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# This Week's Citation Classic®

**Woodward R B, Sondheimer F, Taub D, Heusler K & McLamore W M.** The total synthesis of steroids. *J. Amer. Chem. Soc.* 74:4223-51, 1952; and, **Woodward R B, Sondheimer F, Taub D, Heusler K & McLamore W M.** The total synthesis of a steroid. *J. Amer. Chem. Soc.* 73:2403-4, 1951. [Converse Memorial Laboratory, Harvard University, Cambridge, MA]

4-Methoxytoluquinone was transformed in 20 steps into dl-9(11),16-bisdehydro-20-norprogesterone (ca. 1g/100g of 4-methoxytoluquinone). This substance, the first totally synthetic nonaromatic steroid, was converted into dl-methyl 3-keto-4,9(11), 16-etiatrienate and resolved. The synthetic dextrorotatory ester was identical with an authentic sample. Reactive functionality in rings A,C, and D of this triene ester permitted its interconversion via known steroidal pathways into androsterone, testosterone, progesterone, cholesterol, and cortisone. [The *SCI*® indicates that these papers have been cited in more than 485 and 45 publications, respectively].

## The Woodward Synthesis

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**R.B. Woodward had long been interested in steroid synthesis; his doctoral work (he received his PhD from MIT in 1937, at age 20) included a Diels-Alder approach to estrone. However, following the synthesis of estrone by Anner and Miescher in 1948, interest focused on the stereochemically more complex nonaromatic steroids. The increased stereocomplexity mandated development and use of stereospecific (or at least stereoselective) approaches to produce the final product in acceptable yield. The striking medical finding, that the 11-keto steroid, cortisone, could alleviate symptoms of rheumatoid arthritis, was a plus for the synthetic scheme, since the latter incorporated ring C functionality that could permit the synthesis of cortisone.**

**Woodward and four postdoctoral associates (Franz Sondheimer, Karl Heusler, William M. McLamore, and myself) began laboratory work in the fall of 1949. From the outset, problems were solved and ideas presented with clarity, rationality, vigor, and style. The synthesis utilized a CD→B→A strategy. By early April 1950, the tricyclic stage was attained with a key *anti,trans* BCD trienone. In the fall of 1950, after we had produced the *anti,trans* tricyclic eneone acetonide, Heusler and McLamore left for more permanent endeavors.**

**Our final product was dl-methyl 3-keto-4,9(11),16-etiatrienate, the infrared spectrum of which was identical in all respects with that of an authentic sample derived from d-hydrocortisone. This result was obtained at 3 a.m., March 30, 1951, in ample time for Woodward to prepare his Chemical Society Centenary Lecture of April 26, 1951. The remaining objectives of obtaining synthetic resolved d-methyl 3-keto-4,9(11),16-etiatrienate and its link up with intermediates of the various connecting pathways to androsterone, testosterone, cholesterol, and cortisone were accomplished over the next several months.**

**The synthesis was stereoselective except for the generation of asymmetry at C-10. However, it was shown later by L.B. Barkley *et al.*,[1] at Monsanto, that by inverting the order of introduction of the 1-carbon and 3-carbon units, the desired stereochemistry would predominate. This group also developed a short, direct route from the tetracyclic acetonide to cortisone.[2]**

**The Woodward steroid synthesis was an early demonstration of the power of stereochemical reasoning in synthetic planning. Comparison with the contemporaneous publications of R. Robinson and his associates is instructive.[3,4] The synthesis is also notable for the effective use of physical measurements (at that time, UV and IR spectroscopy) for rigorous structural characterization, and as an early example of what became a favorite Woodwardian motif—the masking of complex functionality in simpler ring systems (e.g., the use of the ring D cyclohexene moiety as the source of the cyclopentene aldehyde grouping). These are the likely reasons why the paper has been highly cited.**

**Woodward went on to surmount synthesis problems of increasing complexity, leading to the Nobel Prize in chemistry for 1965.[5] Franz Sondheimer achieved fame and a place in organic chemistry textbooks for his discovery of the annulenes; Karl Heusler went to Ciba-Geigy where his research accomplishments led him to its higher echelons; and Bill McLamore and I had rewarding and productive careers in Pfizer Research and in the Merck Sharp & Dohme Research Laboratories, respectively.**

1. **Barkley L B, Knowles W S, Raffelson H & Thompson Q E.** Studies in steroid total synthesis. IV. A stereoselective Ring A synthesis. *J. Amer. Chem. Soc.* 78:4111-6, 1956.
2. **Barkley L B, Farrar M W, Knowles W S & Raffelson H.** Studies in steroid total synthesis. III. Preparation of cortisone and compound F. *J. Amer. Chem. Soc.* 76:5017-9, 1954.
3. **Cardwell H M E, Cornforth J W, Duff S R, Holterman H & Robinson R.** Experiments on the synthesis of substances related to the sterols part LI. Completion of the synthesis of androgenic hormones and of the cholesterol group of sterols. *J. Chem. Soc.* 1953:361-384.
4. ----------. Total synthesis of androgenic hormones. *Chem. Ind.—London* (20):389-90, 1951.
5. **Stork G.** R.B. Woodward, 1917-1979. *Nature* 284:383-4, 1980.

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*Retired

On April 10 and 11, the Beckman Center for the History of Chemistry in Philadelphia will celebrate the seventy-fifth anniversary of RBW's birth, with an international symposium, "Organic Worlds," and the opening of a traveling exhibit, "R.B. Woodward and the Art of Organic Synthesis." The center and the ACS plan to publish a Woodward volume, including the steroid paper.