

Saxitoxin

...from food poisoning to chemical warfare...

[Molecule of the Month - September 1998]

By Neil Edwards

The Chemical Laboratories

School of Chemistry, Physics
& Environmental Science

University of Sussex at Brighton

...and the waters that were in the river were turned to blood. And the fish that were in the river died; and the river stank and the Egyptians could not drink of the water of the river...

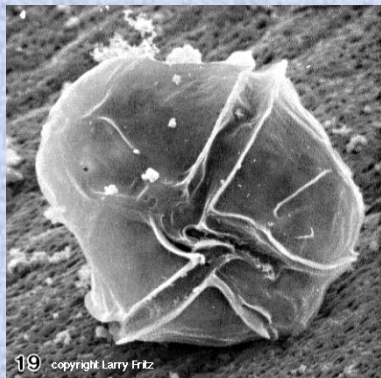
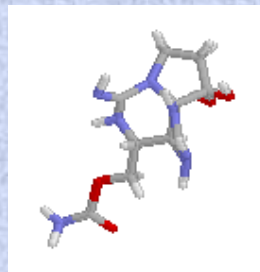
Exodus 7: 20-21

Introduction

In 1987, marine scientists were presented with a series of very disturbing mass die-offs involving humpback whales and other sea-life. In the case of the whales, the number of deaths represented **50 years of natural mortality**. The cause of these puzzling deaths was eventually **blamed on pollution**, since none of the animals showed any signs of disease following post-mortem examination.

By the end of the same year, there had been **two more major incidents** involving, in these cases, mass **poisoning of humans**. A whole array of symptoms were reported, including dizziness, diarrhoea and vomiting, disorientation, respiratory distress, and eye irritation. By the end of these poisoning episodes, **three people were dead and over a hundred had been severely incapacitated by illness**.

The cause of these incidents was eventually traced to a natural source; in fact, several sources were identified: a series of **algal species each producing their own potent biotoxins**. One of these naturally occurring poisons is called saxitoxin, reported to be one of the **most toxic non-protein substances known**. The LD50 in mice is approximately 8 microgram/kg which means that a single **dose of 0.2 milligram would prove fatal for the average weight human**. The causative algal species are actually dinoflagellates, which include *Alexandrium tamarense*, *Gymnodinium catenatum*, and *Pyrodinium bahamense*, and although they, themselves, do not usually affect humans, filter-feeding molluscs may ingest them, thereby concentrating the toxins which they produce.



When people **consume these contaminated shellfish**, they very quickly succumb to the effects of the toxin, a syndrome known as **paralytic shellfish poisoning (PSP)**. Death can usually occur within 2-12 hours in untreated cases, and there is **no cure**. Timely medical assistance, in the form of mechanical **artificial respiration is essential**, with the result that **most human intoxications are non-lethal**.

Left: Alexandrium tamarense (c) Larry Fritz

The algal species itself can grow incredibly fast when conditions are right, leading to spectacular phenomena like that shown above, which are called **red tides** (or harmful algal blooms). The red tide problem is becoming increasingly prevalent, and has been blamed on pollution in coastal areas, and also on farmland run-off into rivers and lakes. Most of the east coast of **North America** is now affected by **harmful algal blooms (HABs)** and also a substantial amount of the west coast. The effects of the toxins produced by these HABs have been suffered by people across the world, eg **in Australia**, and such blooms have resulted in the **closure of shellfish farms near the Orkneys** for several months each year, subject to results obtained through an extensive monitoring programme.

From Food Poisoning to Chemical Warfare!

The obvious dangers of saxitoxin to public health via contamination throughout the food-chain have been aluded to earlier. A more insidious aspect of the colourful history of saxitoxin has to be its involvement in **covert government operations and in chemical warfare**. Saxitoxin is about 1000 times more toxic than a typical synthetic nerve gas such as sarin, and it is perhaps not surprising that in the 1950s, the **CIA began experimenting with it**, reportedly using it in suicide capsules provided to its agents (notably U-2 pilot **Francis Gary Powers**).

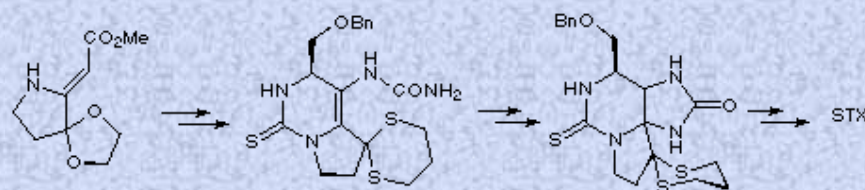
In 1970, President **Nixon ordered the CIA to destroy its entire stock of saxitoxin**, painstakingly collected over several years, as part of the US commitment in accordance with the **United Nations agreement on biological weapons**. Nowadays, saxitoxin and ricin are the only two natural toxins classified as **Schedule 1 Chemical Warfare Agents**. However, in 1975 William Colby, the CIA Director, revealed to Congress that they still possessed over 10 grammes of the material in downtown Washington. Luckily, this supply of saxitoxin was eventually **distributed to scientists and medical researchers** under the auspices of the National Institutes of Health (NIH).

In connection with this, STX, like many other naturally occurring toxins, has been an indispensable tool in medical research. It is a **potent and extremely selective sodium-channel blocker**, having no effect on potassium or calcium channels, or the flux of chloride ions, or indeed on acetylcholine release (whereas other marine toxins have similarly selective effects on these aspects of nerve function). Saxitoxin has been used for the labelling, characterisation and isolation of various sodium channel components, and this has **opened up new avenues for the study of various nervous disorders**.

Chemical Synthesis

The first synthesis of STX was completed by [Kishi and co-workers](#) at Harvard in 1977 (*J. Am. Chem. Soc.* 1977, 99, 2818).

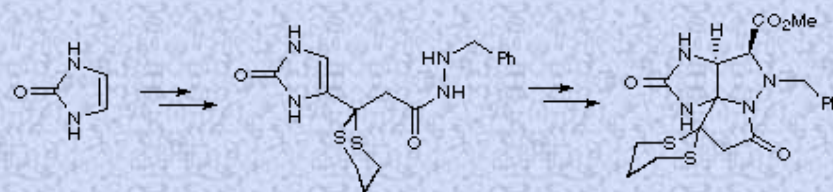
Kishi's synthesis relied on a condensation of a vinylogous carbamate with benzyloxyacetaldehyde and silicon tetraisopropoxide to produce an intermediate thiourea-ester which was converted to a thiourea-urea using standard methods. Cyclisation to provide the saxitoxin skeleton was accomplished readily by treatment with acid, the reaction proceeding via the intermediacy of an iminium ion. Functional group transformations were then carried out to achieve the first total synthesis of racemic saxitoxin.



Kishi later published a modified synthesis using chiral auxiliaries to construct (-)-saxitoxin in optically pure form.

The second synthesis was carried out by [Jacobi and his collaborators](#) whilst at Wesleyan University, Connecticut (*J. Am. Chem. Soc.* 1984, 106, 5594).

The key step of Jacobi's synthesis of saxitoxin relied on formation of a benzylhydrazide intermediate, which was subjected to methyl glyoxylate hemimethyl acetal and a Lewis acid, in order to construct a highly reactive azomethine imine, which subsequently underwent an intramolecular 1,3-dipolar cycloaddition reaction, leading to an advanced tetracyclic intermediate. This was readily elaborated to accomplish a formal synthesis of the racemic natural product.



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