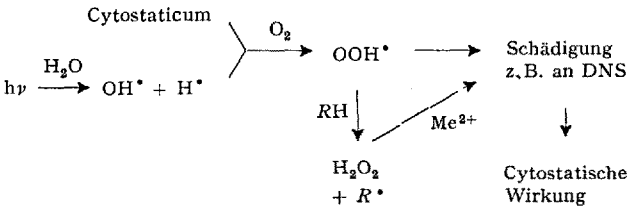
obachtungen unterstützen die Gültigkeit der von uns verfolgten Hypothese, dass sowohl chemisch wie radiobiologisch cytostatische Effekte nach folgendem Schema (2) zustande kommen können:

Schema (2)



Offen bleibt die Frage, ob im einen oder anderen Fall die primär gebildeten Radikale die Träger der schädigenden Reaktion sind. Das sich bildende H_2O_2 könnte dann eine inaktive Form dieser Partikeln darstellen, die erst sekundär durch Metallionen wieder aktiviert werden kann und zwar nach Diffusion auch an Stellen, die vom Entstehungsort der Radikale räumlich entfernt sind.

Chemischer Schutz vor der biologischen Wirkung ionisierender Strahlen und Krebstherapie lassen sich, wie diese Zusammenhänge zeigen, in ein gewisses Reziprozitätsverhältnis setzen: Im einen Fall soll der Ablauf der Reaktionskette (2) möglichst minimiert, im anderen Fall in möglichst selektiver Weise maximiert werden. Radioprophylaktisch wirksame Substanzen müssten dann den Effekt auch der genannten cytostatischen Verbindungen herabsetzen[16]. Wir fanden, dass bei der Autoxydation der Aminoketone Serotonin die Ausbeute an H_2O_2 auf ein Mehrfaches erhöht – ähnlich wie auch bei der Bestrahlung O_2-haltiger wässriger Lösungen durch Zusatz reduzierender Stoffe die H_2O_2-Ausbeute erhöht werden kann[17] – während mit ca. 1 Cysteamin pro Mol Aminoketon die H_2O_2-Bildung am Anfang nahezu völlig ausbleibt. In welchem Sinne diese Versuche als Hinweise auf ein verschiedenartiges Eingreifen der beiden untersuchten Verbindungen in die mit der Autoxydation verbundenen Reaktionsvorgänge zu deuten sind, werden erst weitere Versuche zeigen.

Wenn Serotonin tatsächlich schädigende Radikale abzufangen vermag, so würde die nach radiotherapeutischen Behandlungen sich einstellende Erhöhung des Serotoninspiegels[18] die angestrebte selektive Maximierung des Reaktionsablaufes (2) verhindern und so eine unerwünschte Strahlenschutzwirkung herbeiführen. Es wäre wünschenswert zu untersuchen, ob einer dadurch bedingten Wirksamkeitsbegrenzung der cytostatischen Therapie entsprechend Schema (2) durch eine Zufuhr von Metallionen entgegengewirkt werden kann.

Summary. Cytostatic α-aminoketones are found to produce H_2O_2 on autoxidation. Possible pathways of radical and peroxidative reactions in cytostatic therapy are discussed.

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[16] K. Berneis et al.[4] fanden, dass das Strahlenschutzmittel Cysteamin den Abbau von Desoxyribonukleinsäure bei der Autoxydation der von ihnen untersuchten Methylhydrazinverbindung hemmt.

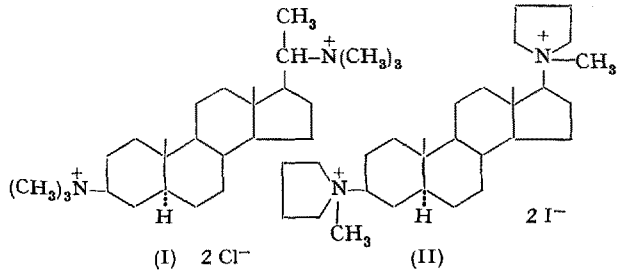
[17] J. Loiseleur und R. Latarjet, Bull. Soc. Chim. Biol. *24*, 172 (1942).

[18] J. Renson und P. Fischer, Arch. int. Physiol. Biochem. *67*, 142 (1959).

Muscle-relaxant Properties of a Steroid bis-Quaternary Ammonium Salt

There has long been a need for a muscle relaxant with a short duration of action, which produces a flaccid paralysis and is free from the initial muscle contracture associated with the depolarizing drug, suxamethonium. We have been interested in this field for many years and some time ago began a search for a synthetic compound possessing these desirable features.

A general interest in the steroid ring system as a skeleton for non-hormonal drugs[1] and a consideration of the curarizing properties reported for the steroid alkaloid malouétine chloride or 3β,20α-bisdimethylamino-5α-pregnane bismethochloride (I)[2] led us to investigate a number of steroid bis-quaternary ammonium salts[3]. Alauddin and Martin-Smith[4] have recently speculated on the properties of salts of this type, and some independent synthetic work has been reported by Crabbé, Durazo, Saloma and Holton[5]. Many of our steroid derivatives had interesting properties and one of them, 3β,17β-dipyrrolidin-1′-yl-5α-androstane bismethiodide, M & B 9105 (II), was selected for detailed pharmacological study.



(I) $2\,Cl^-$ (II)

[1] M. Davis, J. chem. Soc. *1962*, 178.

[2] A. Quevauviller and F. Lainé, Ann. pharm. franç. *18*, 678 (1960). – M.-M. Janot, F. Lainé, Q. Khuong-Huu, and R. Goutarel, Bull. Soc. chim. Fr. *1962*, 111. – M.-M. Janot, Plenary Lectures presented to the International Symposium on Pharmaceutical Chemistry, Florence, 1962 (Butterworth, London 1963), p. 451.

[3] May & Baker Ltd., British Patent Application No. 9262/62.

[4] M. Alauddin and M. Martin-Smith, J. Pharm., Lond. *14*, 325 (1962).

[5] P. Crabbé, M. J. Durazo, R. M. Saloma, and P. G. Holton, Bull. Soc. chim. Belg. *71*, 203 (1962).

The quaternary steroid was tested either as the iodide, M & B 9105, which is about 1% soluble in water at room temperature, or as the freely soluble chloride, M & B 9105A. Both salts form neutral solutions which can be sterilized by boiling. The compound was examined in several animal species.

In the rabbit, cat and monkey the quaternary steroid produced a flaccid paralysis of short duration, when injected intravenously, the onset of paralysis being noted by drooping of the head and loss of muscular tone in the limbs. As soon as the effect was observed, the injection was stopped so that respiration was not impaired to any extent. The doses in mg/kg of cation necessary to produce paralysis were 0.033 ± 0.002 (rabbit), 0.034 ± 0.013 (monkey) and 0.063 ± 0.006 (cat), whilst the duration of action ranged from 40 to 234 sec, being shortest in the rabbit.

In cats under chloralose anaesthesia, intravenous injection of M & B 9105 produces a short-lasting block of transmission from the sciatic nerve to the tibialis muscle. The block can easily be antagonized by an anti-cholinesterase such as neostigmine, or by a tetanus applied to the nerve. That the block was of a competitive nature, and not of the depolarizing type, was shown by the ability of the compound to antagonize the twitch caused by the close arterial injection of acetylcholine. Further evidence of the mode of action of M & B 9105 was provided in experiments in the conscious chick and in the hen under pentobarbitone anaesthesia. In both it caused a flaccid paralysis unlike the contracture found with suxamethonium. Although experiments in the rabbit, chicken and cat showed the duration of action to be similar to that of suxamethonium, in the monkey it had a longer effect, similar to that of gallamine. In man[6] the effect was similar to that found in the monkey. M & B 9105 has been found to be devoid of androgenic, oestrogenic and progestational activity.

Several views have been put forward relating neuromuscular paralysis to the size, shape and other properties of active molecules. Synthetic compounds with two quaternary heads have been for the most part flexible molecules, and peak activity has usually been observed when the nitrogen atoms are connected by ten other atoms, equivalent to a maximum separation of about 14 Å[7–9]. None of the four possible stereoisomers of *d*-tubocurarine is rigid, and an examination of models shows that the maximum interquaternary distance is 11–12 Å[9,10].

Flexibility of the molecule, however, is not essential for this type of activity. The cation of M & B 9105 is a rigid structure with the quaternary centres separated by nine carbon atoms, giving an inter-nitrogen distance of about 11 Å. For malouétine the ring system is similarly rigid, but the inter-nitrogen distance can vary from 11 to 12.5 Å, because of rotation of the side chain.

Fuller details of the pharmacology of M & B 9105 will be reported elsewhere.

Résumé. Un stéroïde quaternaire (3β,17β-dipyrrolidin-1′-yl-5α-androstane bisméthiodide) administré par voie intraveineuse provoque une paralysie neuromusculaire compétitive d'une durée fugace chez le lapin, le poussin, le chat et le chien, mais l'action est un peu plus prolongée chez le singe et chez l'homme.

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Research Laboratories, May and Baker Ltd., Dagenham, (Essex, England), December 10, 1963.

[6] W. W. MAPLESON and W. W. MUSHIN, personal communication.
[7] W. D. M. PATON and D. R. WAUD, Brit. J. Anaesth. *34*, 251 (1962).
[8] C. J. CAVALLITO, *Curare and Curare-like Agents* (Ed. by A. V. S. DE REUCK, J. & A. Churchill Ltd., London 1962), p. 55.
[9] D. BOVET, *Curare and Curare-like Agents* (Ed. by D. BOVET, F. BOVET-NITTI, and G. B. MARINI-BETTOLO, Elsevier, London 1959), p. 256.
[10] J. B. STENLAKE, *Progress in Medicinal Chemistry* (Ed. by G. P. ELLIS and G. B. WEST, Butterworth, London 1963), vol. 3, p. 18.

Indirect Effect of Ultrasound on Water Permeability of the Connective Tissue

Great importance is attached to the changes in permeability of biological membranes under the effect of ultrasound[1,2]. The ionization of water, production of peroxides and other chemically active compounds can play an important role in the mechanism of this biological effect[3]. In order to prove the possibility of such an indirect effect, the following experiments were performed.

To follow the process of permeability of a liquid irradiated by ultrasound, the principle of DAY's method[4] applied to the connective mesenteric membranes of rats was used[5]. The membranes were fixed to the end of a glass tube and the time of flow of 2 ml of distilled deionized water through the membrane was measured. The same membrane was perfused twice, at a time interval of 3 min. In control experiments, using untreated deionized water, a decrease of permeability in the second measurement was observed (Table), conditioned by the swelling of the connective tissue[5]. In further experiments the water treated by ultrasound (2 or 30 min before) was used for the

	Controls	Water irradiated 2 min prior to use	Water irradiated 30 min prior to use
Mean % of change of flow time[a]	+19	−21	−22
Number of samples increasing permeability	0	8	7
Number of samples decreasing permeability	17	0	0

[a] Against the value of the first measurement (= 100%).

[1] C. HAGEN, H. H. RUST, and F. LEBOWSKY, Naturwissenschaften *38*, 1 (1951).
[2] TH. TARNÓCZY and G. TAMÁS, Electromed. *5*, 222 (1960).
[3] D. E. HUGHES and W. L. NYBORG, Science *138*, 108 (1962).
[4] T. D. DAY, J. Physiol. *117*, 1 (1952).
[5] M. POSPÍŠIL and J. DVOŘÁKOVÁ, Fol. biol. (Praha) *8*, 178 (1962).