

PROFILE AND SCIENTIFIC CONTRIBUTIONS OF

PROFESSOR TETSUO NOZOE

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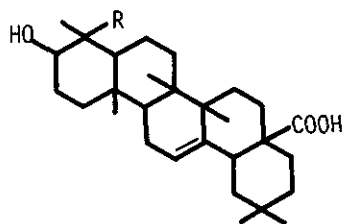
Sendai, 980 Japan

Professor Tetsuo Nozoe was born in Sendai on May 16, 1902, as the sixth son of Mr Juichi and Mrs Toyoko Nozoe. His father was a prominent lawyer in Sendai and also served as the Chairman of a municipal Assembly and a member of the national Assembly. Professor Nozoe graduated from the former middle school in Sendai (Sendai Dai-Ichi Chugaku) and the National Second High School. During middle school he had a deep interest in chemistry and enjoyed performing chemical experiments in his private laboratory in the warehouse of the residence. In 1923 he entered the Faculty of Science, Tohoku Imperial University, and carried out his thesis work for graduation in organic chemistry under the supervision of Professor Riko Majima, who was an authority in organic chemistry.

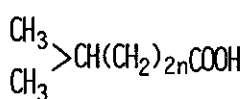
Immediately after graduating from Tohoku Imperial University in 1926, Professor Nozoe started his professional career as a staff member of the Central Research Laboratory of the Monopoly Bureau of the Taiwan Government-General and studied the chemistry of terpenoids^{3,4} under Dr. Kinzo Kafuku. His first research subject was "a Study on the Essential Oil of Arisan-Hinoki (*Chamaecyparis taiwanensis*, Masamune et Suzuki)". He was appointed an assistant professor in 1929 under concurrent Professor Kafuku when the institute for organic chemistry was opened in the Faculty of Science and Agriculture,

Taihoku Imperial University, and was promoted to a full professor in 1937. During those days he married Miss Kyoko Horiuchi, a niece of Mrs Kafuku.

His major research subjects in those days were concerned with the chemistry of organic natural products such as saponin and sapogenin, and the color reaction of saccharides and lipids of wool and animal-skins. In 1936 Professor Nozoe received the degree of Doctor of Science from Osaka Imperial University. The thesis, "Studies on Polyterpenoids and their Glycosides",⁷⁻²¹ was referred by Professor Majima, who had moved to Osaka from Tohoku Imperial University. Professor Nozoe continued his studies in these fields until around 1940 and achieved great success. We can find several prominent attainments among these studies, such as the structural studies on oleanaic acid (1, R=CH₃) and hederagenin (1, R=CH₂OH)²²⁻²⁵ published in 1937, and also the studies on the components in the lipid of wool (lanolin) presented orally in 1939. In the latter studies he made the important discovery that there is a regularity in the occurrence of branched fatty acid (C₄ - C₂₁) with odd carbon atom (2) and even carbon atom (3).¹⁰⁰

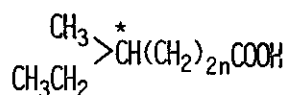


(1)



Lanolic acid series

(2) n=1-16



Agnolic acid series

(3) n=1-16

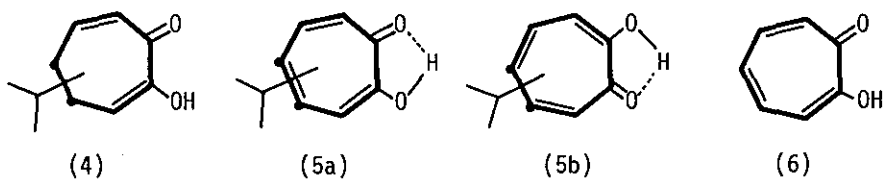
As long as the structure is planar, formula (1)²⁵ was correct and is still referred to the literature. Professor Haworth included this formula in his review article on polyterpenoid in 1937 [Haworth, Ann. Rept., 34, 327 (1938)], but the author did not cite the names of the investigator and the journal due

to a mistake, probably because Professor Nozoe made his report as a communication in Japanese.²⁵ By this misunderstanding Professors Ruzicka and Barton had thought that structure (1) had been proposed by the reviewer.

The structures of branched fatty acids (2 and 3) were orally presented by Professor Nozoe at the annual meeting of the Chemical Society of Japan [cf. T. Nozoe and T. Kinugasa, Nippon Kagaku Zasshi, 60, 486 (1939)]. Details of the structural studies were described in patents [T. Nozoe and Y. Kawakami, Jpn. Patent, No. 145, 450; No. 147, 111, 677; No. 150, 520; No. 153, 629, 653 (1941)]. These results were also described partly in a special monograph¹⁰⁰ written by Professor Liu who was one of his coworkers, but most of them were not published in any chemical journal. Professor Nozoe was awarded the Majima Prize in 1944 from the Chemical Society of Japan for his great contribution to "the Studies on Organic Natural Products".

Among his achievements, the most significant is the establishment of the troponoid chemistry which originated in his study on "Hinokitiol". In 1935 Professor Nozoe started a study on the acidic components of Taiwan cypress and found an entirely new compound, having the molecular formula of $C_{10}H_{12}O$, which reacts easily with iron and other metal ions to give the complexes. This compound was named "Hinokitiol"¹⁸ and later proved to be α -enolone with an unsaturated seven-membered ring. For several reasons the structure (4), which lacked one double bond, was orally presented for "Hinokitiol" in 1940 at the meeting of the Pharmaceutical Society of Japan and was published in 1944.²⁷ Later Professor Nozoe, however, established the structure (5) for "Hinokitiol"; this is in a resonance hybrid between (5a) and (5b) because of its stability and amphoteric nature.^{424,504}

During World War II, which made it difficult for Taiwan to keep contact with mainland Japan, the study on "Hinokitiol" had to be discontinued owing to



urgent demands of wartime researches and the evacuation to escape from air raids. When the war ended in 1945, the university was transferred to and controlled by the Chinese Government, but Professor Nozoe remained there as a professor of chemistry at the faculty of science of the reorganized National Taiwan University (Republic of China) by their request and again started his work on "Hinokitiol". However, the war incidentally gave Professor Nozoe one piece of good luck for his research, that is, the iron salt of "Hinokitiol" (hinokitin) was found in the factory waste of Takasago Perfumery K.K. which produced fairly large amounts of hinoki oil for floating oil or as a substitute for gasoline during the war. This was the only advantage of the war, as Professor Nozoe told us later. Thus, hinokitiol became much more easily available for carrying out a wider investigation including the substitution reactions like halogenation, nitration, and diazo coupling as well as rearrangement reactions leading to benzoic acid derivatives. The study on aromaticity of hinokitiol was almost completed when Professor Nozoe returned to Japan in 1948.²⁹ The mother skeleton (6) of hinokitiol (5) was proposed by Professor Dewar as a new aromatic nucleus [M. J. S. Dewar, *Nature*, 155, 50 (1945)], but this proposal was not directly communicated to chemists in Taiwan and Japan in the days of disorder immediately after the war. Although Nozoe's formula (5) had been referred in the medical journals by his coworker, Professor Katsura [S. Katsura, *Saishin Igaku*, 2, 295 (1947); *Medical Time*, 3, 29 (1948)], it was unfortunate that the confusion after the war prevented

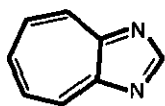
Professor Nozoe from publishing it in a chemical journal. In 1948, when Professor Nozoe returned to Japan from Taiwan and was appointed as a professor of chemistry at the Faculty of Science, Tohoku University, where he spent his college days, Professor Erdtman and his coworker isolated α -, β - and γ -thujaplicin from the heartwood of *Thuja plicata* D. Don, to which they gave the structure (5) and the isomeric structures. We had to wait until 1949 for the publication of a review article about Professor Nozoe's work in Taiwan.^{29,43} However, hinokitiol, which he had brought along from Taiwan, initiated his research activities at Tohoku University, which soon resulted in the excellent research works of the Nozoe group, including the first syntheses of tropolone,³⁰ hinokitiol,³¹ and α -thujaplicin³² (1949-1950). In addition to these synthetic studies he pursued thoroughly the electrophilic and nucleophilic substitutions, aromaticity and olefinic property of tropolone derivatives and established the Troponoid Chemistry of non-benzenoid aromatic compounds²⁶⁰ [P. L. Pauson, Chem. Rev., 55, 9 (1955); L. Crombie, Chem. Ind., 663 (1978)].

At the time Professor Nozoe joined Tohoku University, Japanese universities were in very hard times and staff members had to sacrifice their academic activities to struggle for their daily life. During such a difficult period he developed an epoch-making new field of chemistry by overcoming all difficulties and carried out many joint projects not only with organic chemists, but also with physical and inorganic chemists. It is worthy of special mention that these attainments were introduced to many universities throughout the country by his lecture tours; these were quite effective for the revival of chemistry in Japan after the war. In such a sense we can call Professor Nozoe one father of the renaissance of chemistry in Japan after World War II.

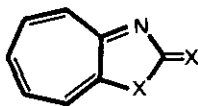
A second prosperity of the troponoid chemistry was brought about by its

development into the azulenoic chemistry, starting from active troponoid derivatives having good leaving groups such as methoxy and halogens at the C₂ position. The success of the synthesis of 1,3-diazaazulene derivative (7) in 1953 was followed in succession by the syntheses of new types of heterocyclic compounds having a condensed seven-membered ring such as (8) and (9),²³⁴ and the reactivities of these compounds were also well investigated. These syntheses had been predicted in his review written in 1949.²⁹ The syntheses of azulenes were initiated in 1953 and the azulene derivatives (10) having the substituent at the five-membered ring was successfully synthesized in 1955.¹⁸⁶ The compound (10) was found to be so versatile as to derive not only a variety of azulene derivatives but also many polycyclic compounds with seven-membered rings. In these works the reactive substituent on the five-membered ring was utilized effectively and this novel type of synthesis, which should be named the "Nozoe's Azulene Synthesis" [R. N. McDonald et al., *J. Org. Chem.*, 40, 1689 (1975)], made a great contribution to the development of the chemistry of azulene. These series of studies expanded into the chemistry of a new class of compounds having seven-membered rings, like heptafulvene (11), quinonetropide (12), and quinarene (13), and established the chemistry of "Tropoid" which was proposed as a genetic term by Professor Nozoe to the compounds having seven-membered tropylium system. These achievements by Professor Nozoe are certainly immortal and have important meanings as the beginning of the chemistry of non-benzenoid compounds. Professor Nozoe also found the rare norsesquiterpenoids (14 and 15) having an acetylenic bond from the heartwood of *Chamaecyparis formosensis*, Matsum.^{428,452,460}

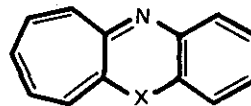
These contributions to science brought him the Asahi Cultural Award in 1952, the Japan Academy Award in 1953, the Order of Cultural Merit of Japan in 1958, and also an honorary citizenship of Sendai in 1959.



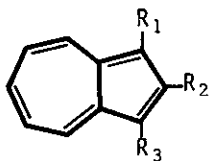
(7)



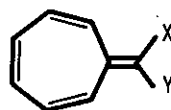
(8) X=O, S, NH



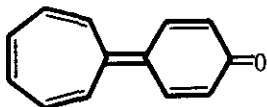
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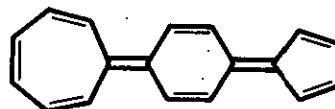
(10)



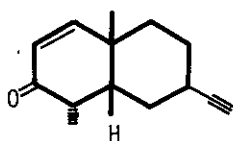
(11) X=Y=CN or COOR



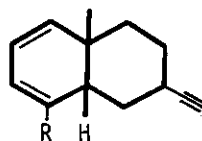
(12)



(13)



(14)



(15) R=CH₂OH or CHO

In addition to these academic achievements he guided the research works of more than a hundred students at Tohoku University before his retirement in 1966, and about twenty of them are professors of chemistry in universities all over the country besides fifteen professors in Taiwan. In 1955 Professor Nozoe opened two sections for troponoid chemistry in the Institute of Non-Aqueous Solutions of Tohoku University and also the "Second Department of Chemistry" in 1960 in the Faculty of Science, Tohoku University. The latter department was founded by adopting Professor Nozoe's idea that the chemistry of great promise must be advanced by keeping a balance in every field. This policy was followed in several national universities and so Professor Nozoe may be one originator of the system of Second Departments of Chemistry in national universities.

He attended or was invited to many international meetings to give lectures or plenary lectures, including the 1953 IUPAC Symposium on Natural Products at Stockholm and the 1957 IUPAC Congress at Paris which was held on the hundredth anniversary of the French Chemical Society. He also contributed to the international exchange by serving as a chairman of the organizing committee of The 1st Japan-U.S. Joint Seminar on Physical Organic Chemistry held at Kyoto in 1965 and a chairman of the organizing committee and a president of The 1st International Symposium of Non-Benzenoid Aromatic Compound (ISNA) held at Sendai in 1970. He served as a member of the Japan Science Council for one term from 1965 and made many contributions to the international exchanges of arts and science. Professor Nozoe had the duty of the presidency of the Chemical Society of Japan in 1975, and was selected as a foreign member of the Swedish Royal Academy of Science in 1972 and as a member of the Japan Academy in 1977. He has been given honorary memberships from the Pharmaceutical Society of Japan, the Society of Agricultural

Chemistry of Japan, and the Chemical Society of Japan.

Currently Professor Nozoe lives in Tokyo and continues to lead an active life unexpected for his age. He has a laboratory in Tokyo Research Laboratories of Kao Soap K.K., where he is reinvestigating the study on the mechanism of azulene synthesis and troponoid chemistry using high pressure liquid chromatography. He has an additional office in the Research Laboratory of Takasago Perfumery K.K., where he carries out literature searches for a monograph of the troponoid chemistry. We understand that Mrs Nozoe is leading a pleasant life too and enjoying the weekends with Professor Nozoe at their resort house in Izu peninsular. Professor and Mrs Nozoe have a son and three daughters. Dr. Shigeo Nozoe, the son, is a professor of chemistry at the Faculty of Pharmacy, Tohoku University. Miss Takako, the eldest daughter, married Professor S. Masamune of Massachusetts Institute of Technology; Miss Yoko, the second daughter, married Professor H. Ishikura of Jichi Medical University; and Miss Yuriko, the third daughter, married Mr K. Higashihara of Wella Cosmetics of Japan.

In closing as a representative of his students, I offer my cordial congratulations to Professor Nozoe on the occasion of his seventy-seventh birthday and wish Professor and Mrs Nozoe a long continuation of healthy life. I also beg his continuous guidance and encouragement of us for our future work in chemistry.

J. Shio Mukai