Woodward's *Pure and Applied Chemistry* Words

by Jeffrey I. Seeman

According to IUPAC, "*Pure and Applied Chemistry* is the official monthly Journal of IUPAC, with responsibility for publishing works arising from those international scientific events and projects that are sponsored and undertaken by the Union." There is no doubt that *PAC* has and continues to achieve its goal of being "an authoritative and indispensable holding in academic and institutional libraries."

But I assert, intentionally and rather provocatively (and certainly dramatically), that hardly anyone reads *PAC*. I must explain what I mean. *PAC*, like all journals, is not a literary work. It is meant for browsing, perhaps even just scanning the table of contents, and then, ultimately and for selected papers only, for careful study. *PAC* is also geared as a resource, even as a dictionary, and as an archival record.

That being said, there really are hidden jewels within *PAC*, so much so that I might even go so far as to suggest instances of *belles lettres*. The goal of this article is to share excerpts from the writings of one organic chemist who, within the bookends of *PAC*, was a true *belletrist*! Between 1961 and 1973, he published six papers in *PAC* [1-6]. Clearly, this wasn't just any organic chemist, for how many scientists are invited to give so many IUPAC plenary lectures within their lifetime, let alone within a 13-year period? We speak of Robert Burns Woodward, arguably the greatest organic chemist of the 20th century, perhaps ever. No further introduction is needed.

Woodward's Words have been published in a series of articles in the journal *Angewandte Chemie*. These articles—collections of carefully chosen anecdotes and excerpts from the writings of Gilbert Stork, [7] Carl Djerassi, [8] John D. Roberts, [9] and Woodward, [10] all eminent chemists of the 20th Century—have had such an appeal that the Editor of *Chemistry International*, Fabienne Meyers, invited this historian and collector of chemical memoirs to similarly entertain her readership. The *entrée* today is *Woodward's Words* from *Pure and Applied Chemistry*. That this article appears in the first 2017 issue of *Chemistry International* is especially appropriate, as this year marks the centennial anniversary of Woodward's birth, on 10 April 1917.

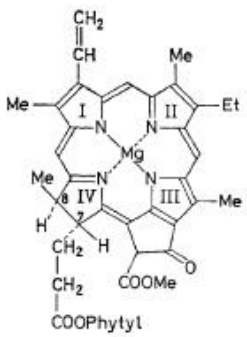
A follow-up feature will appear in the next issue and hint at emulating Woodward's writing style.

A jewel in this very issue of *Chemistry International* is Dan Rabinovich's Stamps International: Woodward's Birth Centennial, page 15. [11] In this little gem, one of Rabinovich's mini-essays, postage stamps issued by the Republic of Guinea and the Republic of Chad in 2015 honoring R. B. Woodward and his chemistry are reproduced and discussed.

Note: None of the following excerpts appeared in the previously published Woodward's Words: Elegant and Commanding. *[10]*

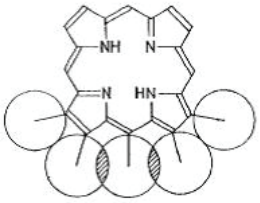
From *The Total Synthesis of Chlorophyll* (1961)

Chlorophyll, reproduced from [1], p. 384



"The structural investigations [of chlorophyll] had been carried out almost entirely during the twilight of the classical period of organic chemistry. Only the very simplest basic elements of theory played any role in the whole vast study. Neither was succour or control sought in chemical principle, nor was any attempt made to place the often striking observations in any generalized framework. Would the conclusions from such a study stand scrutiny from the viewpoint of the present day? Was the structure proposed for chlorophyll correct? When we embarked upon the examination of these questions, we entered a chemical fairyland, replete with remarkable transformations which provide unusual opportunities for the testing and further development of principle, and we cannot but urge others to follow us in penetrating what must have seemed to many the monolithic wall of a finished body of chemistry." [1]

"All of these observations baffled us for some time, until they received a very simple rationalization in terms of the principle that two things cannot take up the same space at the same time." [1]



Porphyrin, structure IV reproduced from [1], p. 385

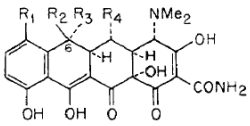
"Now, the porphyrin syntheses of an earlier day, magnificent for their time, were most ill-suited to our purpose. Carried out under bold but brutal conditions, they led in almost all cases to very complicated mixtures of porphyrins, in small, frequently microscopic, yields . . . By contrast, we required a method which would lead in high yield to a single product of known structure, containing substituent groups of variegated character—for we were well aware that we might have some distance to go after this primary objective had been achieved." [1]

" . . . which, after oxidation with iodine, small amounts of porphyrin were formed, and more so to succeed, after assiduous variation of experimental conditions, in preparing the porphyrin in the pure condition in a yield approaching 25 per cent. By any previous standard, this result approached the fabulous, but we knew that for our purpose it was still far from satisfactory." [1]

"Such inelegance, not to say impracticality, could not be tolerated. Our plan for expunging it was simple in principle . . . [but] was by no means mirrored in a comparable ease of its reduction to practice." [1]

"It will be recalled that we considered in our planning the possibility that hydrogen atoms might be induced to wander to the desired positions from another site in a suitably constructed porphyrin. [Since we had] such a suitably constructed porphyrin, it was now time for the wandering to begin—and begin it did—though it stopped short of our desire!" [1]

From *The Total Synthesis of a Tetracycline* (1963)



	R_1	R_2	R_3	R_4
CHLOROTETRACYCLINE (AUREOMYCIN)	Cl	OH	Me	H
OXYTETRACYCLINE (TERRAMYCIN)	H	OH	Me	OH
TETRACYCLINE	H	OH	Me	H
6-DIMETHYL-6-DEOXYTETRACYCLINE	H	H	H	H

". . . the complicated tetracyclic assemblage, adorned with an unusual number of contiguous reactive functional groups of different kinds, and replete with stereochemical imperatives, has presented a synthetic challenge to which many have responded." [2]

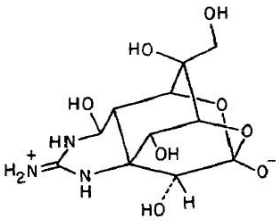
"We cannot but direct attention to the fact that it is less remarkable that the discovery of proposer conditions for the cyclization was difficult, than that they could be found at all." [2]

"Among several instances encountered in our work, this final cyclization . . . must hitherto have been regarded as difficult to the point of improbability." [2]

" . . . could be isolated in 25 per cent over-all yield. This easy statement should not be allowed to conceal the formidable effort which was required to bring us to a favourable outcome. The detailed mechanism of the oxygenation reaction is obscure—though there is little doubt that metal chelate formation must play a rôle—and the definition of useful reaction conditions required much experimentation; in view of the number of possibly relevant variables, it may strongly be doubted that the optimum has yet been achieved." [2]

Woodward at the Woodward Research Institute, Basel, Switzerland, 1972, and with a copy of a PAC *reprint on his desk, recognizable by the original IUPAC logo. Photograph courtesy of Novartis.*

From *The Structure of Tetrodotoxin* (1964)



Tetrodotoxin, Fig. 35 reproduced from [3], p. 73

"Certain varieties of puffer fish, especially the *tora fugu*, or tiger puffer (*S. rubripes*), and the closely related *ma fugu*, or common puffer (*S. porphyreus*), are highly prized as comestibles in Japan. The indulgence of the taste is fraught with some peril, since the livers and ovaries of the fish contain a powerful poison. The presence of this poison has been known though its effects since antiquity, but its labile nature and its extremely low concentration in its natural milieu made the isolation of the toxic principle extraordinarily difficult . . . Although nearly five hundred persons died from its effects in Japan during 1956-58, the toxic dose for man is not known; if the physiologically absurd equation of men with mice be made, it may be anticipated that half a milligram of tetrodotoxin should be sufficient to deprive an average-sized man of his life." [3]

"Now, in a wholly imaginary experiment, . . . " [3]

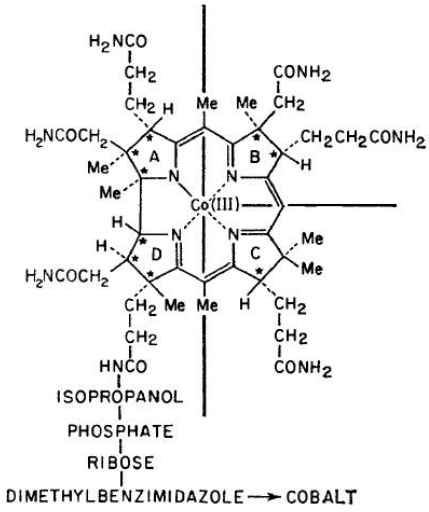
"The simplest manner in which the expression (XVIII) might be disabused of its unwanted carboxyl group was to . . . " [3]

"At this point, however, the argument was simplified through the obtention of the almost ocular evidence provided by a complete three dimensional X-ray crystallographic analysis . . . " [3]

"We see that in the final structure every carbon atom but one bears at least one oxygen or nitrogen atom, while one carbon atom bears two, and two carbon atoms are attached to no less than three hetero atoms. Further, one of the latter arrays—the hemilactal function—is entirely unique, not having been observed before in the structure of any organic molecule, whether of natural or purely synthetic origin." [3]

"The appearance of the array in the tetrodotoxin molecule presents a clear lesson for the future in its intimation that if normally non-interacting groups are appositely attached to a rigid skeleton, or otherwise brought into forced proximity, they may be expected to co-operate in the formation of structural groupings which are not observed in simpler systems. It is worthy of note that tetrodotoxin is yet another in the long series of natural products whose study has time and again turned up for the first time new and unique systems, and provided stimulating insights into the fundamental behaviour of organic chemical systems." [3]

From *Recent Advances in the Chemistry of Natural Products* (1968)



Vitamin B_{12}, sketch reproduced from [4], p. 520

". . . the crowded concatenation of six contiguous asymmetric centers embedded within the A/D moiety represents a formidable challenge." [4]

"Perhaps also this is the point at which I should emphasize explicitly the importance of the availability of the 'unnatural' enantiomer. Much as had been our progress at this point, we were not unaware that we still had far to go, and that it might be either necessary or desirable—as indeed it turned out to be—to investigate a considerable number of alternatives for further advance. In these explorations we were able to utilize [the enantiomer of the natural series], confident that whatever new route we might establish through its study would be applicable to its counterpart of the natural series; our experience has been such that this is just about the only kind of model study which we regard as wholly reliable! And in fact, although the reactions I shall describe in the sequel will be presented for compounds in the natural series, almost all of them were first discovered using the enantiomeric substances." [4]

Woodward, with pencil in hand at the Woodward Research Institute (WRI) in Basel, ca. 1965. His offices, either at Harvard or WRI, were often decorated with colorful flowers and cigarette-containing ashtrays. Photograph courtesy Chemical Heritage Foundation.

"Only a single substance was produced . . . we possessed no means of ascertaining which of the two *a priori* possible orientations might be present. Nor in this instance did we have any particularly convincing argument as to which assignment should be made. As we shall see in the sequel the newly placed hydrogen atom appears . . . in the *undesired* orientation. After the fact, we can present a reasonable defense of Nature's action in this respect, but I should hardly feel justified in taking some of the limited time available here today to put forward arguments which we did not regard as convincing before we knew the result. How does it happen that we were so little concerned with the orientation at the centre at issue, by contrast with the very great care we had exercised in the establishment of the desired configuration at each of the other centres? Essentially because we were cognizant of the fact that this centre [would] be susceptible of inversion." [4]

"Quite as important as these changes which do occur is one that does not . . . the survival of the oxime grouping has enabled us to traverse a relatively simple path among a plethora of more complicated possibilities . . . " [4]

"In the light of these considerations we were not surprised to find that our mesylate was indeed quite extraordinarily loath to undergo the desired transformation." [4]

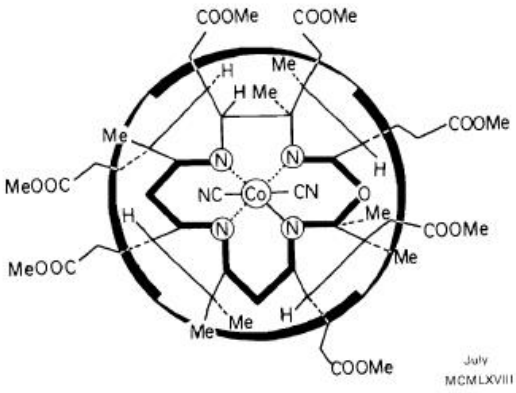
"Many ingenious schemes were devised in attempts to coax the recalcitrant ring to behave properly; their ingenuity was exceeded only by the uniformity with which they turned out to be unsuccessful. The temptation at this stage of our work was to feel that we had been hoist with the petard of a subtle and inherent flaw in our plan was strong, but fortunately a most remarkable observation came to our rescue . . . " [4]

"But the danger of such far-flung extrapolations is all too clear, and essentially we regarded the matter as *sub judice*. Now, when our fortunes in our battle . . . were at their lowest ebb, we became mindful of a most remarkable fact . . . seemed so astonishing as perhaps to call in question our [understandings]. However, further reflection not only permitted the rationalization of the remarkable observations in terms of the accepted hypothesis, but provided an insight which was of very great consequence for our further progress, both in understanding and in practice." [4]

"We all know that enforced propinquity often leads on to greater intimacy, and we were able to provide a new illustration of that maxim." [4]

" . . . it need present no occasion for surprise that the real case has exhibited substantial difference in behaviour from the simple analogues." [4]

From *Recent Advances in the Chemistry of Natural Products* (1971)



The symbol of the 1968 International Symposium on the Chemistry of Natural Products, London, "which we could not but regard as exhortatory," according to Woodward in 1971, reproduced from [5], p. 283

"This might have seemed a modest objective to those unfamiliar with the magnitude of the challenges which synthetic work with molecules of such complexity and variegated reactivity present, but the event has shown that Professor [Albert] Eschenmoser and I judged our adversary well." [5]

"Such is the sensitivity of the reactants, and particularly the product, that the successful execution of this operation requires rigorous adherence to the highest standards of experimental precision." [5]

"The situation at this point may be summarized by depicting the [product] as a substance precariously balanced on a precipice, off of which all of our efforts pushed it into the valley represented by the dormant [compound]. Needless to say, innumerable early efforts to effect [reaction] were made—alas, with anything but encouraging results." [5]

"This is no place to describe in detail the plethora of mysterious factors which seemed to affect the outcome of the reactions . . . so variable in fact were our experiences that the occasionally successful practitioner was regarded by his frustrated colleagues as quite as much a wizard as a scientist." [5]

"It remains only to mention that the isolation and purification of [product] presented obstacles only less formidable than those attendant upon the discovery of a satisfactory method for its preparation." [5]

From *The Total Synthesis of Vitamin B_{12}* (1973)

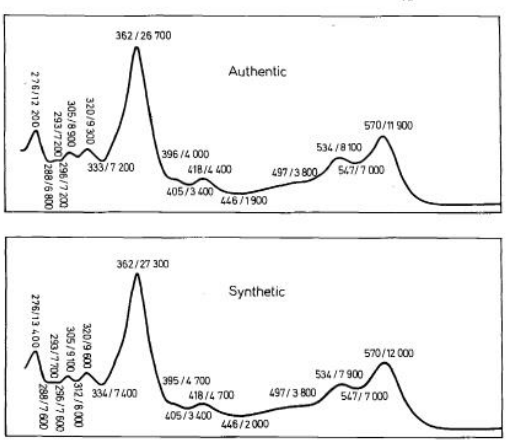


Figure 3 reproduced from [6], p. 147

"In Figure 3 you will see the comparison of the electronic spectra of the synthetic heptamethylbisnorcobyrinate and the authentic heptamethylbisnorcobyrinate. Now I do myself rather object to that term 'authentic'. I don't know what's more authentic about the material derived from natural sources than the synthetic material; so I attribute to Professor Eschenmoser the choice of this somewhat misleading word." [6]

"Now about the time that we had the thioester in hand, we thought perhaps we should do some of this reading that I am so famous for, and find out about the properties of thioesters. Certainly the idea is current in the minds of most chemists, I think, that thioesters are very much more reactive than the corresponding oxygen analogues. In fact it turns out on examination of the literature that the statement must be severely qualified." [6]

"You can see what a diabolically clever scheme this is. I didn't invent it, so I can give it that accolade." [6]

Conclusions

For 56 years, *Pure and Applied Chemistry* has served the chemical community well. I applaud the numerous lectures given at over 50 IUPAC conference series which have been permanently archived as publications in *PAC*. I know this value as a chemist who frequently uses these papers in my own research, as a historian who has cited these papers frequently—this very paper being a prime example!—and as a lecturer myself, for I've published one of these conference papers myself. But I now suggest another value of *PAC*, and that is to read the papers therein for their beauty as well as their scientific and historical value.

What do I mean by "beauty" in this context? It is a characteristic of the publication that combines an aesthetic piece (artistic, beautiful, sensorial compelling) with a chemical piece. Let us consider this proposal using the quote from Woodward's 1968 *PAC* article,

"We all know that enforced propinquity often leads on to greater intimacy, and we were able to provide a new illustration of that maxim." [4]

As lovely and loving as the phrase "enforced propinquity often leads on to greater intimacy" is, for us chemists, knowing that Woodward is referring to the rate enhancing (entropic) effect in, for example, intramolecular reactions, the synergy between the words and the chemistry make the saying ever more entrancing.

Indeed, in the quote immediately below (not from *PAC*), Woodward lamented that non-chemists cannot possibly be enthralled by some of the pleasures a chemist can, when reading or hearing about an unusual chemical phenomenon. Woodward wrote,

"Not infrequently 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 reactants, undergoes unusual transformations which are of great

utility in progress toward the objective. The impact on an observer may perhaps be compared with that on the traveler down an uninteresting street, who turns through a small hidden doorway into a delightful and charming garden. This kind of satisfaction in chemical synthesis is by its nature suited only for the special delectation of the initiated, and its pleasures are, alas, not transferable to those not fortunate in the possession of detailed chemical knowledge. I am confident that the chemists who read this will share my regret that non-chemists who may venture this far cannot savour with me anew the delights of this short sequence of operations..." [12]

In the same way, non-chemists cannot share the specialness of some of Woodward's writings when they combine linguistic aesthetics and chemical beauty.

Coda

Chemistry International's editor has supported my decision to focus on excerpts from Woodward's *PAC* articles that were not published in my earlier Woodward's Words. [10] She is rightfully quite proud of IUPAC publications. However, she lamented that perhaps the best of Woodward were already placed elsewhere, and not in this publication. I thus turned the tables around and asked her to choose her favorites from that earlier *Words* paper. Somewhat intrigued by the beauty of Woodward's words, Fabienne Meyers wondered if the younger Woodward wrote already so elegantly or if his style came later with his notoriety. We find *de facto* many excerpts in Woodward's earlier writing that show his tastefulness and the following two excerpts, among Fabienne's favorites, are from when he was not yet 40 years old.

(1956) "In the century that has passed since Berthelot's words were uttered, organic chemistry has literally placed a new Nature beside the old. And not only for the delectation and information of its devotees; the whole face and manner of society has been altered by its products. We are clothed, ornamented, and protected by forms of matter foreign to Nature; we travel and are propelled in, on, and by them. Their conquest of our powerful insect enemies, their capacity to modify the soil and control its microscopic flora, their ability to purify and protect our water, have increased the habitable surface of the earth and multiplied our food supply; and the dramatic advances in synthetic medicinal chemistry comfort and maintain us, and create unparalleled social opportunities (and problems). We do not propose to examine this vast domain in detail, or to prognosticate the direction of its advance, in response to the need, desire, and fancy of man. We shall leave it that the evidence is overwhelming that the creative function of organic chemistry will continue to augment Nature, with great rewards, for mankind and the chemist in equal measure." [13]

(1955) "Modern organic chemistry possesses a splendid and powerful armamentarium for the attack on the problems which excite the attention of its devotees. From time to time here mention has been made of some of these weapons, and it is certainly worth emphasizing that this campaign could not have been concluded without constant use of the very great body of principle and mechanism which our theorists have placed at our disposal, and without the beautiful physical tools which we now have." [14]

But I urge those who have enjoyed these excerpts, please find your way to the earlier paper [10] or perhaps just go directly to Woodward's very own publications. Much joy awaits you.

Dr. Seeman <jseeman@richmond.edu> is at the University of Richmond. His professional activities include research in the history and sociology of science including responsible conduct of research.

References

1. R. B. Woodward, *Pure Appl. Chem.*, **2**:383-404, (1961).
2. R. B. Woodward, *Pure Appl. Chem.*, **6**:561-573, (1963).
3. R. B. Woodward, *Pure Appl. Chem.*, **9**:49-74, (1964).
4. R. B. Woodward, *Pure Appl. Chem.*, **17**:519-547, (1968).
5. R. B. Woodward, *Pure Appl. Chem.*, **25**:283-304, (1971).
6. R. B. Woodward, *Pure Appl. Chem.*, **78**:145-177, (1973).
7. J. I. Seeman, *Angew. Chem. Int. Ed.*, **51**:3012-3023, (2012).
8. J. I. Seeman, *Angew. Chem. Int. Ed.*, **53**:3268-3279, (2014).
9. J. I. Seeman, *Angew. Chem. Int. Ed.*, **54**:15901-15913, (2015).
10. J. I. Seeman, *Angew. Chem. Int. Ed.*, **55**:12898–12912, (2016).
11. D. Rabinovich, *Chem Int*, **39**(1):23 (2017)
12. R. B. Woodward, "Art and science in the synthesis of organic compounds" in *Pointers and pathways in research: Six lectures in the fields of organic chemistry and medicine* (Ed.: M. O'Connor), CIBA of India Limited, Bombay, India, 1963.
13. R. B. Woodward, "Synthesis" in *Perspectives in Organic Chemistry* (Ed.: A. R. Todd), Interscience, New York, 1956, pp. 155-185.
14. R. B. Woodward, *Experientia*, **12**(Sup. II):213-238, (1955).