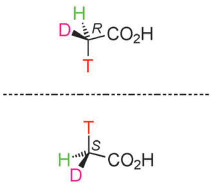
Courtesy of Philippa Cornforth

Sir John Warcup Cornforth



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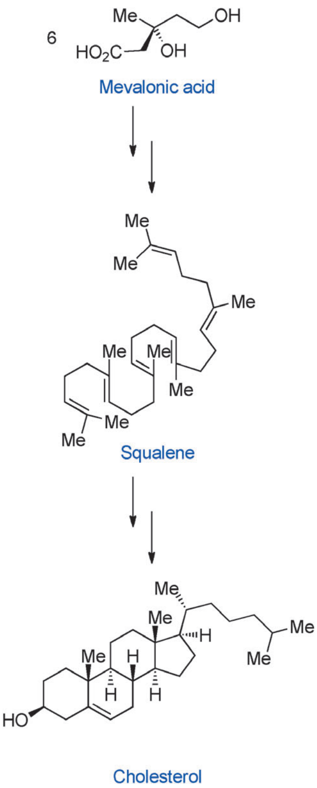

Sir John Warcup Cornforth (1917–2013)

With the death of the remarkable organic chemist Sir John Warcup Cornforth, an era of biological chemistry has ended. All who met Sir John, a name always supplanted by the familiar "Kappa", at once recognized a unique and amazing scientist. He was endowed with a quick incisive mind married with a mercurial sense of humor that peers out from the accompanying portrait. His scientific achievements, recorded in 200 publications between 1937 and 2002, ranged across quite diverse areas. They display not only a lifelong love of heterocyclic chemistry, especially oxazoles, but also natural product isolation, synthesis, and biosynthesis, anti-tubercular agents, enzyme models, and most recently, reflections on the origin of life and the role of scientists in society. There were numerous honors, capped by the 1975 Nobel Prize in Chemistry (shared with Vladimir Prelog), which above all recognized his exquisite stereochemical studies of enzymatic reactions aided by judicious isotopic labeling.

John Cornforth was born in Sydney and was of English, German, and Irish ancestry, with the latter line originating from a police sergeant John Kingsmill, who was transported from Cork to Australia in 1824 following a misdemeanour for which he was later pardoned. Cornforth attended Sydney High School and University, graduating in chemistry with a university medal in 1938. Already in his youth he had become completely deaf from otosclerosis, but surmounted this handicap, which inevitably limited the size of his research group throughout his scientific career, by conducting many of his own experiments. As an undergraduate, he is said to have marked his glassware ιωκ, which defined his lifelong epithet Kappa. His experimental wizardry was perhaps best illustrated by the purification of milligram quantities of (*R*)- and (*S*)-monodeuteriosuccinic acid in capillary tubes, a critical step in the elucidation of the absolute stereochemistry of hydride addition/abstraction at C-4 of the nicotinamide cofactors.

Kappa travelled to Britain in 1939 at the outbreak of World War II with his future wife Rita Harriet Harradence, where they initially undertook doctoral research with Sir Robert Robinson at the University of Oxford. After completing their theses in 1941, they married and joined the "backroom boys" studying penicillin under Robinson's direction as a scientific contribution to the war effort. After the war, Kappa moved to Hampstead and then Mill Hill in London, working at the laboratories of the Medical Research Council from 1946 to 1962. He became director of Shell's Milstead Laboratory at Sittingbourne (1962–1975), where he was free to pursue his studies of enzyme mechanisms, far removed from the company's commercial interests. Finally, he moved to the University of Sussex, first as Royal Society Research Professor and then emeritus professor, and continued to work in the laboratory until his nineties.

What was Kappa's "Meisterwerk"? Although we are both connected to the studies, we believe that his synthesis of chiral methyl groups, that is, containing all three isotopes of hydrogen, and their application in enzymology, stands out. The basis of this work was the synthesis of "chiral" acetic acid by a route that is wonderfully simple. (*Z*)-[$^2H_1$]Styrene was epoxidized and the resulting enantiomers were reduced with [^3H]$LiAlH_4$ to a mixture of 1-phenylethanols of which the 1*R* isomer contained a methyl group with *R* chirality and the 1*S* isomer a methyl group with *S* chirality. Resolution of this pseudoracemate and oxidation afforded (*R*)- and (*S*)-[$^2H_1$,^3H]acetates. Following a procedure originally proposed by Duilio Arigoni, ETH Zürich, Kappa's collaborators in Munich (WB being one of them) condensed these acetates via the corresponding coenzyme A esters with glyoxalate, to give malate. This reaction, with a kinetic isotope effect of 4 and inversion of configuration at the methyl group, was catalyzed by the yeast enzyme malate synthase. The malate obtained from (*R*)-acetate, after equilibration with fumarase, had lost 20 % tritium, whereas that from (*S*)-acetate had lost 80 % tritium into the water. By using this method, Kappa solved the 14th and last stereochemical ambiguity in squalene biosynthesis from mevalonate.

As a person, Kappa was kind, liberal-minded, and a lover and writer of poetry, as well as provocative in argument and a great raconteur. He gave freely of his time to train students in the experimental arts and scientific methods. His writings are an exemplar of clarity and grammatical precision. He was a dedicated gardener as all who visited his house in Lewes, Sussex know well. And he was a great chess player, already precocious by winning the New South Wales boys' championship in 1933 and later playing for Hampstead in the 1950s. As Kappa always emphasized, his scientific achievements owed much to his wife Rita (1915–2012), herself a brilliant chemist, who collaborated on many projects, as well as nurturing their three children. We mourn our friend, collaborator and mentor, and will remember all he stood for.

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