Yadav *et al.*, 2001)[66] Presence of acetylcholine like moiety in ring A enhances the neuromuscular blocking activity. They have synthesized bisquaternary azasteroid having acetylcholine like moiety at 4th position in ring A while retaining structural features of chandonium iodide. The compound was found to be half as active as chandonium. Jindal *et al*, reported the design of some quaternary ammonium steroids in pregnane series, which have in part structural features corresponding to HS-467 or chandonium **(17)** (Abraham *et al.*, 1993).

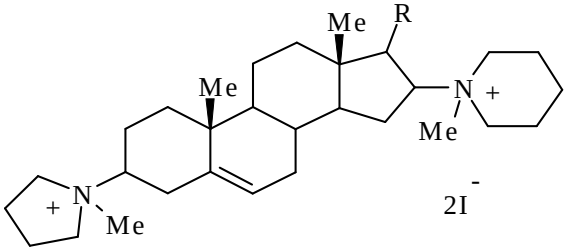
Among these compounds **(31)** found to be more potent with free hydroxyl group at position 20.



(**30**)

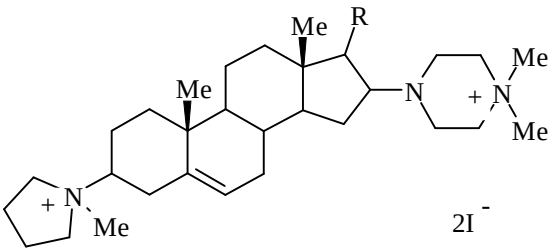


(**31**) R = H
(**32**) R = $COCH_3$



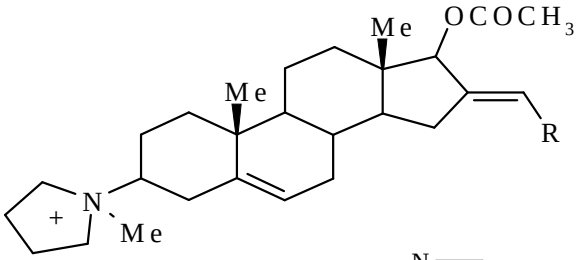
(**33**) R = H
(**34**) R = $COCH_3$

Jindal *et al* in his next research he synthesized 16β-piperidinosteroidal derivatives (Jindal *et al.*, 2001). Among these compounds **(34)** was found to be more active than d-tubocurarine. Jindal *et al*, synthesized 16β-N-methylpiperazino steroidal derivatives (Jindal *et al.*, 2002) 16-Acetoxy derivative **(36)** was found to be more potent than pipecuronium bromide.

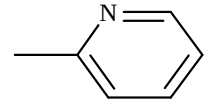


(**35**) R = H
(**36**) R = $COCH_3$

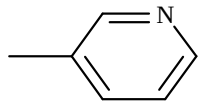
Dubey *et al*, synthesized 16-(2- and 3-pyridylmethylene) dehydroepiandrosterone derivatives (Dubey *et al.*, 2010).

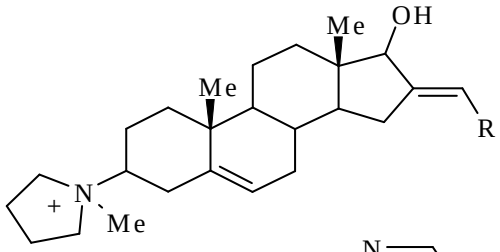


(**39**) R =

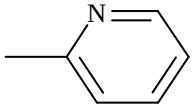


(**40**) R =

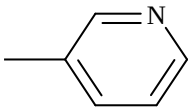




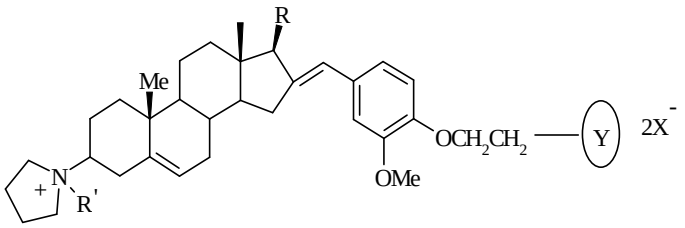
(**41**) R =

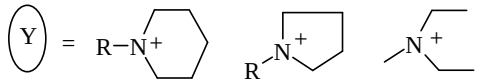


(**42**) R =



All the synthesized compounds show good depolarizing, competitive neuromuscular blocking activity, particularly 17-acetoxy derivatives **(37), (38)** than 17-hydroxy derivatives **(39), (40)** ease in interoinium distance between two nitrogens decreseases the activity.



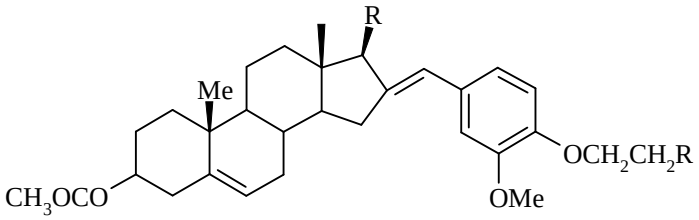


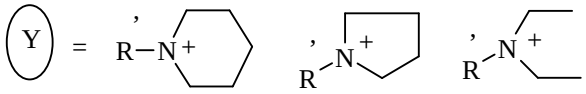
(**43**)a-d (**44**)a-d (**45**)a-d

Comp	R	R'	X
a	OH	CH_3	I
b	$OCOCH_3$	CH_3	I
c	OH	CH_2-CH=CH_2	Br
d	$OCOCH_3$	CH2-CH=CH_2	Br

Ranju Bansal *et al*, synthsised eighteen newquaternary ammonium salts16E-arylidene androstene derivative as skeletal muscle relaxant (Bansal *et al.*, 2011).

Among this series **(41 d)** was found to be having rapid onset of action at 1µM concentration in 2minutes for fifty percent blockade of chick beventer cervices preparation.





, (**46**)a-d (**47**)a-d (**48**)a-d

	R'	X
a)	CH_3	I
b)	$CH_2CH=CH_2$	Br

Among this series **(47 b)** show activity at higher dose of 200µM in 5-7 minutes.

CONCLUSION

In the near future "ideal" short-acting or other side effect–free NMBs may be discovered assuming new promises of Molecular Biology and Genetic sciences will be realized by creating optimally acting new anesthetic agents that will produce skeletal muscle relaxation matching the pharmacokinetic patterns of all anaesthesia, analgesia and amnesia components. The anesthesia professional should be aware not only of the latest developments in biomedical sciences related to the profession.

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