

The changing culture of chemistry

We all appreciate how chemical knowledge has advanced over the years, but **Bruce C. Gibb** reminds us that chemical culture has similarly made great advances.

Human nature being what it is, we tend to look at the past through a rather distorted lens; this is because of a combination of many factors. For example television and our own environment and experiences give us preconceived notions of what things were like back then and, additionally, we have a general tendency to imagine that things were just better back then. Ah, the good old days!

Unsurprisingly, these romanticisms apply equally to chemistry as they do to any other human endeavour. When we think of Valerius Cordus¹ carrying out the first example of a concise chemical reaction protocol², mixing alcohol and oil of vitriol (sulfuric acid) to form sweet oil of vitriol (diethyl ether), we tend to bathe it in a golden, Hollywood-esque light, whilst also transferring our modern lab culture and our own personal experiences to the picture. Whatever details you imagined when you first thought about this story, rest assured that in one or more ways the reality was quite different. Thus, for the record, Cordus of course wasn't a chemist, and just in case it crossed your mind, at the time of his discovery he wasn't a bearded old man either — he was a bearded 25 year-old botanist/pharmacist. There were probably more plants in his lab than chemical apparatus; you can drop that thought too. Moreover, as this was 1540, any apparatus on show was as sophisticated as curiously shaped earthenware, and mortar and pestles. And as for the chemicals on the shelves, expect small clay pots of 'tincture of weeping willow bark' and the likes.

And then there's the condition of the substrate and reagent he used. Whether Cordus made or procured his oil of vitriol, the green vitriol (iron (II) sulfate) used to make it through dry distillation was probably not pure, the water used to dissolve the evolving gases not deionized, and the resulting dilute sulfuric acid undoubtedly contaminated with considerable amounts of SO₂. Presumably it stank. And as for the alcohol Cordus used, it was triply distilled, strong, sharp wine; aka bad vodka. So forget the nice glass bottles of absolute ethanol and fuming sulfuric acid. For the reaction itself, the vessel was a cucurbit containing Venetian glass, and after the alcohol and acid



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were added, the vessel was sealed with clay and the reaction left at room temperature for a month or two (yes, the reaction time was that vague). Once this time had elapsed, the sweet oil was distilled off and the best you could say about it was that it was contaminated with considerable amounts of oily, diethylsulfate.² If it hadn't been, Cordus would probably have called his product sweet aithër of vitriol rather than sweet oil of vitriol.

And if your comedic side imagines Cordus staggering about the lab, giggling, in a half-anaesthetized state, he in fact made no note of the anaesthetic qualities of ether. The first observation of this property is attributed to Philippus Paracelsus who noted¹ that: "it possesses an agreeable taste; even chickens will eat it, whereupon they sleep for a moderately long time and reawaken without having been injured". Presumably, like any good scientist of his time, Cordus did taste his sweet oil — the sweet smell of ether, combined with the peppermint bouquet of diethylsulfate, must have been quite, quite alluring. We may

never know if his early death at the age of 29, ostensibly from malaria, was in part due to the highly toxic and carcinogenic properties of diethylsulfate.

But if you want to truly appreciate the difference between chemistry in the here-and-now and chemistry in the years-gone-by, you have to come forward in time and take advantage of improved record keeping. And in that regard there is nowhere better to turn than asparagus, for the chemical history of asparagus is a fine educational tale illustrating the differences between chemistry then and now (although I must admit, Paracelsus' aforementioned quote about ether and chickens is also right up there).

There are two facts you need to know about the chemistry of asparagus — why your urine smells after eating it, and that it furnished the first amino acid ever isolated — and in both cases going back to the original published works reveals much about how chemistry has changed over the years. The first interesting thing about asparagus is that it contains asparagusic acid (1,2-dithiolane-4-carboxylic acid): the first confirmed dithiol reported from a natural source³, and the only sulfur-containing compound unique to asparagus⁴. Now its kind of obvious for the older readers, but it needs to be pointed out that when the work identifying this acid was published back in 1948, there were only melting points, elemental analyses and comparisons to previously identified compounds for characterization. It was, for example, four more years before the first commercial NMR (a 30 MHz Varian instrument) became available⁵. And so in those days characterization relied on chemical conversions that changed your unknown into a known compound; a process that when well designed was logically flawless, but rested on the countless assumptions that you 'knew' what each chemical conversion was doing to every molecule along the chain linking known and unknown. Think about having to do that now for the project you're working on in the lab.

However, what really catches the eye in this short paper is the off-the-cuff comment at the end of the discussion, the

one pertaining to the source of the smell of urine after the consumption of asparagus. The authors came to the conclusion that asparagusic acid was not the precursor of the characteristic odour of urine after the ingestion of asparagus because: “no odor resulted when two individuals took 10 mg each of dithiolisobutyric acid orally.” Who were these gambling chemical gourmards? One might first think of the authors, but there was only one. Then who sacrificed themselves for science and received no acknowledgement? One possible clue is the expression of gratitude to “Mr. Arthur Bevenue and Mr. L. M. White of the Western Regional Research Laboratory for many of the analyses reported.” Perhaps that included the tasting? Regardless of who the volunteers were (and it is, I confess, an assumption that they were volunteers), try publishing a paper with such statements whilst at the same time acknowledging the support of the National Institutes of Health or your favourite funding agency. Chemistry was definitively more whimsical back then.

Parenthetically, one would be remiss not to mention in passing that by concentrating the fetid urine of a group of volunteers persuaded to each consume four pounds of asparagus, it is possible to identify in their rancid water, methanethiol, dimethyl sulfide, dimethyl trisulfide, *S*-methyl thioacrylate, *S*-methyl-3-(methylthio)thiopropionate and tetrahydrothiophene^{4,6–8}. Moreover, there is evidence supporting the idea that dimethyl sulfoxide and dimethyl sulfone modify the smell to impart a ‘sweet’ aroma to urine⁹. Where do these compounds all come from? The evidence garnered over the years counters the findings from the small human trial outlined above — asparagusic acid is now presumed to be the source, and the negative results from the two unlisted volunteers can be attributed to the fact that roughly one-third of the population doesn’t produce graveolent tinkles upon asparagus consumption.

The second fascinating fact about asparagus is that it was the source of the first amino acid ever isolated¹⁰. This small chemical milestone arose in 1806, when Vauquelin and his assistant Robiquet reported the isolation of what ultimately was named asparagine. The paper is illuminating for both its scientific approach

and its frankness...on all sorts of levels. For example, the second sentence in the introduction is not so much background scientific information, but a ringing endorsement of assistant Robiquet’s capabilities. Specifically, that he brought the great skill of solid reasoning to the experiments he performed. Could you imagine inserting a reference letter for the lead author within your next publication?

And so it was that whilst working with concentrated asparagus juice that the authors obtained what appeared to be two new substances. Now at the time of this work, Antoine Lavoisier had already invented elemental analysis, however the intrepid Vauquelin and Robiquet instead characterized the substances by examining the shape of their crystals and what the compounds and their combustion products did to the human body. For example, the first compound identified (asparagine) had a fresh, if slightly nauseous taste that excited the secretion of saliva. Yum! In contrast the other was quite sweet and had a taste akin to manna. The small amounts of the latter unfortunately precluded detailed analysis.

Thankfully there was sufficient asparagine for an initial analysis. They found it to be essentially insoluble in alcohol and possess limited water solubility. Furthermore their analyses revealed no sign of acidity or alkalinity, and gave negative results for a number of tests for salts. These included using an infusion of oak galls (abnormal growths on trees rich in polyphenols such as tannic, gallic and gallotannic acids) to test for iron, using lead (II) acetate to test for sulfur, ammonium oxalate to probe for calcium, barium chloride for sulfate determination, and K₂S to test for a broad range of heavy metals. Nor did their unknown give off ammonia when treated with KOH. Moreover, on burning the substance, it first became swollen and gave off pungent vapours that affected the eyes and nostrils “like wood smoke”. At the end of combustion it furnished much coal that was devoid of flavour (yum yum!), and after incineration left an almost imperceptible trace of inorganic materials. Furthermore at the end of the decomposition, the odour it emanated was somewhat analogous to that of animal matter, but also a little ammonical.

The authors then carried out a simple xanthoproteic reaction, decomposing the asparagine with nitric acid to give a nitrous gas and a yellow liquor with a bitter taste akin to “animal substances” (yum again!). When the action of the nitric acid was complete, addition of calcium hydroxide liberated significant amounts of ammonia.

The conclusion from this work was that their unknown was not a metal salt, but as burning gave the same products as vegetables the material was probably an immediate principle of asparagus. Moreover, they concluded that it was probably composed of hydrogen, oxygen and carbon in particular proportions, and probably a small quantity of nitrogen.

Alas, their studies had to stop at this juncture. As the authors candidly stated, although they had obtained a large quantity of this substance, they could not continue their experiments because most of it went astray somewhere in their laboratory. Try that excuse these days! Unperturbed by what would undoubtedly now be seen as amateurish science, Vauquelin and Robiquet decided to publish their results because they thought it their duty to inform the Institute. I do not recommend trying that with the half-written paper you have sitting on your desk. That said, in their defence Vauquelin and Robiquet did finish off with a reassurance to continue work when asparagus season arrived. Maybe that eased acceptance of the manuscript.

How times have changed. □

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