Ever since its isolation in 1820, Quinine has played a crucial role in the development of organic chemistry, chemical industry and modern medicine. The total synthesis of quinine, widely regarded as an event of epochal importance was claimed by Woodward and Doering in 1945. This work, however, heavily relied on unsubstantiated literature reports and it appears that Woodward’s work fell short of a total synthesis of quinine. The first stereoselective total synthesis of quinine was accomplished only in 2001, by Stork, who incidentally is the originator of the concept of stereoselectivity in total synthesis. Naturally, this work has been attested as a landmark in organic synthesis by leaders in the field.

Quinine, the seemingly simple looking molecule \(1\) (Structure 1), has an important place in the history of mankind. Its impact, direct or indirect, on human health, wealth and civilization is hardly equalled by any other chemical. This cinchona alkaloid’s original claim to fame was its antimalarial activity, identified ages ago by the natives of South America and later popularized by the Jesuit missionaries in Europe and other parts of the world. Parenthetically, it may be added that malaria has been the most dreaded disease for the human race and it is estimated that it has killed more people than all the wars put together. Until the advent of synthetic antimalarials such as mepacrine, chloroquine and mefloquine, quinine was the only drug available to combat malaria, thus justifying the importance attributed to this drug. Quinine exerts its antimalarial activity by binding to the DNA of the \(Plasmodium\) parasite transmitted by the female mosquito \(Anopheles balabacensis\), thereby inhibiting its replication. Although synthetic drugs have largely replaced quinine, as resistance of mosquitoes to the latter has been on the rise, quinine itself is being
more widely used again. As an interesting aside, it may be mentioned that the bitter taste of tonic water used in gin and tonic, the popular drink of the British soldiers, is due to quinine. Quinine was used in such drinks for prophylactic effect against the *Plasmodium* parasite. Is it then too far fetched to consider that quinine has played an important role in extending the British rule in India?

Isolation and Structure of Quinine

The active ingredient of cinchona bark, quinine, was isolated for the first time by Pierre-Joseph Pelletier and Joseph B Caventou in 1820. The legendary Louis Pasteur showed that quinine is levorotatory and on acid hydrolysis could be converted to a compound that he called quinotoxine. Shortly thereafter, Adolph Strecker established the empirical formula of quinine as $\text{C}_{20}\text{H}_{24}\text{N}_{2}\text{O}_{2}$. Paul Rabe, the German chemist worked for nearly four decades on the ‘quinine problem’, finally established the atom connectivity of quinine in 1907. But long before that, a synthetic endeavor, outrageously ambitious by present day standards, had given birth to the first organic chemical industry in England. In 1865, William H Perkin, inspired by his mentor A W Hofmann, set about to synthesize quinine by the oxidation of $N$-allyltoluidine and in the process isolated an analogue of what we call today Perkin Mauve. This gave birth to aniline dye industry which prospered in the following years and launched many other chemical industries. It was the quest for quinine that started it all; serendipitously, of course. In this article we have attempted to provide a concise account of the synthesis of quinine from a historical perspective.

Synthetic Approaches to Quinine

Starting from Perkin’s historic failure, there have been a number of attempts to produce quinine in the laboratory. The initial efforts in this direction were driven by the fact that a reconstruction of quinine from its degradation products was the only reliable method available for the chemist, since organic synthesis had not emerged as a viable discipline. Admittedly such reconstructions
have no practical import, except in the context of structure elucidation of the original molecule. Nevertheless, later attempts were motivated by factors like pressing war-time demand for the substance, the quest for knowledge or even the thrill of accomplishing something that once was a daunting task for chemists.

In 1918, Rabe claimed a partial synthesis of quinine from quinotoxine by aluminum powder reduction (Scheme 1). However, in Rabe’s own words, the procedure for the reduction “is not described yet in detail”. Rabe had little knowledge of the complete stereochemistry of quinine and even a successful realization of the Rabe protocol would have produced all the four possible stereoisomers of quinine.

Access to quinine and therefore the cinchona plantations was critical for the European powers to maintain their supremacy in the colonies of Africa and Asia since malaria was rampant in those days, still is, in some African countries. As World War II rearranged the geo-political equations of the globe, western countries were deprived of natural quinine supply from the east and the quest for synthetic quinine was a burning problem for Europe and America. It is against this backdrop that the world received the claim of a successful laboratory synthesis of quinine by a young Harvard chemist. Not surprisingly, this feat instantly catapulted Robert B Woodward, only 27 years of age then, to international stardom. The achievement was much publicized by the print media; for example, The New York Times declared “Synthetic Quinine Produced, Ending Century Search”. Woodward synthesized protected homomeroquinene from 3-hydroxybenzaldehyde.
by a series of transformations. Homomeroquinene was earlier converted to quinotoxine by Vladimir Prelog. Woodward followed Prelog’s synthetic sequences and resolved the racemic quinotoxine to afford the pure $d$-quinotoxine (Scheme 2). This, in principle, constituted a formal total synthesis of quinine assuming the validity of Rabe’s claim. However, it should be emphasized that no experimental evidence for the synthesis of quinine from quinotoxine was provided by either Rabe or Woodward. In any case, there was no justification whatsoever in claiming a total synthesis of quinine.

Later, investigations carried out by Hoffman–La Roche researchers headed by Milan R Uskokovic, demonstrated that the Rabe protocol would not yield quinine unless modified seriously. The first stereoselective total synthesis of quinine, was achieved by Gilbert Stork in 2001 and it is considered to be a remarkable feat of synthetic organic chemistry. Before Stork entered the scene, most of the approaches to quinine depended on the C8-N bond formation, the so-called Rabe route, because this single retrosynthetic disconnection would simplify the target enormously. But Stork, who introduced the concept of stereoselective synthesis, realized the pitfalls of this strategy with regard to the stereoselectivity of the synthesis. He took a novel approach which consisted of a C6-N bond formation strategy (see Structure 1 of Quinine for the atom labels).

**Scheme 2. Woodward’s 1944 ‘quinine’ synthesis.**

Any reaction in which only one of a set of stereoisomers is formed exclusively or predominately is called a stereoselective synthesis.

A reaction in which an optically inactive substrate is converted selectively to one of the two enantiomers is called an enantioselective reaction.

Retrosynthesis refers to the concept of thinking backwards from relatively complex molecules to simpler ones. This is achieved by transforming a target molecule into simpler precursor structures without prior assumptions regarding starting materials. Each precursor material is analyzed further using the same method. This procedure is repeated until simple or commercially available structures are reached.
Stork envisaged that the C8 asymmetry could be created by a closure to a piperidine and the disconnection led to a substituted tetrahydropyridine 8 as the starting point for the construction of the bicyclic ring. Lithium anion of 6-methoxylepidine 6 was added to azidoaldehyde 5, which was followed by the oxidation of the secondary alcohol to the corresponding ketone 7. An intramolecular Staudinger reaction of the azido-ketone afforded the tetrahydropyridine 8. A completely stereoselective reduction of the imine, followed by an intramolecular nucleophilic displacement to form the bicyclic system produced deoxyquinine 9 which was subjected to auto-oxidation conditions to complete the first ever stereoselective total synthesis of quinine (Scheme 3).

Stork’s quinine synthesis was hailed as a landmark in the history of organic chemistry by leading personalities of the field. Prominent chemist Steven Weinreb remarked, “The Stork paper is written with an insight and historical perspective (as well as correcting some myths) rarely seen in the primary chemical literature, and should be a required reading for all students of organic chemistry”, and Stanford University professor Paul
Wender, a trendsetter in organic synthesis compared the accomplishment to a ballet: “One schooled in the field will see the exquisite choreography, the remarkable timing, the efficiency of execution, and the economy of movement—and leave inspired.” Another leading synthetic chemist Amos B Smith III considered it so important an event that he proclaimed that Professor Stork did “set the record straight” by synthesizing quinine, an obvious reference to the much-publicized myth that Woodward and Doering synthesized quinine in 1944.

In 2003, Eric Jacobsen and co-workers at Harvard University published a catalytic asymmetric total synthesis of quinine. The key feature of this synthesis was the revival of the original Rabe strategy, involving a C8-N bond formation. Jacobsen’s synthesis of quinine with 16 steps and an overall yield of 5% is by far the most economical of them. Recently, Yuichi Kobayashi employed a strategy very similar to that of Jacobsen in his approach to the synthesis of quinine. Jacobsen and Kobayashi worked out a strategy to overcome the inherent lack of stereoselectivity in Rabe’s approach by employing asymmetric epoxide \textsuperscript{10} for the C8-N cyclization.

**Conclusion**

In conclusion, it may be emphasized that Stork’s approach was different and novel because he opted to explore a brave new strategy. Apart from the stereoselectivity, Stork’s synthesis of quinine is remarkable for its conceptual uniqueness and retrosynthetic novelty.

Evidently, notwithstanding the importance of the molecule in its own right, attempts to synthesize quinine have contributed a lot to the welfare of mankind, Perkin mauve is the most obvious example to cite. A mere unconfirmed claim of the synthesis of this alkaloid made a young chemist a hero who went on to become a world leader in organic synthesis. Many natural products incredibly more complex than quinine were synthesized by aspiring chemists, but somehow a stereoselective synthesis of quinine

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**Suggested Reading**


eluded the grasp of organic chemists in the last century. The recent synthetic endeavors towards this alkaloid were not intended to generate bulk quantities of the substance, but as Professor Stork puts it, “the value of a quinine synthesis has essentially nothing to do with quinine ... it is like the solution to a longstanding theorem in mathematics; it advances the field”.

It is noteworthy that in a paper published after this manuscript was submitted [5], the authors have reported that the contentious Aluminum powder reduction of quininone to quinine is reproducible, albeit quinine was obtained only in 5% yield. Evidently, this work adduces validity to the Rabe–Kindler–Woodward–Doering route to the formal total synthesis of quinine, a fitting finale for the saga of this unique molecule.