

ISSN 2050-0424



Historical Group

OCCASIONAL PAPERS

No 9

Series Editor: Dr Anna Simmons

Robert Burns Woodward
in his Own Words

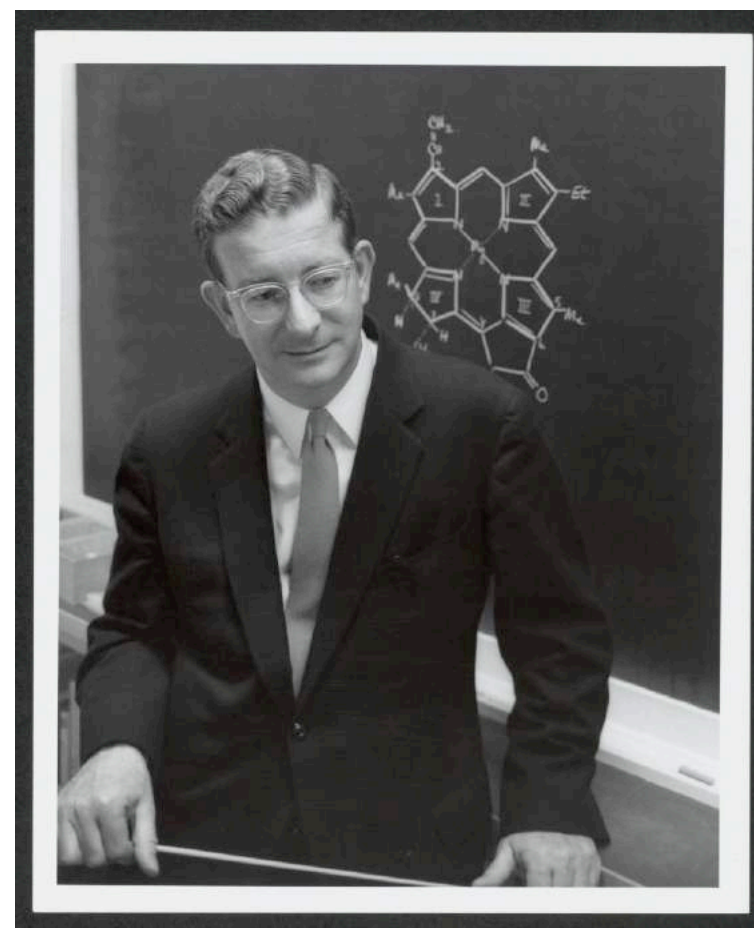
Dr Peter J.T. Morris

April 2017

**A Biography to Mark the Centenary of the Birth
of Robert Burns Woodward**

*Honoured by a meeting of the RSC Historical Group
on 10 May 2017*

Dr Peter J.T. Morris
Science Museum, London



Robert B. Woodward [photographic portrait], Nov. 6, 1965
HUP Woodward, Robert Burns (8),olvwork727971. Harvard University Archives.

What happened on Tuesday 10 April 1917? The Second Battle of Arras started on the Western Front and the British Army made major gains on the first day. Only four days earlier the USA had entered the First World War on the side of the Allies, as a consequence of the Germans' unrestricted submarine warfare. A munitions factory in Eddystone, Pennsylvania, blew up killing 133 workers. Just over a month earlier, revolution had broken out in Russia and the monarchy had been overthrown. Lenin arrived in Petrograd in his infamous sealed train supplied by the Germans on 16 April 1917. In Boston, Massachusetts, Mayor John Michael Curley gave permission for the Ninth Regiment to use the Fire Department's animal hospital for storing its horses whenever they were in the city. There was a raging debate about the reliability of Boston's German-Americans and fears, which as it turned out were unfounded, that the 1917 Boston marathon on 19 April would have to be cancelled. There was even a rush to get married in order to be exempt from the military draft. The weather in Boston was described as being fair, with strong winds, and the temperature was around freezing all day.

And in the midst of all this, Robert Burns Woodward was born at 3.39 am at the Boston Lying In Hospital for Women, the son of Arthur Chester Woodward and Margaret (née Burns) [i]. Little is ever said about Woodward's paternal family and it is usually assumed it was undistinguished. This was far from being the case. Arthur was a scion of a family which was notable in its own way, even if they did not aspire to be Boston Brahmins. The family can be traced back to the time of the American Revolution, and Arthur's great-grandfather, Caleb Woodward, was a veteran of the War of 1812. Arthur's grandfather W. Elliott Woodward was an apothecary in Dearborn (south of Boston), a well-known numismatist and coin dealer who was also a publisher. More importantly, he was a property dealer and even gave his name to a street, Woodward Avenue, in Roxbury, just south of Boston. His son, Harlow Elliott Woodward, started up a magazine which he then sold and later became absorbed into the *Ladies' Home Journal*. He then followed in his father's footsteps as an apothecary and coin dealer. Woodward appears to have been unaware of this family history (or at least claimed he was). Although Harlow died at the relatively young age of sixty in 1911, Arthur Woodward did not follow in his footsteps as an apothecary nor does he seem to have shared in the family's presumed wealth. This was probably because he was the third son, although one wonders if there was a deeper estrangement. He worked as a book binder and moved away from Roxbury, living a rather restless existence around the Boston area until he married Margaret Gavitt in Somerville, Massachusetts, in September 1913. Margaret was six years older than the twenty-seven-

year-old Arthur and she worked as a bookkeeper. She was also a widow, having presumably been married to a Mr Gavitt, of whom there is no trace. She had been born in Glasgow, Scotland, in 1880, the daughter of a working-class couple, John Burns who was from Glasgow and Annie (née Hind) who had been born in England but brought up in Glasgow. The Burns family appears to have emigrated to America in the mid-1880s but the precise details are lacking. It appears from Woodward's own remarks that Margaret fondly imagined that she was a descendant of Robert Burns the poet, possibly to in an attempt distinguish her family from the vast majority of the Burns in Glasgow who were from Ireland; she thus named her son in honour of Scotland's bard. Arthur Woodward registered for the draft in September 1918, but he was already being treated for a heart problem. He died during the great influenza epidemic on 10 October 1918, presumably already weakened by his heart condition.

By 1921 Margaret had married her third husband, Wallace Chase, who was the proprietor of a garage in Wakefield, north of Boston, but in 1930, the family was living in Quincy, south of Boston. Wallace was now a machinist, resembling Margaret's Glaswegian grandfather Hugh Burns who was an "engine man", and Margaret herself was a supervisor. It is not clear how well Woodward got on with his step-father and it is sometimes implied that Margaret brought up her son on her own. This was clearly not the case as Wallace and Margaret were living together until Wallace's death in the early 1950s. Margaret Chase herself lived until 1963 when she died at the age of eighty-three. She built up a library of newspaper cuttings about her son, which she kept almost up to the time of her death [ii]. Woodward went to North Quincy Junior High School, a fifteen minutes' walk from his home in Holbrook Road, where he was a member of the chem club, the math club and the newswriters' club. He started to do chemistry experiments with his friend Robert Putnam, which his mother at least tolerated. He started to work his way through Ludwig Gattermann's *Practical Methods of Organic Chemistry* (usually known as Gattermann's *Kochbuch*) and realised that the preparations had originally appeared in German journals. While he might have been able to gain access to these journals in libraries in the Boston area, he had the idea of writing to the German Consul-General in Boston, Baron Kurt von Tippelskirch, probably around 1930. Von Tippelskirch was in Boston from 1926 to 1938, and died in Soviet internment in 1946 after his home town of Jacobsdorf, west of Berlin, was overrun by the Red Army in early February 1945 [iii]. Tippelskirch kindly sent Woodward copies of German chemistry journals including *Berichte der deutschen chemischen Gesellschaft* and *Liebigs Annalen*.

Woodward then went to the nearby Massachusetts Institute of Technology at the age of sixteen and took his B.S. in 1936. He failed to achieve passing grades at the end of his first year and resumed his studies a year later following a programme laid down by the chemistry department. Woodward never fitted in well with any regime and he was fortunate to have the kindly James Flack Norris as a mentor and protector. Norris's own interests were in the reactivity of organic compounds and he was one of the founders of physical organic chemistry. He also ensured that Woodward could take his PhD in the space of a year without any of the usual requirements or regulations. Woodward later remarked, exaggerating the situation in his customary manner, that he regarded his PhD as the first of his honorary degrees [iv]. He was also awarded the Austin Research Fellowship which was probably essential as his family was not well off, although they could afford to own their own house in a nice neighbourhood [v]. Woodward wrote his thesis on the synthesis of oestrone, the synthesis of steroids being a hot topic at the time. His doctoral advisors were Norris and his collaborator Avery Ashdown. While they were both very good chemists, their main interest lay outside of organic synthesis and one wonders what might have happened if Woodward had been supervised by James Conant, Elmer Kohler or Louis Fieser at neighbouring Harvard University. Certainly, Norris appears to have passed his interest in the history of chemistry, which he in turn had gained from his supervisor Ira Remsen, to Woodward.

After lecturing at a summer school at the University of Illinois, where his relationship with the staff was rather sour at best, Woodward moved back to Harvard University, to become an assistant to Elmer P. Koehler, an organic chemist with a particular interest in unsaturated and conjugated systems. A year later he became a member of Harvard's prestigious Society of Fellows. Woodward then rose rapidly through the academic ranks at Harvard, becoming a full professor in 1950, Morris Loeb Professor of Chemistry three years later and finally Donner Professor of Science in 1960. Woodward first came to international attention in 1941 with his development of the Woodward rules for the ultraviolet spectra of conjugated unsaturated compounds at the age of only twenty-four. He showed how the absorption maxima of the ultraviolet spectrum could be used to show what kinds of unsaturated bonds a compound contained. Nowadays such a correlation would seem limited in scope, even trivial, but at the time ultraviolet spectroscopy was one of the few physical techniques available to organic chemists apart from the refractive index or surface tension (which itself gave rise to the rather similar parachor developed by Samuel Sudgen). Furthermore, steroids, which were being intensively investigated at the time, often contain unsaturated and conjugated bonds (e.g. as conjugated ketones).

If one could surmise at least some of the steroid's molecular structure from Woodward's new rules, its structural determination (which in those days could take decades) would be speeded up.

Woodward's first major synthesis, which gained considerable publicity at the time, was his formal total synthesis of the anti-malarial quinine with his colleague William von Eggers Doering in 1944. The origins of this synthesis lay in the desperation of the US Government to find a new source of quinine after the world's supply from Java was cut off by the Japanese in 1942. By a happy coincidence a local businessman, Edwin Land, was using quinine (as iodoquinine sulphate) to make the polarising sheets which were the basis of his Polaroid sunglasses. Land sponsored the synthetic work, although he soon switched to polyvinyl alcohol doped with iodine for his filters. It was a formal total synthesis because Woodward and Doering only synthesized quinotoxine, and relied upon the 1918 publication of the German chemists Paul Rabe and Karl Kindler, who had reported the conversion of quinotoxine into quinine. This step was later allegedly discredited and hence the validity of the 1944 synthesis was thrown into doubt for many years until 2007 when an evaluation of the historical literature by Jeffrey Seeman concluded that the Rabe-Kindler work was valid. As a direct consequence of that publication, experimental work published in 2008 by Robert Williams and Aaron Smith showed that the conversion of quinotoxine into quinine could be achieved using as best as could be determined reagents barely characterized by Rabe and Kindler nearly ninety years earlier. This synthesis shows how Woodward, like all other organic chemists, always carried out his syntheses within a framework of rules which were almost as rigid and arcane as the rules of chess. A total synthesis had to be carried out from compounds which in theory could be made from the elements, although this was rarely tested after the early work of Hermann Kolbe and Marcellin Berthelot. At the same time, however, if part of a synthesis, particularly at the beginning or end of the synthetic chain had already been achieved, there was no need to repeat it. Somewhat more controversially, once an intermediate had been synthesised, its further use in the synthesis could be "refreshed" (augmented) by material obtained from natural sources.

Before we move on to assess Woodward's later career as a renowned chemist, we should briefly note his life outside the laboratory, although given his dedication to his chemical work, it could be considered surprising that he had a personal life. It is thus perhaps a little less surprising that he was twice married and twice divorced and was living on his own when he died. His first wife was Irja Pullman, who had been a classmate at Quincy High and was of Finnish origin and from Vermont. They were married in 1938, once Woodward was settled at Harvard, and they had two daughters

Siiri Anne (born 1939) and Jean Kirsten (born 1944). Irja Woodward died in Newton, Massachusetts, in 1996. They were divorced in 1946 and Woodward married again in the same year, to Eudoxia Muller, the daughter of an architect and sculptor in New York City. A graduate of Smith College, she was employed by the Polaroid Corporation and met Woodward through his work for Edwin Land. After her marriage she taught in schools in Belmont, to the west of Cambridge, Massachusetts, where they lived. She also became an artist. Perhaps significantly her daughter Crystal (born 1947) is also an artist and her son Eric (born 1953) became an architect. Woodward and Eudoxia were divorced in 1972. She died in Belmont in 2008.

Before we describe at least a few of the many syntheses of Woodward, we have to consider his role as a lecturer. He was famous for his flamboyant and intricately choreographed lectures which often lasted for several hours. Before Woodward, chemistry lectures had been sedate affairs in which a chemist would report on their latest work using the blackboard to draw any necessary structures. Some chemists were famous for giving lively, even dangerous, lecture demonstrations, but they were usually directed at students or the general public rather than their fellow chemists. Woodward's approach was very different. He turned the writing of reaction steps on the blackboard into a fine art, adding to the drama of the lecture, for example laying out his coloured chalks on the bench beforehand. For Woodward, the lecture was a piece of drama, filled with extravagant gestures and vivid turns of speech. He also showed slides, but no demonstrations. His ability to smoke cigarettes continuously during this performance was also impressive. Many chemists were rather stunned by his flamboyant style, which as we will see below was also evident in his written work, and by the sheer length of his lectures. However they helped to establish organic synthesis as a major intellectual achievement at a time when it was still relatively new. Above all, Woodward's lectures had a powerful effect on the rising generation of organic chemists as he showed how chemical problems could be solved by the power of logical thought and creative processes, rather than merely being an empirical process of guesswork and experimentation. In this respect Woodward was aided, on one hand, by his voracious reading and his phenomenal memory and, on the other, by the development of organic reaction mechanisms and the introduction of physical instrumentation into organic chemistry. Woodward's lecturing career was also assisted by the rise of international meetings following the healing of the break caused by the Second World War and the greater ease of international travel, thanks to the jet airliner. Of particular importance for Woodward were the biennial congresses of the International Union of Pure and Applied Chemistry (better

known as IUPAC) and the International Symposium on the Chemistry of Natural Products which were held in the intervening years. For example, Woodward gave his paper on the total synthesis of strychnine at the IUPAC congress in Zurich in 1955, and two seminal papers on the synthesis of vitamin B₁₂ at the International Symposium on the Chemistry of Natural Products in London in 1968 and at the following meeting in Riga in 1970. As a result, several important papers appeared in the journal of IUPAC, *Pure and Applied Chemistry*. As these papers were discursive, they were in any event unsuitable for a more mainstream journal such as the *Journal of the American Chemical Society* or *Tetrahedron*. As we will see below, Woodward often used these papers as a home for his breathless rhetoric. We also have to note the importance of Woodward's famous (or infamous) Thursday night seminars. Once the speaker, usually one of Woodward's collaborators, had delivered his lecture, Woodward would open the discussion with a problem from the audience or pose one himself. After everyone else had had a go, Woodward would deliver an impeccably elegant and logical solution as the seminar continued well into the night.

As Woodward embarked on his major programme of organic synthesis in the late 1940s, the field was undergoing three major changes. The first was the change in the nature of organic synthesis. Hitherto synthesis had been the handmaiden of analysis: the determination of the structure of organic compounds by breaking them down into smaller compounds which were already known. Once a compound's molecular structure had been tentatively proposed, there was no way of "proving" this structure except by rebuilding the original molecule from known compounds. A synthesis which could take three or four years was simply the culmination of a structure determination that might have taken several decades. Once the structure could be at least partly determined by use of physical instrumentation, this *raison d'être* for synthesis disappeared. Henceforth, organic synthesis would become an intellectual endeavour in its own right. Compounds were synthesised simply because the process was either interesting and/or challenging. For a period in the mid-twentieth century organic synthesis became a rather "macho" activity, in which leading chemists implied that their synthetic target was bigger (or at least more complicated) than those of their rivals. Into this competitive framework, Woodward fitted perfectly. Secondly, the interest of synthetic chemists shifted from natural pigments, synthetic dyes and sugars to compounds of pharmaceutical interest, obviously with the encouragement of the rapidly expanding pharmaceutical industry, which also gave the field a new *raison d'être*, namely to improve human health. Finally, the introduction of physical instrumentation on one hand and the development of organic reaction mechanisms on the other both assisted organic synthesis

and changed the way it was planned. The physical instrumentation allowed the reactions to be monitored and the products to be traced. The new theories of organic chemistry (organic reaction mechanisms and theories of stereochemistry) now allowed the organic chemist to predict the course of hitherto unknown reactions or how a small change in a reactant, the use of a catalyst or a change of solvent would alter the course of the reaction. Synthetic chemists now had great new powers in their hands and Woodward made full use of them.

Woodward's early synthetic work, up until the early 1950s, was the then fashionable field of steroids. Between the 1930s and 1950s, steroids were seen as wonder drugs capable of changing the face of medicine, a hope which, as is so often the case, turned out to be largely ill-founded. For their part, chemists found the stereochemistry of the fused rings of the steroids and its impact on their reactions of great interest. Woodward established himself as one of the leaders of organic synthesis with his synthesis of cholesterol and cortisone in 1951, cleverly introducing a double bond into the "C" ring which allowed him to proceed to both cholesterol and cortisone, although this achievement was rather overshadowed by Louis Sarrett's elegant synthesis of cortisone at Merck a year later. Woodward's rivalry in the field of natural products chemistry (structure determination *and* synthesis) with the British chemist, Sir Robert Robinson, began with Woodward's correct (and Robinson's incorrect) structure assignment of penicillin and then was heightened even more by the American chemist's entry into the field of strychnine, whose complex structure was a matter of controversy for many years. Woodward proposed the correct structure of the poisonous compound in 1948 and carried out its synthesis six years later. His route was a masterclass in the use of stereochemical control, which was still in its infancy. The greatness of his achievement is shown by the fact that the next successful synthesis of strychnine was not carried out until 1992 (by Philip Magnus).

Like quinine, Woodward's next major synthesis was born of necessity. CIBA had been developing a compound called reserpine which came out of Indian Ayurvedic medicine as a tranquiliser (again the high hopes for it were not in the end fulfilled) when the Indian government banned its export. CIBA turned to Woodward for help and he relished its synthesis. Woodward decided to get as many of the chiral centres in place early in the synthesis and then gradually unveil the final structure. Although it was not a well-known synthetic target, this was Woodward's favourite synthesis and unusually for a laboratory synthesis, it was used on an industrial scale by Roussel-Uclaf.

Woodward now entered a field associated in the interwar period with the German chemist Hans Fischer, namely the porphyrins. Fischer's own work in this field was cut short by his suicide at the end of the Second World War, although his colleagues Alfred Triebs and Martin Strell perpetuated his legacy in Munich. Once again, Woodward's synthesis was a demonstration of precise chemical control. It was an illuminating synthesis as it showed how organic synthesis had moved on since the pioneering work of Fischer in the 1930s, for example its use of photooxidation to cut a cyclopentene ring. Woodward then turned to a larger and even more formidably complicated porphyrin, so complicated in fact that it was the first chemical compound to be determined by X-ray crystallography rather than by chemists. I refer, of course, to vitamin B₁₂ or cyanocobalamin. Thanks to his early friendship with Leopold Ružička and then with Vladimir Prelog, Woodward was familiar with the work at ETH Zurich. He came to appreciate that the work on the synthesis of vitamin B₁₂ being carried out by Albert Eschenmoser and his team at ETH was by good fortune complementary to the ongoing research at Harvard. The two groups then agreed in 1965 on a then unusual transatlantic collaboration between the two groups. It helped that the Woodward Research Institute had been set up by this time which gave Woodward a Swiss base (see below). Woodward had already decided (as in the case of chlorophyll) to construct the ring as two halves and then join them together. It was thus agreed in a neat reflection of geography that the Harvard group would concentrate on the left-hand or "western" half of the ring while the group at ETH Zurich would construct the right-hand or "eastern" half. The enormously long multistep synthesis was completed in 1973, but strictly speaking it was the total synthesis of cobryic acid not vitamin B₁₂, as cobryic acid had already been converted into cyanocobalamin. Perhaps troubled by the controversy over his quinine synthesis - who can say? - Woodward marched on with one of his final graduate students Mark Wuonola to finally reach the total synthesis of vitamin B₁₂ on 17 March 1976.

Even if Woodward (and his team) had to share the glory of the vitamin B₁₂ synthesis with the chemists in Zurich, there was an unexpected spin-off from the earlier vitamin B₁₂ research which was to crown Woodward's career and dominate his later years, namely the principle of the conservation of orbital symmetry. Woodward had long been interested in the Diels-Alder reaction, allegedly ever since he received the 1928 issue of *Annalen* that contained Otto Diels and Kurt Alder's paper from von Tappeler, but had never really come to grips with it successfully in theoretical terms. In 1963, as part of the ongoing vitamin B₁₂ synthesis, a postdoc Subramania ("Ranga") Ranganathan made a compound which could be converted into a closed ring

and the closed ring could be reopened by a photochemical process. As the group was very concerned with stereochemistry, they could easily see that the photochemical opening of the ring produced the opposite isomer to the one which on heating formed the ring compound being photolysed. Clearly there was a fundamental process at work here and Woodward was determined to get to the bottom of it. However Woodward, although well versed in organic reaction mechanisms, was not a theoretical chemist and he soon realised he needed help. By good fortune a young theoretical chemist called Roald Hoffmann was a member of the Society of Fellows. Woodward's initial insights sharpened by Hoffmann's deep understanding of molecular orbital theory quickly produced a set of rules (the Woodward-Hoffmann rules) about how certain concerted intramolecular cyclic chemical reactions, which they called pericyclic reactions, took place in stereochemical terms. The best known of these pericyclic reactions is of course the Diels-Alder reaction. These rules, first published in the *Journal of the American Chemical Society* in early 1965, show which reactions could take place ("allowed") and what the resulting stereochemistry would be on the basis of the signs of the molecular orbital lobes of the reacting molecules. Crucially photochemical reactions behave in the opposite way to thermal reactions. Woodward and Hoffmann continued to develop these rules and their implications over the next four years culminating in a major (and lengthy) publication in *Angewandte Chemie* in 1969.

In our whistle-stop tour of Woodward's syntheses, there is much we have had to leave out. One thinks for example of his synthesis of the crocus-derived alkaloid colchicine with four competing groups (including his later collaborator Eschenmoser), lysergic acid (the basis of LSD), and the tetracycline antibiotics. Nor have I mentioned his other brilliant structure determinations (or more precisely his structural deductions) including the antibiotic streptonigrin or tetrodotoxin, the neurotoxin of the puffer fish. There is however, one other synthesis that we must mention, cephalosporin, as it was the subject of his Nobel Prize lecture in 1965. Woodward was awarded the Nobel Prize for "for his outstanding achievements in the art of organic synthesis", a rare example of the Nobel Prize being awarded for an entire body of research rather than a specific achievement. It is interesting to note in passing that Woodward was first nominated for the Nobel Prize (at the remarkably young age of twenty-nine) by the Harvard astronomer Harlow Shapley in 1946 [vi]. The problem with cephalosporin was that like many antibiotics it was a very delicate compound and carrying out the wrong reaction would cause it to fall apart. Woodward developed a series of reactions which transformed its β -lactam core into the final cephalosporin target, including an unusual condensation with dimethyl azodicarboxylate,

and a later stage which involved refluxing the molecule with pyridine for three days. Woodward then had the idea combining the active sites of penicillin and cephalosporin into a new type of compound now called penems. The Woodward Research Institute synthesised the first penem in 1976.

Thanks to the "pharmaceutical turn" in organic synthesis, Woodward enjoyed close relationships with several pharmaceutical companies who supported his research either by direct sponsorship or by providing chemicals. These were mostly American firms such as Merck, Pfizer and Eli Lilly. However Woodward had several Swiss doctoral students and postdoctoral assistants. One of them, Karl Heuser, went back to Switzerland to accept a research position at CIBA. In 1963 he became head of the Woodward Research Institute, which had been proposed by Woodward's good friend Prelog who was close to CIBA and financially supported by the firm but strictly was speaking not part of it, as symbolised by the glass door between the Institute and CIBA's own facilities. This allowed Woodward to carry out any research he chose with younger chemists, usually his former students and co-workers (for example, Ranganathan), and to utilise the battery of physical instrumentation that only a major pharmaceutical company could afford in the early 1960s. Two of the research areas covered by the Institute were the synthesis of prostaglandins and antibiotics.

Alas, space does not permit of the description of Woodward's practical jokes, often based on a verbal deception [vii], his frequent bets with his colleagues or his love of bridge, but one cannot conclude his biography without mentioning his love of the colour light blue. Why light blue is unclear, the colour of Harvard is crimson red, but perhaps Woodward was alluding to Harvard's English counterpart, Cambridge. Hence, he always wore a light blue tie, often wore blue suits and had a blue car; his students even painted his car parking space at the laboratory light blue.

Woodward's father had suffered heart trouble at an early age and his grandfather had died at the age of sixty. Woodward himself smoked cigarettes constantly and drank significant quantities of whisky and martinis. He survived on a few hours' sleep a night, which also has health implications. It is therefore not surprising that he died at his home in Cambridge of a heart attack on 9 July 1979 at the age of sixty-two [viii]. At the time of his death, Woodward was working on the synthesis of the antibiotic erythromycin which was completed by his collaborators in 1981. But for his premature death, he almost certainly would have shared the 1981 Nobel Prize with Roald Hoffmann and Kenichi Fukui [ix] for his work on the Woodward-Hoffmann rules. But truth be told, he was probably glad to

depart for the great chemistry laboratory in the sky when he was still at the peak of his powers rather than endure a prolonged dotage troubled by health problems and loneliness. Although he had students who became eminent chemists, he did not found a school in the manner of Liebig or even Derek Barton, and he did not develop any specific methodology of synthesis unlike his colleague Elias Corey's retrosynthetic analysis. Even the use of the term Woodward-Hoffmann rules has declined since 1995 and the Woodward reaction is not well-known. For all that, we are still left with the inspiring memory of one of the greatest chemists the world has ever known.

Sources for the Biography

It seems pointless to give specific citations for most of this material when it is largely overlapping and reinforcing. Most of the material in this biography has been taken from Alexander Todd and John Cornforth, "Robert Burns Woodward", *Biographical Memoirs of Fellows of the Royal Society*, 1981, 27, 629-95, especially the personal biography by Todd which forms the first part of this obituary. Other sources are Elkan Blout, "Robert Burns Woodward, 1917-1979", *Biographical Memoirs of the National Academy of Sciences*, 2001, 80, 367-90; W. David Ollis, "Robert Burns Woodward: An Appreciation", *Chemistry in Britain*, April 1980, 16, 210-16; Frank Westheimer, "Robert Burns Woodward: Scientist, Colleague, Friend", in *Robert Burns Woodward: Architect and Artist in the World of Molecules*, eds. Otto Theodor Benfey and Peter J.T. Morris (Philadelphia: Chemical Heritage Foundation, 2001), pp. 13-20; and Robert C. Putnam, "Reminiscences from Junior High School" in Benfey and Morris, *Robert Burns Woodward*, pp. 11-12. I have also drawn other material from Benfey and Morris, *Robert Burns Woodward*, including my earlier attempt at a biography with Mary Ellen Bowden (pp. 3-12), my introductions to Woodward's most important papers, and the semi-autobiographical Cope lecture given by Woodward in 1973 (pp. 418-452), which obviously has to be treated with caution.

For his family background, I drew on three online compilations, one on the earlier Woodward family written as a biography of his great-grandfather W. Elliott Woodward: <http://www.quotesquotations.com/biography/w-elliott-woodward/> (accessed 17 March 2017), a family tree by Tim Dowling: <http://gw.geneanet.org/tdowling?lang=en&p=robert+burns&n=woodward&oc=0> (accessed 17 March 2017) and a very detailed description of the more recent family history by a cousin which I do not wish to cite as it contains some rather personal information about the family. I also carried out my own genealogical research on FamilySearch.org and Scotlandspeople.gov.uk.

Local information, especially in the opening paragraph, was taken from the online archives of the *Boston Globe*.

For the history of the Woodward Research Institute, see G. Wayne Craig, "The Woodward Research Institute, Robert Burns Woodward (1917-1979) and Chemistry behind the Glass Door", *Helvetica Chimica Acta*, 2011, 94, 923-946. For the biography of James Flack Norris, see John D. Roberts, "James Flack Norris, 1871-1940", *Biographical Memoirs of the National Academy of Sciences*, 1974, 45, 413-26. For the historical background to the chemical revolution that took place in Woodward's lifetime, see Peter J. T. Morris, ed., *From Classical to Modern Chemistry: The Instrumental Revolution* (Cambridge: Royal Society of Chemistry, 2002), especially the paper by Leo Slater, "Organic Chemistry and Instrumentation: R.B. Woodward and the Reification of Chemical Structures", pp. 212-228. Also see Leo Slater, "Instruments and Rules: R.B. Woodward and the Tools of Twentieth-Century Organic Chemistry", *Studies in History and Philosophy of Science Part A*, 2002, 33.1, 1-33; and Leo Slater, "Woodward, Robinson, and Strychnine: Chemical Structure and Chemists' Challenge", *Ambix*, 2001, 48, 161-89. For the resolution of the issue over the validity of the Rabe-Kindler transformation of quintonine to quinine, see Jeffrey I. Seeman, "The Woodward-Doering/Rabe-Kindler Total Synthesis of Quinine: Setting the Record Straight", *Angewandte Chemie International Edition*, 2007, 46, 1378-1413; and Aaron C. Smith and Robert M. Williams, "Rabe Rest in Peace: Confirmation of the Rabe-Kindler Conversion of d-Quinotoxine Into Quinine: Experimental Affirmation of the Woodward-Doering Formal Total Synthesis of Quinine", *Angewandte Chemie International Edition*, 2008, 47, 1736-1740.

I wish to thank Jeffrey Seeman for his very kind assistance with this biography and warmly refer readers to his ongoing series of papers on Woodward and the Woodward-Hoffmann Rules, far too numerous to be listed here, but which can mainly be found in *Angewandte Chemie International Edition*. Needless to say any mistakes which remain are entirely my own.

References for the Biography

- i) For the precise time and place, and the casting of a horoscope for Woodward by David Dolphin see David Dolphin, "Robert Burns Woodward: Three Score Years and Then?" *Heterocycles*, 1977, 7.1, 29-35 [originally published in *Aldrichimica Acta*, 1977, 10.1, 3-9].

ii) Now stored as part of the Woodward papers at the Harvard archives, <http://oasis.lib.harvard.edu/oasis/deliver/~hua06001> (accessed 17 March 2017), call mark HUGFP 68.32f.

iii) Information about von Tippleskirch's internment and death was taken from correspondence of the period sold on eBay in 2013.

iv) R.B. Woodward, "The Arthur C. Cope Award Lecture", in *Robert Burns Woodward: Architect and Artist in the World of Molecules*, eds. Otto Theodor Benfey and Peter J.T. Morris (Philadelphia: Chemical Heritage Foundation, 2001), pp. 418-452, on p. 426.

v) The Austin Research Fellowship is mentioned in the acknowledgements of his 1937 thesis which can be downloaded from the MIT website: <http://hdl.handle.net/1721.1/12465> (accessed 17 March 2017).

vi) See http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1965/woodward-nomination.html (accessed 17 March 2017).

vii) Two examples are given by Frank Westheimer in his recollections of Woodward, see *Sources for the Biography* above.

viii) Although it was a Sunday, it was unusual that he was at home as he rarely took time off, so one wonders if he had been feeling unwell beforehand.

ix) Fukui, a Japanese chemist of similar age to Woodward, had independently been working on the relationship between the symmetry of molecular orbitals and chemical reactions.

RSCHG Occasional Paper No. 9, published April 2017

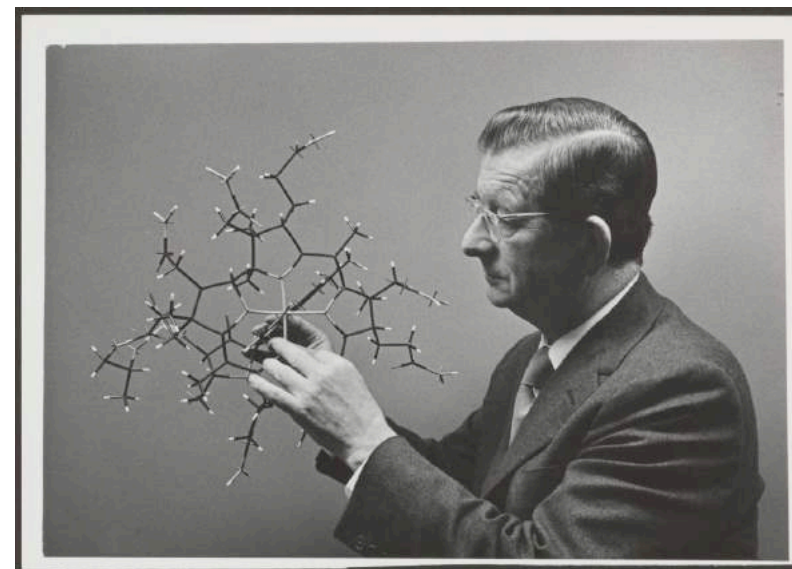
Series Editor: Dr Anna Simmons

Robert Burns Woodward in his Own Words

Dr Peter J.T. Morris
Science Museum, London

The Sixth Wheeler Lecture

Royal Society of Chemistry, 17 May 2013



Robert Burns Woodward holding model of Vitamin B12, photograph, c. 1973.

HUGFP 68.38.1p (Box 2), olvwork294150. Harvard University Archives

I must begin by thanking the Historical Group for its kindness in giving me its Wheeler Award.

But every privilege carries with it some kind of responsibility, and I have, at this moment, a responsibility which I cannot but regard as a heavy one—that of presenting to all of you a lecture, appropriate to the occasion, and it may be hoped, of some general interest to an audience among whose members there must certainly be a wide diversity in background.

...

Well, then, here I stand with the problem still before me WHAT TO SAY? And now, the solution. I present it with considerable diffidence, since what I am about to describe is highly personal, idiosyncratic and very far removed from the kind of lecture with which I am familiar!![1]

By now you may have guessed that these words are not my own, but those of Robert Burns Woodward taken from the opening of his famous Cope Lecture. Originally, I intended to explain why Woodward became a great chemist - that he was a great chemist is beyond dispute and easily explained - and I found this completely impossible. He seems to have been a prodigy from the age of twelve without the need for any external assistance apart from the fabled Baron von Tappelskirch [2]. Kurt von Tappelskirch was the German Consul in Boston in the 1920s who obtained copies of German chemistry journals for the twelve-year old Woodward, one of which was the 1928 issue of *Annalen der Chemie* containing the first paper by Otto Diels and Kurt Alder [3]. My next idea was to discuss various aspects of Woodward's thinking and personality, but any comments seemed very thin without quoting the great man himself. This in turn gave me the idea of giving the stage over to Woodward so that his words would more or less speak for himself - and for me! I downloaded or otherwise collected all of the known papers of Woodward (he did not publish any books) and searched them for suitable material. As they are chemical papers, they do not give much insight into the personal aspects of Woodward's life. Additionally, it was not feasible to consult the Woodward archive at Harvard for this lecture. There are relatively few papers which are useful for a lecture of this type, but they are excellent in their own way. These include the paper on "Synthesis" that Woodward wrote for *Perspectives in Organic Chemistry* in 1956; the paper on "Art and Science in the Synthesis of Organic Compounds" which appears in a very rare book called *Pointers and Pathways in Research* published in 1963; his Harvey Lecture on colchicine delivered in 1963; and, finally, his Cope Lecture of 1973, published in the volume I edited with Ted Benfey [4]. Familiarity with these lectures will vary, but I will use this Wheeler Lecture to draw general themes from this corpus.

I shall make a valiant effort to limit the discourse to a respectable number of milli-woodwards. No doubt, many of you have heard of the unit of lecture time established by the distinguished theoretical chemist Edgar Heilbronner. His procedure was not unlike that of using the King's arm as a unit of length—the yard. Heilbronner used as a standard the amount of time I devoted to a lecture at Karlsruhe—on orbital symmetry, beginning at 8 pm—five hours and twenty minutes.

Thus the usual 50-minute exposition favoured by most professors constitutes a lecture of ca. 156 milli-woodwards. [5]

Woodward again in the Cope Lecture and certainly I will try to keep to a limit of 156 milli-Woodwards! I wish to begin, as Woodward did in that lecture, with a theme close to our own heart, the history of chemistry.

In one of his early papers, on the synthesis of quinine, a feat now confirmed some sixty years later [6], Woodward added a historical note at a time when William Henry Perkin was less well known:

Earlier attempts had been made, notably that of Perkin, who attempted to convert allyl toluidine to quinine by oxidation. An interesting account of this work, which led directly to the establishment of the coal tar color industry, and hence of the organic chemical industry, is given by Perkin himself in the Hofmann memorial lecture. [7]

And later in the same paper, he showed a good historical grasp of Pasteur's work on optical activity even citing an Alembic Club Reprint:

This is in despite of the fact that *dl*-tartaric acid is smoothly resolvable by natural *d*-quintoxine. It is a little known albeit historically an important fact, that this and the similar resolution by cinchotoxine were the first examples of the now universally used method of resolution of a racemic compound [8].

He then goes on to discuss the confusion that had been caused by Pasteur using the old names for quintoxine and cinchotoxine.

Woodward was also aware that Kolbe's synthesis of acetic acid was the first true total synthesis not Wöhler's so-called synthesis of urea [9].

But it is in the Cope Lecture that he makes his major excursion into the history of chemistry, to support the claims of a fellow Scots chemist:

In that literally astonishing paper [by Couper], one may see presented for the first time STRUCTURAL FORMULAE, identical with those we use today—and these are of course the most fundamental theoretical tools of organic chemistry.

...

NOW Couper has received little credit for his brilliant contribution, no doubt because not long after his paper was published, he returned to his mother's house in Scotland, went mad and played no further role in chemistry.

OF WHAT RELEVANCE is this history to the story of my personal scientific saga? I will admit freely that in some measure, I have just arbitrarily seized the occasion to right what I consider a grievous historical injustice. BUT there are connections. We can dismiss the obvious ones briefly and in a jocular vein. It is true that like Couper I bear Scottish blood. But I left my mother's home early, never to return. Let there be no unduly adverse implications here. Glad as I was to escape the maternal wing, I know that my mother was a powerful and very helpful positive force in my development. To conclude this category, I did not go mad - or if I did, at least I think I have been able, relatively successfully, to conceal the more obviously anti-social manifestations of the condition. [10]

I might add in passing that the leading historian of biochemistry Robert Kohler, whom I knew well at the University of Pennsylvania, was one of Woodward's students and is mentioned by name in Woodward's Nobel lecture.

Theory

The reference to Couper's work on structure theory shows one of Woodward's major themes: the crucial importance of chemical structure to organic synthesis and, in particular, his own work. Woodward refers several times to the importance of theories and principles. However, until the advent of the conservation of orbital symmetry in the mid-1960s, by theory he largely meant chemical structure, with the new stereochemical insights gained by Derek Barton in 1950 added to the classical understanding of structure. We know that Woodward used organic reaction mechanisms at an early stage and appreciated the new insights in chemical reactivity they delivered, not least because he showed mechanisms (including curly arrows) from the 1940s onwards. However, he never explicitly referred to mechanistic chemistry in his discussion of synthesis. Here is what Woodward said on the subject in "Art and Science":

The discovery just about a century ago that the structure and form of molecules provide the fundamental basis for the differentiation of all forms of matter was one of man's greatest discoveries, and laid the foundation for a breath-taking acceleration in his understanding of the physical environment. [11]

And earlier in "Synthesis":

The structure theory recognized that the maintenance of nearest-neighbor relationships amongst the elements was responsible for the variety and individuality of the material components of the physical

world. The great advance of the recent past has been the recognition of the entities responsible for the maintenance of those nearest-neighbor relationships, and a description in simple general terms of wide applicability and precision, of their fluid nature, and of the laws to which they are subject. The resulting edifice of organic chemical theory enables us, with obvious consequences for organic synthesis, to assert that the outcome of very few organic reactions is unexpected, and fewer inexplicable. [12]

Instrumentation

At the same time, Woodward realised that the determination of structure was in the process of being transformed. While he advocated the use of the new physical instrumentation, and to some degree used it himself, for example the UV rules for the structure of steroids he developed when he was still in his early thirties, Woodward was always rather guarded in his attitude towards instrumentation, in contrast to say Carl Djerassi. In 1956, in "Synthesis", he wrote:

To have placed primary emphasis on the importance of theory in providing a basis for the synthetic achievement of the present day is not to derogate a second factor of very moment—the development of and application of physical methods. ... Ultraviolet spectra have long been with us, and during the last decade have come into the prominent use which they deserve. But no single tool has had a more dramatic impact upon organic chemistry than infrared measurements. ... The routine examination of virtually every reaction mixture, however crude, or lacking in tangible prospect of yielding a desired product, often provides a clue to important developments which otherwise could not be made. ... The capacity of the physical specialist to place his results properly in the context of an organic chemical investigation is often narrow and unrealistic, and the organic chemist will find himself magnificently rewarded, who takes the pains to be himself in a position to understand and interpret the physical aids he wishes to use. In any event, physical methods, *and the principle that they should be used whenever possible*, are now part of our armamentarium, and we may expect no surcease of further developments in this direction. Nuclear magnetic resonance is even now on the horizon, and we shall be surprised if it does not permit another great step forward. [13]

Woodward noted that the determination of the structure of quinine took ninety years after it was isolated in 1820, strychnine 140 years after its discovery in 1818, and reserpine only three years after it was isolated in 1952. In "Art and Science", he commented:

The determination of a complicated structure can be—at least it was, in general in the past—a very complicated and difficult task. ... However, with advances in the science of organic chemistry, the task has become less difficult. With greater understanding of chemical principles, with advances in experimental methods, and with an increasing use of ancillary physical disciplines, structures may now be determined in a small fraction of the time once required. [14]

Purpose of Synthesis

Woodward realised that the key role of synthesis up to the 1950s at least was the proof of structure, following its determination by degradation. When employed for this purpose, the chemical reactions used had to be well-understood and should not produce any unexpected rearrangements of structure. In “Synthesis”, he remarked that “A traditional task of organic synthesis has always been the verification of structure. Furthermore, while analytical and degradative work must always be primary, it is often synthesis which provides the simplest, most rigorous and final proof.” [15]

Referring to the uncertainties in structure thrown up by early infra-red and NMR studies, he saw a continuing use for synthesis in structure determination which in fact was short-lived, since improved NMR techniques were introduced in the 1970s and 1980s: “Again, developments in physics are very likely to revive, for some time at least, the function of synthesis in dealing the *coup de grace* to problems of structure.” [16]

But if synthesis was to lose its purpose as a way of confirming structure, it could also use less predictable reactions, the products of which could be confirmed by infra-red spectra, and thus become more creative. In his “Synthesis” paper, Woodward saw synthesis as a supremely creative activity:

I for one will not conceal my hope, contrary though it may be to the often too narrowly utilitarian spirit of the day, that synthesis for its own sake will continue. There is excitement, adventure, and challenge, and there can be great art, in organic synthesis. [17]

And later in “Art and Science”, he waxed lyrically in his typically florid style:

I would like to mention here a basis for action more related to the spirit of man. The structure known, but not yet accessible by synthesis, is to the chemist what the unclimbed mountain, the uncharted sea, the untilled field, the unreached planet, are to other men. The achievement of the objective in itself cannot but thrill all chemists, who even before they know the details of the journey can

apprehend from their own experience the joys and elations, the disappointments and false hopes, the obstacles overcome, the frustrations subdued, which they experienced who traversed a road to a goal. The unique challenge which chemical synthesis provides for the creative imagination and the skilled hand ensures that it will endure as long as men write books, paint pictures and fashion things which are beautiful or practical or both. [18]

And according to Woodward, in “Synthesis”, the achievements of the chemical industry in his lifetime also displayed this creativity:

No discussion of the accomplishments, functions, and prospects of organic synthesis would be complete without some mention of its more general creative capacity. In the century that has passed since Bertholet’s words [chemistry creates its object] were uttered organic chemistry has literally placed a new Nature beside the old.

We are clothed, ornamented, and protected by forms of matter foreign to Nature; we travel and are propelled in, on, and by them.

We shall leave it that the evidence is overwhelming that the creative function of organic chemistry will continue to augment Nature, with great awards, for mankind and the chemist in equal measure. [19]

Planning Synthesis

Woodward certainly thought that syntheses had to be planned, how it could be otherwise? In “Synthesis”, he stated:

Synthesis must always be carried out by plan, and the synthetic frontier can be defined only in terms of the degree to which realistic planning is possible, utilizing all the intellectual and physical tools available.

... modern theory permits synthetic planning, and reduction of plans to practice, on a scale which was hitherto quite as impossible as were the simpler syntheses of the last century before the elaboration of the structure theory. [20]

However, he did not believe in any kind of schematic or theoretical planning process, something which he saw as the enemy of creativity and dare I say it, fun? In “Art and Synthesis”, he declaimed:

... chemical synthesis is essentially entirely a creative activity, in which art, design, imagination and inspiration play a predominant rôle. For there is no fixed, pre-ordained or pre-determined method, design or pattern for the synthesis of any complicated molecule. ...

[the synthesis of new substances] is an area which is entirely creative in spirit, and in which there is unlimited opportunity for art and imagination. [21]

Speaking of the possible synthesis of large biomolecules consisting of repeated units in that paper, he said:

If combination reactions of especially high efficiency can be developed, it is possible that the sequential use of such reactions can be standardized and then mechanized. ... I hasten to apply the obvious palliative that although the experimental aspects of some kinds of synthetic activity may be susceptible of mechanization, the creative aspects of synthetic design will not! [22]

This does of course run counter to modern efforts to use computer-based expert systems to develop syntheses!

Rather than seeing synthesis as a previously computed path, like the travel plan of a robotic spacecraft for example, the Romantic Woodward saw it as a military campaign. When he completed the strychnine synthesis in 1954, he sent David Ollis, who was a former member of the strychnine group, a telegram which read “We have met the enemy and they are ours. Warmest congratulations. R B Woodward Commandant Beresina Group.” [23] Beresina was a famous victory by Napoleon’s Swiss troops near Moscow, and Karl Schenker and Hans Ulrich Daeniker in the strychnine group were Swiss. Furthermore, in his paper on chlorophyll, Woodward exclaimed “Fresh from his dramatic conquest of the blood pigment, Fischer hurled his legions into the attack on chlorophyll, and during a period of approximately fifteen years, built a monumental corpus of fact.” [24]

Woodward doubtlessly saw himself in the same vein! The translator of the paper into German refused to translate this passage. Later on, when the syntheses became ever more complex, Woodward began to see them more as mountain climbs, an analogy used by other organic chemists some of whom (unlike Woodward who strenuously avoided any form of exercise) were serious Alpinists: In the paper on strychnine he said “So far our operations had proceeded very directly towards our objective. Now we were to embark on a brief excursion, which is not without intrinsic interest, and necessitated a minor tactical change in our plans.” [25]

In the paper on the so-called “western half” of B₁₂ (a term that is itself redolent of mountain ascents), he remarked:

First, the relatively simple method of producing this important intermediate, which I have just described, was not that by which we made it for the first time. It was in fact first produced by an

alternative, experimentally very elegant, but far longer and less practical route, and subsequently several other paths were laid down before the one outlined here was discovered. [26]



Photograph of the 1958-59 chlorophyll group, July 1959.

From left to right: Shô Itô, Hans Dutler, Woodward, Raymond Bonnett, Jürgen Sauer and Heinrich Volz.

Woodward and Bonnett are holding a branch of a tree, alluding to the chlorophyll in leaves.

Photography courtesy of Professor Ray Bonnett and © Raymond Bonnett.

Sensuous Nature of Chemistry

Woodward’s concern with creativity was linked to his concept that new substances were new forms of matter. I wonder how many other organic chemists consciously perceive compounds (rather than subatomic particles) as a form of matter? In “Art and Science”, Woodward said:

What basic tools does the chemist have for use in synthetic activities? Essentially two. The first is the science of chemistry—the body of laws, principles and generalizations which govern the interactions and transformations of matter. The second is the body of experimental, manipulative techniques which enables the chemist to place various forms of matter in contact with one another, separate the products of the resulting interactions, and ascertain the nature and structure of these substances. [27]

And the organic chemist had the thrilling ability to create new forms of matter:

Crystallization is one of the most beautiful processes known and no true chemist fails to experience a thrill when he brings a new form of matter into the crystalline state for the first time. [28]

And again in his Harvey Lecture:

Each of the intermediates along our progression to the colchicine molecule is a beautifully crystalline substance, an entirely new form of matter, persuaded into being in response to the challenge of an often remote objective. It is delightful to work with such things, and the delight which the experimenter experiences in his manipulation contributes in no small measure to the skill required to create them. [29]

Crystals were very important to Woodward, he even named his daughter Crystal, and they were almost invariably beautiful. In an early paper on the synthesis of oestrone, based on his PhD thesis, he used the word “beautiful” five times in a paper only four and a half pages long!

- it forms a beautifully crystalline dibromide [30]
- A beautifully crystalline addition product (mentioned twice) [31]
- a solid mass of beautiful needles [32]
- crystallized quantitatively in beautiful transparent rosetts [33]

Looking back over his life in the Cope Lecture, Woodward explained that it was the sensuousness of chemistry that drew him to chemistry rather than mathematics:

...mathematics lacks the sensuous elements which play so large a role in my attraction to chemistry. I love crystals, the beauty of their form—and their formation; liquids, dormant, distilling, sloshing!; the fumes; the odors—good and bad; the rainbow of colours, the gleaming vessels, of every size, shape and purpose. Much as I might think about chemistry, it would not exist for me without these physical, visual, tangible, sensuous things. [34]

This is in spite of the fact that he rarely worked in the laboratory himself! I am not sure all mathematicians would agree that mathematics cannot be sensuous, one only has to think of Klein bottles for example, but this was certainly Woodward’s view.

Nature

Allied to this sensuous and Romantic view of chemistry, Woodward also saw Nature (which he always capitalised) as a bountiful source of material, an ally, and a model to emulate, rather than something to be tortured or subdued in a harshly Baconian manner. While he saw each new synthesis as a challenge, they were a challenge thrown down by Nature rather than a part of Nature that had to be conquered. In “Synthesis” he remarked:

A little reflection will reveal the enormous extent to which the study of natural products has contributed to the development of organic chemical theory. It could hardly be otherwise, for the substances provided by Nature were those at hand, and it was the first task of the chemist to understand and generalize their behaviour. [35]

And again in the “western half” paper:

The history of organic chemistry provides in abundance instances of the major role played by the study of natural products in revealing, extending, and shaping the fundamental bases of the science. Time and again the penetration of a new sector of the vast, often surprising and always beautiful panorama of natural products has led to new insights which could hardly have been achieved by more self-conscious fundamental investigations. This role of natural product studies is in no way diminished in our day, and it will certainly continue in the future; the proposition cannot be better illustrated than by my alluding to the fact that the principle of orbital symmetry conservation arose directly from our studies on vitamin B₁₂ synthesis. [36]

And in “Art and Science”:

Synthetic work offers ample opportunity for another kind of surprise. Not infrequently, Nature is more knowledgeable and artful than the chemists and devises combinations between, or transformations of, reacting molecules which the designer has not anticipated at all. [37]

Woodward describes his collaboration with Nature in the Harvey Lecture. This is one of his most lyrical passages, in a style one cannot imagine any senior organic chemist using today, more’s the pity:

Our investigation now entered a phase which was tinged with melancholy. Our isothiazole ring had served admirably in every anticipated capacity and some others as well. With the obtention of [a tropolone], it had enabled us to construct the entire colchicine skeleton, with almost all the needed features properly in place, and

throughout the process, it and its concealed nitrogen atom have withstood chemical operations, variegated in nature and in some instances of no little severity. It had mobilised its special directive and reactive capacities dutifully, and had not once obtruded a willful and diverting reactivity of its own. Now it must discharge but one more responsibility—to permit itself gracefully to be dismantled, not be used again until someone might see another opportunity to adopt so useful a companion on another synthetic adventure. And perform this final act of grace it did. [38]

Before returning to the notion of surprise that has already been mentioned, I first wish to consider the restraints on the sensuous and fun elements of chemistry.

Constraints

While he greatly enjoyed the creative aspects of synthesis, Woodward also believed it was important that this almost frivolous creativity was constrained by the need to obey the laws of Nature; hence organic chemistry was both art and science. In the Cope Lecture, he said:

While in mathematics, presumably one's imagination may run riot without limit, in chemistry one's ideas, however beautiful, logical, elegant, imaginative they may be in their own right, are simply without value unless they are actually applicable to the one physical environment we have—in short, they are only good if they work! I personally very much enjoy the very special challenge which this physical restraint on fantasy presents. [39]

And earlier in the “Art and Science” paper:

... at each of the many stages of such syntheses the chemist is ordinarily creating entirely new forms of matter which have never existed before. This circumstance will make it clear that the chemist can in fact create at will an uncounted variety of entirely new substances, limited only by the known laws governing the interrelationships of atoms within molecules. [40]

The ability to create new molecules while being able to predict and obey the rules laid down by nature showed the power of chemistry. He claimed in “Synthesis” that:

It can scarcely be gainsaid that the successful outcome of a synthesis of more than thirty stages provides a test of unparalleled rigor of the predictive capacity of the science, and of the degree of its understanding of its portion of the environment. Since organic

chemistry has produced syntheses of this magnitude, we can, by this yardstick, pronounce its condition good... [41]

An Enlightenment Chemist?

The milli-Woodwards march remorselessly onward, but there is one last aspect of Woodward that I would like to discuss. This paper has emphasised the importance of sensuousness and creativity for Woodward. These aspects of his chemistry make him very much a Romantic chemist and are illustrated by his prose style, as is shown, for example, in the opening of his key paper on the strychnine synthesis:

Strychnine! The fearsome poisonous properties of this notorious substance attracted the attention of XVIIIth century Europe to the *Strychnos* species which grows in the rain forests of the Southeast Asian Archipelagos and the Coromandel Coast of India, and gained for the seeds and bark of those plants a widespread use for the extermination of rodents, and other undesirables, as well as a certain vogue in medical practice—now known to be largely unjustified by any utility. [42]

But he was of Scottish blood, as he put it himself, and there is more than a trace of the Scottish Enlightenment in his thinking:

For almost 50 years now, I have been involved in an affair with chemistry. It has been throughout—and still is—a richly rewarding involvement, with numerous episodes of high drama and intense engagement, with the joys of enlightenment and achievement, with the special pleasures which come from the perception of order and beauty in Nature—and with much humour. [43]

An important element of this enlightenment through engagement with Nature was the aspect of surprise: surprise at the failure of a reaction to take place, which often happened, or surprise at a seemingly inexplicable reaction, of which he listed “four mysterious reactions” that surprised him around 1960 [44]. It was another mysterious reaction three years later that led to the development of the Woodward-Hoffmann Rules. He had already commented in his “Art and Synthesis” paper that “the unexpected is always important and its study should be welcomed, since it is likely to lead to further understanding...” [45], but in the same paper, he noted that surprise could occur in other ways:

It is possible to introduce delightful elements of surprise into synthetic work. An apparently rather dull grouping of atoms suddenly, under the impact of especially chosen reagents, undergoes unusual transformations which are of great utility in progress towards the

objective. The impact on an observer may be compared with that of the traveller down an uninteresting street, who turns through a hidden doorway into a delightful and charming garden. [46]

Perhaps this desire to liven things up with surprises explains his love of practical jokes.

However, what has surprise to do with the Enlightenment? A Scottish Enlightenment philosopher wrote at length on the phenomenon of surprise and its relationship with scientific discovery, using the case of astronomy. His name may surprise you: he was Adam Smith, better known today for his economics. However, he was also a friend of William Cullen and Joseph Black and he taught at the university in Woodward's mother's home city. This is what Smith wrote in one of my favourite passages:

When one accustomed object appears after another, which it does not usually follow, it first excites, by its unexpectedness, the sentiment properly called Surprise, and afterwards, by the singularity of the succession, or order of its appearance, the sentiment properly called Wonder. We start and are surprised at feeling it there, and then wonder how it came there. The motion of a small piece of *iron* along a plain table is in itself no extraordinary object, yet the person who first saw it begin, without any visible impulse, in consequence of the motion of a loadstone at some little distance from it, could not behold it without the most extreme Surprise; and when that momentary emotion was over, he would still wonder how it came to be conjoined to an event with which, according to the ordinary train of things, he could have so little suspected it to have any connection.

Philosophy, by representing the invisible chains which bind together all these disjointed objects, endeavours to introduce order into this chaos of jarring and discordant appearances, to allay this tumult of the imagination, and to restore it, when it surveys the great revolutions of the universe, to that tone of tranquillity and composure, which is both most agreeable in itself, and most suitable to its nature. [47]

I doubt if Woodward ever read Smith's *Essays on Philosophical Subjects*, but I think he would have agreed with the sentiments expressed.

As my allotted milli-Woodwards have now ended, I will conclude with remarks that Woodward made at the Nobel Prize banquet in 1965:

Alfred Nobel intended his prizes to be awarded for personal achievement. If I search for my personal achievement, it may be that I have led these men and women—and perhaps in some measure all organic chemists — to the higher ground of a greater appreciation of

the power, and above all of the beauty of their science. If I have done this during the last almost thirty years, I have done it in circumstances which have been enormously exciting and quite rewarding enough in themselves. [48]

Acknowledgements

I would like to mention my debt to Crystal Woodward's paper on her father in *Creative People at Work*. This covers some of the same territory, but in a rather different way [49]. I also want to thank Jeffrey Seeman for many conversations (mainly by email) about Robert Burns Woodward and his writings. Seeman has, completely independently, published his own paper on Woodward's literary style [50].

References for the Wheeler Lecture

1. R.B. Woodward, "The Arthur C. Cope Award Lecture", in *Robert Burns Woodward: Architect and Artist in the World of Molecules*, eds. Otto Theodor Benfey and Peter J.T. Morris (Philadelphia: Chemical Heritage Foundation, 2001), pp. 418-452, on pp. 418-419 and p. 420 (hereafter "Cope Lecture").
2. "Cope Lecture", pp. 425-426. See the first half of this publication, Peter J.T. Morris, *A Biography to Mark the Centenary of the Birth of Robert Burns Woodward*, and the accompanying sources for more on the life of Robert Burns Woodward
3. Otto Diels and Kurt Alder, "Synthesen in der hydroaromatischen Reihe", *Justus Liebig's Ann. Chem.*, 1928, **460**, 98-122.
4. Robert Burns Woodward, "Synthesis", in *Perspectives in Organic Chemistry*, ed. Alexander Todd (New York: Interscience Publishers, 1956), pp. 155-184 (hereafter "Synthesis"); R.B. Woodward, "Art and Science in the Synthesis of Organic Compounds: Retrospect and Prospect", in *Pointers and Pathways in Research*, ed. Maeve O'Connor (Bombay: CIBA India, 1963), pp. 23-41 (hereafter "Art and Science"); R.B. Woodward, "A Total Synthesis of Colchicine", in *The Harvey Lectures Delivered under the Auspices of the Harvey Society of New York, 1963-1964* (New York and London: Academic Press, 1965), pp. 31-47 (hereafter "Total Synthesis").
5. "Cope Lecture", pp. 422-423.
6. Aaron C. Smith and Robert M. Williams, "Rabe Rest in Peace: Confirmation of the Rabe-Kindler Conversion of *d*-Quinotoxine Into Quinine: Experimental Affirmation of the Woodward-Doering Formal Total Synthesis of Quinine", *Angewandte Chemie International Edition*,

- 2008, **47**, 1736-1740. Also see Jeffrey I. Seeman, "The Woodward-Doering/Rabe-Kindler Total Synthesis of Quinine: Setting the Record Straight", *Angewandte Chemie International Edition*, 2007, **46**, 1378-1413.
7. Robert Burns Woodward and William von Eggers Doering, "The Total Synthesis of Quinine", *Journal of the American Chemical Society*, 1945, **67**, 860-874, on p. 860 (footnote 2). This paper is reproduced in Benfey and Morris, *Robert Burns Woodward*, pp. 63-77.
 8. Benfey and Morris, *Robert Burns Woodward*, p. 867 (footnote 48).
 9. "Synthesis", p. 156.
 10. "Cope Lecture", pp. 421-422.
 11. "Art and Science", p. 25.
 12. "Synthesis", p. 156.
 13. "Synthesis", p. 157.
 14. "Art and Science", p. 25.
 15. "Synthesis", p. 165.
 16. "Synthesis", p. 165.
 17. "Synthesis", p. 165.
 18. "Art and Science", p. 41.
 19. "Synthesis", p. 180.
 20. "Synthesis", p. 155.
 21. "Art and Science", p. 28 and p. 40.
 22. "Art and Science", p. 41.
 23. Reproduced in Benfey and Morris, *Robert Burns Woodward*, p. 125.
 24. Robert Burns Woodward, "The Total Synthesis of Chlorophyll", *Pure and Applied Chemistry*, 1961, **2**, 383-404, on p. 383. This paper is reproduced in Benfey and Morris, *Robert Burns Woodward*, pp. 256-277.
 25. Robert Burns Woodward, *et al.*, "The Total Synthesis of Strychnine", *Tetrahedron*, 1958, **19**, 247-288, on p. 253. This paper is reproduced in Benfey and Morris, *Robert Burns Woodward*, pp. 136-177. For the similarities between mountaineering and organic synthesis, see Peter J.T. Morris, "Reaching the Summit", *Chemistry and Industry*, 10 July 2000, 433-435.
 26. Robert Burns Woodward, "Recent Advances in the Chemistry of Natural Products", *Pure and Applied Chemistry*, 1968, **17**, 519-547, on p. 535. The synthesis of the corrin nucleus of Vitamin B₁₂ had been divided between Woodward's group at Harvard and Albert Eschenmoser's group at ETH, Zurich. The Harvard group had referred to the left and right halves of the nucleus, whereas the Zurich group had used west and east (probably with the geographical position of the two groups in mind as well as the spatial arrangement of the molecule). Woodward abandoned left/right when he realised the negative connotations of "sinstraline" for an intermediate rather than "hesperimine" (see pp. 538-539). This paper is reproduced in Benfey and Morris, *Robert Burns Woodward*, pp. 314-342.
 27. "Art and Science", p. 28.
 28. "Art and Science", p. 31.
 29. "Total Synthesis", p. 46.
 30. Robert Burns Woodward, "Experiments on the Synthesis of Oestrone. I. The 2-(p-Phenylethyl)-furans as Components in the Diene Synthesis", *Journal of the American Chemical Society*, 1940, **62**, 1478-1482, on p. 1478.
 31. Robert Burns Woodward, "Experiments on the Synthesis of Oestrone", p. 1479 (twice).
 32. Robert Burns Woodward, "Experiments on the Synthesis of Oestrone", p. 1482.
 33. Robert Burns Woodward, "Experiments on the Synthesis of Oestrone", p. 1482.
 34. "Cope Lecture", p. 427.
 35. "Synthesis", p. 176.
 36. Woodward, "Recent Advances in the Chemistry of Natural Products", p. 519.
 37. "Art and Science", p. 37.
 38. "Total Synthesis", pp. 45-46.
 39. "Cope Lecture", p. 427.
 40. "Art and Science", pp. 39-40.
 41. "Synthesis", p. 155.

42. Robert Burns Woodward *et al.*, “The Total Synthesis of Strychnine”, p. 247.
43. “Cope Lecture”, p. 420; for his “Scottish blood”, see p. 422.
44. “Cope Lecture”, pp. 432-433.
45. “Art and Science”, p. 37.
46. “Art and Science”, p. 36.
47. Adam Smith, “History of Astronomy”, in *Essays on Philosophical Subjects by the Late Adam Smith LLD*, eds. Joseph Black and James Hutton (London: T. Cadell, 1795), pp. 1-93, on pp. 13-14 and p. 20 (II.6 and II.12 in modern editions).
48. Robert Burns Woodward, banquet speech, 10 December 1965, taken from http://www.nobelprize.org/nobel_prizes/chemistry/laureates/1965/woodward-speech.html (accessed 3 March 2016).
49. Crystal F. Woodward, “Art and Elegance in the Synthesis of Organic Compounds”, in *Creative People at Work: Twelve Cognitive Case Studies*, eds. Doris B. Wallace and Howard E. Gruber (New York: Oxford University Press, 1989), pp. 226-253. Also see Crystal F. Woodward, “A Little Artistic Guide to Reading R.B. Woodward”, in Benfey and Morris, *Robert Burns Woodward*, pp. xvi-xxvii.
50. Jeffrey I. Seeman, “Woodward’s Words: Elegant and Commanding”, *Angewandte Chemie*, 2016, **55**, 12898-12912.

Editor’s Note

Every effort has been made by the author to obtain the necessary permissions with respect to copyright material. Should there be any omissions in this respect we apologise and shall be pleased to make the appropriate acknowledgements in a future edition of the Newsletter published by the Royal Society of Chemistry Historical Group.