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KEN'ICHI TAKEDA

1907 - 1991

Ken'ichi Takeda was born on January 27, 1907 in Kamichikugo-machi, Nagasaki, as the first son of Shin'ichi Takeda, an employee of Mitsui Bank Ltd. He moved to Tokyo with his family and spent his school years there. He successfully passed the very difficult entrance examination for the First Higher School, the renowned national college for general education. His interest in organic chemistry of natural products, especially alkaloids, was aroused during this period. In 1928, he matriculated at the Pharmaceutical school, Medical Department of Tokyo Imperial University (now the Faculty of Pharmaceutical Sciences, University of Tokyo), which was the most well-known institute in Japan for natural products chemistry at that time. In 1930 he enrolled in the Laboratory of Pharmaceutical Chemistry and started his career in organic chemistry under the guidance of Professor Heizaburo Kondo. Professor Kondo (1877-1963) was head of this laboratory as the successor of Professor Nagayoshi Nagai (1845-1929), who had been an assistant of Professor A. W. von Hofmann of the University of Berlin and, after returning to Japan, founded the Pharmaceutical School at Tokyo Imperial University. Mr. Takeda was fortunate to form friendships with many excellent scientists there. One was Professor Eiji Ochiai, who later succeeded Professor Kondo. Both professors were to become his lifelong advisers.

The memorable theme of Takeda's first piece of research was the synthesis of an analog of quinine methylated at the 9 position. This research, although interrupted temporarily because of his graduation from the university, was resumed during the war at the Itsuu Laboratory, where Professor H. Kondo was serving as director after his retirement from the university. This work led Takeda to discover that phenolic aromatic hydrocarbons could undergo the Diels-Alder reaction, thus expanding the scope of this famous reaction.

After graduation from the university in 1931, Takeda was appointed an assistant in the Medical Department of Tokyo Imperial University and started his professional career with Professor Kondo. His research program at Kondo's laboratory was the structural elucidation of lindenenol (named linderene at first), linderane, and linderalactone, which are components of the Chinese herb medicine Tendai-U-Yaku, the root of *Lindera strychnifolia* Vill. He had a difficult time studying the structure of lindenenol, but made much progress when he isolated naphthofuran and an azulene by zinc dust dehydrogenation of lindenenol in 1937, proving that the compound was a sesquiterpene. Unfortunately, however, this study was interrupted because he had to serve in the war in Central China for five years. The work was resumed at Itsuu Laboratory which he entered after returning in 1942. The laboratory had been established for Professor Kondo with a donation from Gisaburo Shiono, the second President of Shionogi & Co., Ltd. The research progressed remarkably, but was again interrupted a year later by wartime work on quinine alkaloids as antimalarial agents. In April 1945, Takeda joined Shionogi Research Laboratories in Osaka, the research unit of one of Japan's three largest pharmaceutical companies. At Shionogi, he was able to resume his work on lindenenol in 1947, and finally succeeded in elucidating the structure of lindenenol and those of its accompanying components with the aid of modern spectroscopic methods. Through this study, he discovered azulenes fused with a furan ring for the first time. This discovery led to subsequent structural studies on perhydroazulene-type sesquiterpenes. In considering a rational mechanism for azulene formation and through the structural elucidation of many minor components, he observed a smooth interconversion between sesquiterpenes of the germacrane type and those of the elemene type.

Takeda contributed nearly a hundred papers to the field of sesquiterpenes and these studies constitute an important part of his life work. His studies on components of the root of *Lindera strychnifolia* Vill. and their related compounds unveiled sesquiterpenes of an entirely new type and added a new page to the history of terpene chemistry.

Perhaps Takeda's even more important contribution to natural products chemistry was his extensive work in the field of steroids. He started his studies on a suggestion from Professor E. Ochiai in 1947 soon after joining the Shionogi research group. Stimulated by the discovery of adrenocortical hormones, steroid research had been the center of interest of many natural products chemists throughout the world at that time. However, this was not the case in Japan, where little scientific information was available because of the war. Therefore, Takeda become a pioneer in steroid research in Japan. His research on steroids which continued up to his death, included (1) isolation, structural determination, and biogenesis of sapogenins and sterols including triterpenes, (2) isolation, structural determination and chemical transformation of bile acids and modified steroids including thiosteroids, and (3) steroid total syntheses. The studies were carried out with many associates and collaborators covering a wide range of topics in the field. Thus, the number of papers published exceeds 200.

The work he began in 1951 to obtain materials suitable for corticoid synthesis in domestic plants led to one of the remarkable achievements in sapogenin research. This work enabled the isolation and structural determination of metagenin, nogiragenin and related sapogenins from *metanarthecium luteo-viride* Maxim. (Japanese name: Nogiran). The sapogenins proved to be uniquely hydroxylated at $C_{11\alpha}$ and thus to be suitable for corticoid synthesis. They could be converted into corticosteroids, but, unfortunately, the scarcity of the plant and the difficulty of its cultivation prevented industrial application. To overcome these problems, Takeda tried tissue culture using callus, but without much success. However, he became very interested in the prompt chemical transformation of a material in the callus body. This triggered biogenetical studies of sapogenins, especially those hydroxylated in the F ring, sterols, and triterpenes. Such research showed that labelled starting materials or intermediates are more efficiently incorporated in a callus than in the corresponding plant itself.

Takeda's studies on bile acids were done with the aim of obtaining material for corticoid synthesis from animal resources. He isolated several new bile acids and prepared interesting conjugates of cholic acid and some amino acids. As for the steroid modifications, Takeda was interested in preparing 11β mercaptocortisol. Although attempted syntheses along this line failed, he ultimately discovered a compound that was very interesting from the biological viewpoint. The compound possessing the structure of 2α,3α-epithio-5α-androstan-17β-ol showed strong antiestrogenic activity and, therefore, was developed for clinical use. The drug, named mepitiostane, is used for patients with anemia and mammary cancer. Other sulfur-containing steroids, such as episulfides, thiocyanates, thiol acetates, oxathiolanes, dithiocarbonates, trithiocarbonates; and dithioethylene ketals, were prepared and examined in circular dichroism studies together with Professor Djerassi of Stanford University.

Takeda believed that total synthesis of steroids was important from the industrial point of view, anticipating future exhaustion of plant resources of steroid hormones. Based on this belief, he started steroid total syntheses in 1957 and succeeded in preparing *dl*-pregn-16-en-3β-ol-20-one in an efficient manner in 1959; this was the first total synthesis done in Japan. The synthesis was unique in that the key intermediate was 18β-carbonitrile, which was easily accessible by application of an improved hydrocyanation method and easily convertible to other important steroids containing 18-functionalized methyl functions, such as aldosterone and connesine.

Takeda's list of noteworthy contributions continues. He was also involved in studies on lycoris alkaloids. Isolation of the alkaloids from *Lycoris radiata* HERB and their chemical degradation had been carried out by Professor H. Kondo's group from 1927 to 1933. After the interruption of World War II, the alkaloid research was resumed by Professor Shojiro Uyeo of Osaka University (later a professor of Kyoto University), a former student of Professor Kondo. He made significant progress in structure elucidation and syntheses of the lycoris alkaloids. Takeda worked with Professor Uyeo on the study of the chemistry of

lycoris alkaloids, particularly on the stereochemistry of the alkaloids which had remained unsolved at that time. The structural elucidation and stereochemical determination of lycoris alkaloids were thus culminated by the joint study of the two research groups.

Besides these scientific achievements as a natural products chemist, Takeda made many contributions as Senior Managing Director of the company, especially in research, development, and production. In 1951 he was appointed Director of Shionogi Research Laboratories at the age of 44. Since then he endeavored to modernize the laboratories during the 22 years until he resigned in January 1973. His efforts were directed towards the construction of a new and well-equipped building for research and the encouragement of research members to develop their research potential. As a result of such efforts a new research laboratory building was completed in 1961, equipped with modern apparatuses and machines and central air-conditioning, something unusual in Japan at that time. Also, during his directorship, the number of research personnel increased five- to sixfold to more than a thousand. But even more important than the growth in number was what he did to develop truly capable scientists. Takeda was an idealist and believed that outstanding discoveries in drug research could only be possible by outstanding scientists. He was convinced that liberty in choosing a research program and flexibility in a research organization were essential for the training of outstanding young research people. With this conviction, as Managing Director, Takeda transformed the old, rigid research organization into a flexible one to encourage active research by the young scientists. He allowed them to choose their own research themes. This policy led them to take on various, rather basic research themes and led to extensive development of their research capability. Thus, papers published from Shionogi Research Laboratories increased markedly and, to this day, continue to be of very high quality. From these laboratories came also many capable and famous scientists. Several useful medicinal drugs were produced during his directorship. They include sulfamethoxazole (Sinomin), a world-famous sulfonamide; cetotiamin (Dicetamin), a modified vitamin B_1; giractide (Acthormon), a synthetic ACTH; perisoxal (Isoxal), an antiinflammatory analgesic; and epitiostanol (Thiodrol) and mepitiostane (Thioderon), anti-estrogenic steroids.

Takeda was a full and later an honorary member of the Pharmaceutical Society of Japan, the Medical and Pharmaceutical Society for Wakan-Yaku (Chinese herb medicine), and also a member of the Japan Endocrine Society and other domestic and international societies. He was on the Board of Directors of the Pharmaceutical Society of Japan several times, served as President in 1976-1978, and was a director of the Research Foundation for Pharmaceutical Science. Here a special note should be made on his contributions to the founding of the French-Japanese Society of Medicinal and Fine Chemistry in 1981 with Professor D. H. R. Barton. These two scientists shared the Presidency for a long time.

From 1954-1991, he served as Inspector and Chairman of Hoansha Foundation, founded by a donation from Gisaburo Shiono, the second president of Shionogi & Co., Ltd., and also as Inspector, Director, and Chairman of Itsuu Laboratory. He was on the board of many international journals, including "Tetrahedron" and "Tetrahedron Letters" in 1959-1987, "Steroids" in 1965-1991, "Chemosphere" in 1971-1988, and "Heterocycles" in 1973-1991.

Takeda's many honors and awards include the Academic Award from the Pharmaceutical Society of Japan in July 1961, the STA (Science and Technology Agency) Director-General's Award in April 1962, the Medal of Honor with Blue Ribbon in November 1972, and the Third Order of the Sacred Treasure, in May 1978.

Takeda was a man of wide cultural interests. He liked playing the piano, painting, writing essays, mountaineering and skiing. He loved "Rakugo" (traditional Japanese popular comic stories full of jokes, ironies, and tidbits of instruction). He used to pepper his conversations with his research staff with quotes from "Rakugo". He also enjoyed botanical excursions very much and urged us to appreciate the greatness and the harmony of nature, especially through botanization. He also thought that harmony is essential in research laboratories and, more widely, in human society in general.

In 1933 Professor Kondo introduced Takeda to Sumiko Shiono, a daughter of Chojiro Shiono, brother of Gisaburo Shiono. They were married and had three

sons and a daughter. He is survived by his wife, Sumiko, his sons, Jun'ichi, Reiji, and Nobuzo, and his daughter, the present Mrs. Yasuko Akao. Takeda, a refined and charming personality, will be missed by his numerous friends in Japan and many countries around the world.

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