On Robert B. Woodward and the Total Synthesis of Quinine

Kauffman, G. B. *Chem. Educator,* **2004,** *9,* 172-176 S1430-4171(04)03786-4, DOI 10.1333/s00897040786a. "Robert B. Woodward: Organic Synthesizer par Excellence. On the 25th Anniversary of His Death ."

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Abstract.- In 1944, Woodward and Doering succeeded in converting 8-hydroxyisoquinoline into (±)-homomeroquinene, a protected form of which was transformed into (±)-quinotoxine, which was optically resolved, yielding *d*-quinotoxine. Quinotoxine is a degradation product of quinine, known since the middle of the 19th century, which Rabe reported to have converted into quinine, in 1918. This constituted the first modern and complex rational approach to quinine and a formal total synthesis of the natural product. Since Woodward's publication, several total syntheses of quinine were disclosed, by Uskokovic (1970-1978), Stork (2001), Jacobsen (2004) and Kobayashi (2004), displaying each new one increasing degrees of stereocontrol and atom economy.

Robert B. Woodward, this great man who is universally considered as one of the fathers of modern synthetic organic chemistry is still today, 25 years after his unfortunate and untimely death, the subject of polemic and debate. The recent and very interesting article by George B. Kauffman, briefly revisiting Woodward's personal and professional life, not only pays tribute to this great and unique scientist; it also confirms the permanent character of the mark he left within the organic chemical community, and the wide variety of contradictory opinions, often passionate, still around about him.

In the article, the author refers to Woodward's synthesis of quinine, which this year celebrates its 60th anniversary and is probably one of the most controversial issues of Woodward's career. This is a polemic in which some scientists are still engaged,[1] while others prudently try to avoid.[2] Perhaps inadvertently, Kauffman made two asserts which are truly inaccurate, referring that Woodward "…completed this successful synthesis [of quinine]…", adding later on that "…another synthesis leading only to quinine and not to it and some of its isomers has yet to be found…". We would like to contribute to clarify these concepts.

Regarding the first statement, on completion of the synthesis of quinine by the Woodward-Doering team, it seems fair to say that they synthesized *d*-quinotoxine in approximately 20 steps, from 3-hydroxy benzaldehyde and employing 8-hydroxyisoquinoline as starting material for the synthesis of (±)-homomeroquinene, a precursor of racemic quinotoxine, which Woodward and Doering prepared and optically resolved.[3] Nevertheless, this was an unsurpassed achievement and an important landmark for its time, not only due to the highly sensitive nature of the synthetic target –quinine–, but also because it was completed in a few months, employing commonly available synthetic reagents and reactions; it was carried out by young scientists (it was finished on April 11, 1944, one day after Woodward's 27th anniversary, and Doering was only a few month younger), was Woodward's first "total synthesis"[4] and it pointed to the way organic synthesis would head the next decades. Through this synthesis, Woodward captured admiration from the public and from many of his colleagues, while he and chemistry as a science captured public imagination.

Nonetheless, there are perhaps the title "*The Total Synthesis of Quinine*" of the 1944 and 1945 papers by Woodward and Doering,[3] the press hailing nationwide the unique and timely accomplishment and quinine's scarcity during wartime, the main sources of the longstanding controversy that Woodward synthesized quinine.[5] To shed some light into this issue, it is worth briefly revisiting some key chemical events which oriented Woodward's work on quinine and constituted the grounds for entitling this way Woodward's above mentioned papers.

After Pelletier and Caventou's isolation of quinine in 1820, an event that is regarded by many as the beginning of the pharmaceutical industry, quinine began to be isolated and purified in mass quantities, but no great advances were made during 30 years, being its molecular formula secured by A. Strecker in 1854.

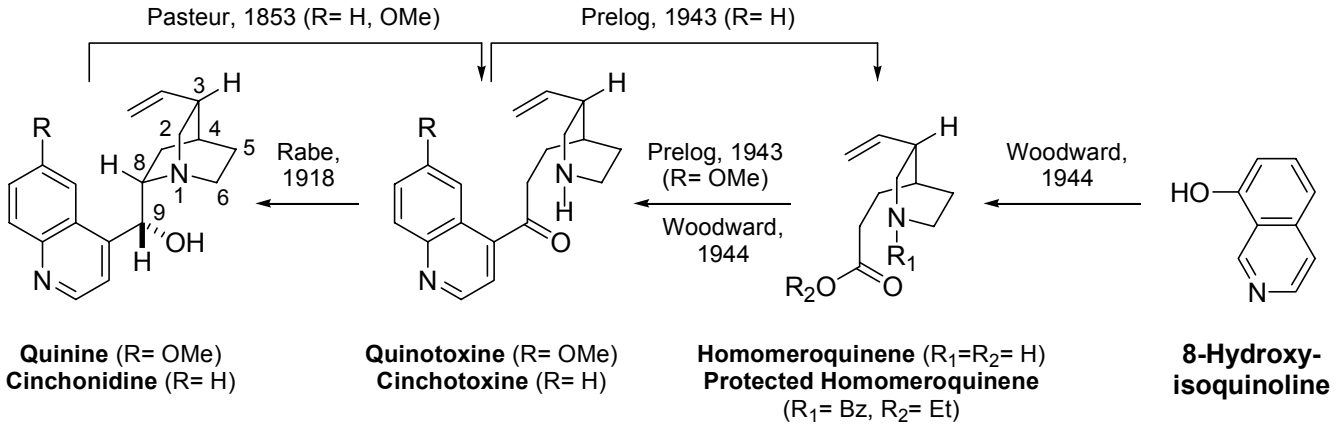
However, one of the initial discoveries which would led to the development of the preeminent and conceptually simple synthetic approach to quinine during the 20th century and on (the C_8-N cyclization approach), was made in 1853 by L. Pasteur, the French scientist who first reported the production of the "cinchona toxines" (cinchotoxine and quinotoxine) by mild acid treatment of the cinchona alkaloids. Pasteur employed optically active *d*-quinotoxine to carry out the first optical resolution ever made.[6]

Quinotoxine was "rediscovered" in the 1890s by von Miller and Rodhe,[7] in middle of a 25-year period of febrile research activity towards the elucidation of the structure of quinine, which took place among the best chemistry laboratories of Europe. The German scientist P. Rabe, who devoted his scientific career to structural and synthetic studies on quinine, was the first in establishing the right connectivity of the natural product during the first decade of the past century and the first in providing structural proof of quinotoxine, in 1909.[8]

Without a complete knowledge of all the structural features of quinine, which would require another 25 years to be fully and unequivocally established,[9] P. Rabe and K. Kindler published in 1918 a very terse report on the reconstruction of quinine from quinotoxine,[10] employing a strategy previously devised by Rabe himself for rebuilding cinchoninone from cinchotoxine.[11] This synthesis, consisting in the elaboration of the quinuclidine moiety (the non-aromatic part) of quinine by ring closure at the C_8-N level, was a major breakthrough towards the total synthesis of the natural product since the initial and failed attempts by the young W. H. Perkin, in 1856 (which gave birth to the synthetic organic dyes industry). A high point among Rabe's contributions to the total synthesis of quinine was reached in the 1930s, when he published a full account on the total synthesis of dihydroquinine (1931), employing the same strategy reported in 1918, disclosing the next year an aluminum-mediated reduction, a key process for his reported cinchona alkaloid syntheses.[12]

These results strengthened the idea that quinine could be totally synthesized by merely devising a route to quinotoxine. Assuming the suitability of Rabe's protocol to prepare quinine, in 1943, V. Prelog succeeded in degrading cinchotoxine to optically active homomeroquinene and reconstructing quinotoxine from this degradation product.[13] This further simplified the elaboration of a prospective total synthesis of quinine, reducing the effort to that of synthesizing homomeroquinene (Scheme 1). The latter objective, which was fully accomplished by Woodward and Doering, would have resulted in what we now call a *relay synthesis* or more accurately a *formal total synthesis* of quinine, provided Rabe's protocol constituted an effective mean for converting quinotoxine into quinine.

Unfortunately, an exhaustive study of Rabe's original protocol which Woodward qualified as "established", carried out in the 1970s, cast serious doubts on its ability of being useful to deliver quinine from quinotoxine, unless substantially modified.[14] In addition, in spite that similar synthetic schemes were elaborated contemporarily to Rabe's one,[15] they were proven to be successful on related targets just a few years after the Woodward-Doering publications on their synthesis of quinine.[16] Most curiously, however, their usefulness for a synthesis of this natural product was never tested.



Scheme 1. Contributions of Rabe, Prelog and Woodward to the synthesis of quinine.

Regarding the second of the above mentioned statements by Kauffman we would like to discuss and amend, it is worth noting that quinine has five stereogenic atoms; however, two of them (the quinuclidine nitrogen and C_4) constitute a single asymmetric unit, due to their bridgehead location. Therefore, a fully stereocontrolled synthesis of quinine has to take care of the configuration of four stereogenic centers (2^4= 16 possible isomers).

Unfortunately, the Woodward-Doering synthetic scheme successfully built only two of them after laborious diastereomer separations and a final optical resolution; in addition, viewed from a modern perspective, Rabe's protocol –if successful- would have generated diastereomeric mixtures at both centers it attempted to build. Moreover, the transformations involved in Woodward's synthesis lacked stereocontrol, a fact that in the 1940s was not considered an important aspect in the planning of synthetic sequences; many times this was even completely disregarded and, surprisingly, some of the great chemistry masters of that time showed no interest in the subject.

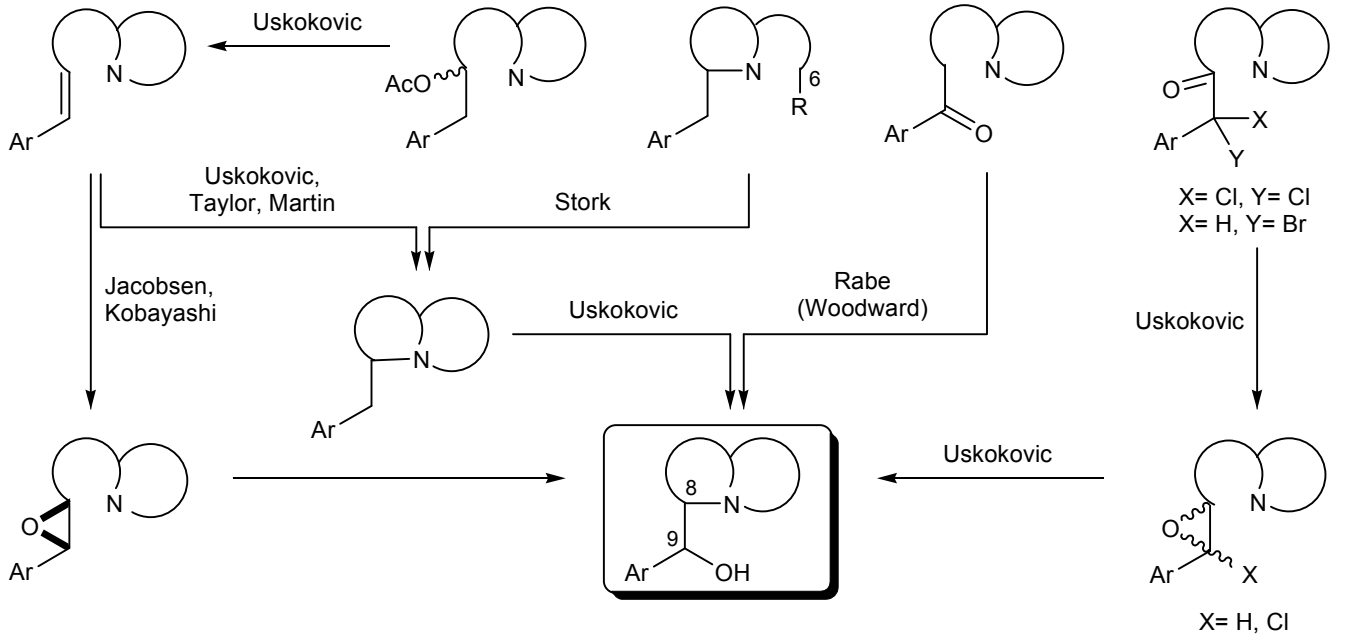
The last steps of the total synthesis of quinine were first successfully solved during the second half of the 1960s by the group of M. R. Uskokovic working for the Hoffmann-La Roche pharmaceutical company. This team produced several total syntheses of the natural product and disclosed their results in a series of papers which began to be published in 1970.[17] These syntheses were based on variations of the intramolecular conjugate addition of a secondary amine to a vinyl arene, a transformation devoid of stereocontrol in the context of the synthesis of quinine. Several modifications of the intramolecular amino-epoxide ring opening reaction were also used, the outcome of which –under the expected S_N2 conditions– depends on the stereochemical characteristics of the oxirane, then unable to be controlled by chemists because of the lack of proper reagents, which begun to be developed approximately a decade later.

Contemporarily and with Uskokovic's assistance, M. Gates and co-workers,[18] as well as E. C. Taylor and S. F. Martin[19] reported their respective syntheses of quinine, all of them resorting to the C_8-N approach pioneered by Rabe. All of these syntheses, carried out in the 1960s and 1970s, beared some degree of stereocontrol and a major feature of them was the highly diastereoselective introduction of the C_9 alcoholic function, optimized by Uskokovic for the synthesis of cinchona alkaloids.[20] This research also resulted in the development of considerably more efficient strategies, that allowed a better control of the configuration of two of the asymmetric carbons in the quinuclidine portion of the molecule.

Retrospectively observed, the lack of C_8 stereocontrol in some of the most promising Uskokovic's protocols resided in the inability of the chemists to achieve in the 1970s the stereoselective synthesis of epoxides from vinylarenes, a fault that also caused lack of stereocontrol on the C_9 position in several syntheses.

No great advances towards quinine were recorded during the next two decades, since the last publications of Uskokovic up to the turn of the century. Curiously, however, in the 1980s, a Japanese team developed a synthesis of racemic meroquinene, claiming a formal total synthesis of (±)-quinine.[21]

The first fully stereocontrolled total synthesis of quinine was accomplished, after working on and off on the problem during half a century, by G. Stork and co-workers in 2001.[22] In this much publicized synthesis, these researchers correctly established all the stereocenters of the quinuclidine moiety, serving Uskokovic's protocol for the final step, the stereoselective oxidation of the C_9 center. Stork's approach, however, relied on a C_6-N bond-forming strategy, an ingenious way to avoid the common pitfalls of the classical C_8-N approach.



Scheme 2. Schematic summary of the multiple approaches to the total synthesis of quinine.

Interestingly, however, in the first months of the current year an increasing interest in the natural alkaloid as synthetic target was witnessed, which manifested through the publication of two different fully stereocontrolled enantioselective total syntheses of quinine, by the groups of E. J. Jacobsen and Y. Kobayashi.[23] Both syntheses are based on Uskokovic's original developments and the still effective C_8-N recipe and, curiously, employ cinchona alkaloids derivatives as chiral auxiliaries for the diastereoselective construction of a key epoxide, suitable for Uskokovic's amino-epoxide ring opening transformation. Scheme 2 graphically

summarizes the different approaches taken towards the synthesis of quinine during the last 85 years.

In conclusion, Woodward's synthesis was a great triumph in its time and one of the first pieces evidencing the power of synthetic organic chemistry. On the other hand, selective total syntheses of quinine are available since the 1970s. However, the three total syntheses of the natural product reported during the present century have the power of highly selectively delivering optically active quinine, in good yields, with great atom economy and as one out of the 16 possible isomers.

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