The chemistry of muscarine according to Sayers

by

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Introduction

The Documents in the Case, a detective story by Dorothy L. Sayers[1] published in 1930, is fairly unusual in several respects. First, it is her only detective novel that does not feature the gentleman-detective Lord Peter Wimsey.[2] Secondly, the *dénouement* depends on a rather difficult question of organic chemistry. Sayers is known for her careful research and attention to detail. On the other hand, she was repeatedly criticised for a considerable number of factual errors in her works, some of them rather surprising ones.[3]

The complicated scientific points are admirably explained, so most readers will have little difficulty in understanding them, even without previous knowledge of chemistry. However, some may ask: *is this really "true"? Could it have happened like this?*

It is the purpose of the present paper to answer the following questions:

- Is the scientific information presented by Sayers correct?
- If it is not correct in the light of today's knowledge, does it represent the state of the art at the time she was writing (about 1930)?
- Could the murder have happened as described?
- Is the way the murderer was convicted a possible one? Could it have happened in 1930, could it happen today?

"Chemical facts" as presented in The Documents in the Case

1. Muscarine is the poisonous principle of *Amanita muscaria*, the fly agaric (*Document 48, Statement by Home Office Analyst Sir James Lubbock*).
2. Natural muscarine has an asymmetric molecular structure and is therefore optically active, i.e. it rotates the plane of polarisation of a beam of polarised light (*Document 52, Explanation by Dr Waters, the "coming man in chemistry", given to John Munting*).
3. The chemical formula of muscarine is $C_5H_{15}NO_3$ (*Document 51, Explanation by Leader, second-year student at St. Anthony's, given to John Munting and Paul Harrison*).
4. Synthetic muscarine is prepared by heating choline with dilute nitric acid (*Document 51, see (3) above*).
5. Artificial (synthetic) muscarine is identical to natural muscarine, except that it is a mixture of its dextro- and laevo-rotatory (rotating the plane of polarisation right and left, respectively) forms. This so-called racemic form is optically inactive (*Document 52, see (2) above*).

1 Robert Eustace, who supplied most of the scientific information, is credited as co-author.

2 The Home Office Analyst, Sir James Lubbock, who plays an important part in the story, also occurs in several of the Wimsey stories.

3 For instance, in *Have His Carcase* a character's haemophilia is cited as evidence for his descent from the Romanovs. Except for the Zarevitch, no Romanov is known to have suffered from haemophilia. Since haemophilia is inherited through the female line – as Sayers expounds at length – the Zarevitch inherited it from his maternal great-grandmother Queen Victoria.

6. The isolation of muscarine itself in a pure state from the fungus is a chemical experiment of considerable difficulty and has been accomplished only by two men, their results have not yet received confirmation (*Document 49, letter by Sir James Lubbock to Paul Harrison*).
7. In a case of poisoning by *Amanita muscaria*, a "considerable quantity" of muscarine can be obtained from the victim's stomach, the vomit and the unconsumed remainder of the dish of fungi. This muscarine is sufficiently pure to allow reliable measurements of its optical activity (*Documents 48 and 52, statements by Sir James Lubbock*).

Present-day knowledge about these "Chemical facts"

1. Muscarine is the poisonous principle of *Amanita muscaria*, the fly agaric.

While muscarine is undoubtedly present in *Amanita muscaria*, the quantities are very small, about 2–3 mg/kg. The contribution of muscarine to the poisonous and hallucinogenic effects of *Amanita muscaria* is minor, the alkaloids mainly responsible are muscimol and ibotenic acid.[4]

Fig.1: Structural formulae of muscimol (left) and ibotenic acid (right)

Dorothy L. Sayers could not possibly have known this: both muscimol and ibotenic acid were discovered well after her death. At the time of her writing it was the received opinion that muscarine was responsible for the poisonous effects of fly agaric.

Poisoning by *Amanita muscaria* is very rarely – if ever – fatal. She seems to have been aware of this and therefore laid the scene of the murder in a remote shack, far from all medical help. Even so, this murder method is very risky and highly unlikely to succeed.

2. Natural muscarine has an asymmetric molecular structure and is therefore optically active, i.e. it rotates the plane of polarisation of a beam of polarised light.

This is perfectly correct.

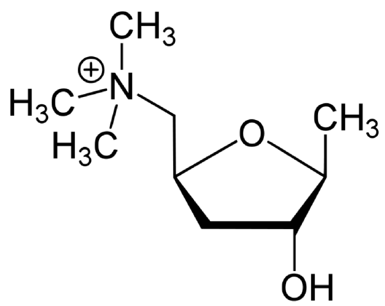

Fig.2: Structural formula of muscarine

4 Theodor Wieland: *Poisonous Principles of Mushrooms of the Genus Amanita*. Science 159, 946 (1968)

Most asymmetric molecules are asymmetric because they contain asymmetric carbon atoms, i.e. atoms with four different ligands. The above structural formula (which was unknown to Sayers, see below) shows no less than three asymmetric carbon atoms at positions 2, 4, and 5 (counting starts with 1 at the oxygen atom and proceeds counter-clockwise). This formula was established in 1957 – the year of Sayers' death. It was the final outcome of a long and difficult research effort,[5] credited mainly to Kögl in the Netherlands and the Swiss chemist Eugster.

3. The chemical formula of muscarine is $C_5H_{15}NO_3$.

This is, alas, utterly wrong. From the above structural formula a sum formula of $C_9H_{20}NO_2^+$ is easily derived. The wrong formula was published by Harnack in 1875 and by Nothnagel in 1893. Harnack and Nothnagel are the only two men who, according to Sir James Lubbock, accomplished the isolation of muscarine in a pure state from the fungus. By 1930, however, their results had been largely discredited, among others by King – who is also mentioned by Sir James – in 1922.

4. Synthetic muscarine is prepared by heating choline with dilute nitric acid.

Here again, she repeats findings of nineteenth-century chemistry which had already been disproved at the time of her writing. Schmiedeberg and Nothnagel claimed that

- "Synthetic muscarine" prepared as described above is identical to natural muscarine.
- It has the chemical formula $(CH_3)_3N^+CH_2(CH)(OH)_2$.

Both of these claims are wrong. This was already well established by the beginning of the twentieth century. Interestingly, the formula proposed above does not contain an asymmetric carbon atom, the corresponding substance is therefore optically inactive.

5. Artificial (synthetic) muscarine is identical to natural muscarine, except that it is a mixture of its dextro- and laevo-rotatory forms. This so-called racemic form is optically inactive.

This is, in principle, correct, but requires some elaboration. As soon as the structure of any organic substance occurring in living organisms is known, chemists try to synthesise it in the laboratory. If the substance is optically active – as most of them are – an "ordinary" synthesis will produce an optically inactive mixture of the left- and right-rotating forms (called enantiomers), one of which is identical to the natural substance and the other one is its mirror image. However, modern chemistry knows many "stereo-specific syntheses" which exclusively produce one of the two enantiomers. Such a synthesis requires, however, some optically active component to begin with.

Synthetic muscarine, whether optically active or not, did not exist in Sayers' time because the structure of muscarine was not known. The substance called "synthetic muscarine" in the book has nothing to do with natural muscarine, it is simply a different compound. Today, many methods of synthesising muscarine are known, several of them stereo-specific.

6. The isolation of muscarine itself in a pure state from the fungus is a chemical experiment of considerable difficulty and has been accomplished only by two men, their results have not yet received confirmation.

In 1930, this was certainly not far from the truth. While there were a few others than Harnack and Nothnagel who worked on isolating muscarine, it was a formidable task, and the results were by no means conclusive.

7. In a case of poisoning by *Amanita muscaria*, a "considerable quantity" of muscarine can be obtained from the victim's stomach, the vomit and the unconsumed remainder of the dish of fungi. This muscarine is sufficiently pure to allow reliable measurements of its optical activity.

5 S. Wilkinson: *The History and Chemistry of Muscarine*. Quarterly Reviews 15, 153 (1961). For the early history of muscarine research I rely largely on this review and have not consulted the original papers mentioned therein.

This is probably the most glaring error committed by Sayers and Eustace: it is an obvious contradiction to the statement that nobody except Harnack and Nothnagel has ever done so. Sir James Lubbock concedes that “I don't altogether guarantee that I have isolated the principle. But it's near enough.” However, measurements of the optical activity are only possible if the sample is fairly pure, otherwise contaminations will make the results meaningless.

In a post-mortem examination the search for organic poisons like vegetable alkaloids is done, then as now, in two parts: in the first step, the suspected poison has to be separated from all the other substances present, then it has to be identified and, if possible, its quantity determined or at least estimated. Today the first step is usually done with some form of chromatography and the second by spectroscopy. The most frequently used combination is gas chromatography with mass spectrometry (GC-MS). In 1930, these techniques were not available, although the principles of chromatography were already known. Forensic scientists used techniques like fractional distillation and crystallisation and extraction by various solvents for separation. The substances found were identified by measuring various properties: Melting point, index of refraction, toxic effect on laboratory animals, and many others. In principle, these methods could also be applied to muscarine. However, because of the very small amounts of muscarine present in *Amanita muscaria* and the limited knowledge about muscarine in 1930 this was not practically feasible.

Sayers and Eustace are also very vague about the quantities involved: what is the “considerable quantity” obtained by Sir James? Compare this to her description of arsenic poisoning in *Strong Poison*: there she is on much firmer ground and explicitly states the quantity of arsenic administered to Philip Boyes – 4 to 5 grains, or about 250 to 300 mg, a reasonable value for a lethal dose. But even there Sayers – or her protagonist Harriet Vane – displays a surprising ignorance of chemistry when Harriet claims to have burnt arsenic.[6]

Sayers probably vastly overestimates the quantities of muscarine involved: Leader jokes about a “teaspoonful” that would “settle your hash and leave a bit over for the dog”. Munting describes the three bottles with muscarine extracted from the stomach, the vomit, and the dish of mushrooms as containing a “white salt”. The total quantity of muscarine in a dish of fly agaric would be about 1 mg or rather less – a few specks of powder or tiny crystals barely visible to the naked eye. In 1931, Kögl extracted 137 mg of muscarine from 1250 kg of fungus – rather less than a “teaspoonful”.

In summary, murder by synthetic muscarine was not possible in 1929[7] because synthetic muscarine did not exist. It was, in principle, possible to distinguish between a natural and a synthetic compound by using the polariscope, but not in this particular case. Today, synthetic compounds are frequently produced using stereo-specific methods and therefore indistinguishable from the natural ones using the polariscope alone. However, there are other methods available, e.g. measuring radiocarbon (^{14}C) content.

Verdict

Dorothy L. Sayers was a scholar rather than a scientist. While she displayed an intelligent layman's interest in the scientific topics of the day, her understanding of natural science was limited and resulted in quite a few mistakes. In her novels she mentions the second law of thermodynamics, the theories of Einstein, Planck, and Freud, together with quite a few popular misconceptions about them. Her religious ideas – that the asymmetry of natural compounds is evidence for a Creator – have few adherents today.

6 Arsenic, properly called white arsenic or arsenic trioxide, As_2O_3, is an oxide and therefore not combustible. Attempts to “burn” it would probably result in highly poisonous fumes.

7 In the book, the murder is committed on the 19th of October 1929.

On the whole, Sayers and Eustace were well informed about the state of the art in forensic toxicology in general and muscarine in particular. They did a lot of research: Eustace visited a laboratory at University College Hospital in August 1928 and had an experiment with the polariscope demonstrated to him.[8] The lively description of Harrison's and Munting's visit to St. Anthony's, where the visitors can roam unchallenged and are largely ignored by the absorbed researchers, catches very well the atmosphere of such a research establishment.

The basic idea of the plot – the "first murderer caught by the polariscope" – is absolutely brilliant. However, some points they could have known better – and possibly did. I suppose they soon encountered some difficulties when they worked out the details, and decided to bend the facts a little to suit their needs. For a scientist, this would be the sin which is not forgiven. For a detective novelist, it is probably a venial sin to depart a little from strict scientific accuracy in the interest of the plot.

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8 Barbara Reynolds; *Dorothy L Sayers: Her Life and Soul*. London: Hodder & Stoughton, 1993.