Professor Yoshio Ban (1921-1994)

Our respected mentor, Professor Yoshio Ban, Professor Emeritus of Hokkaido University, passed away suddenly on July 16, 1994 at the age of 73 of a heart attack.

He was born in Tokyo in 1921. He grew up there and after finishing junior high school, moved to Kyoto where he studied at the famous "The Third High School (national high school under the old educational system)" for three years. He stayed in the dormitory and enjoyed his school life. Then, he came back to Tokyo and graduated from the Department of Pharmaceutical Sciences, University of Tokyo, in 1945. After graduation, he worked as a research associate in Professor Shigehiko Sugasawa's group. He experienced extremely hard times during World War II as well as immediately after the war in a laboratory under poor conditions. Under the guidance of Prof. Sugasawa, he got his Ph. D. degree in 1955 on the synthesis of emetine. In the same year he joined Professor William G. Dauben's lab in the University of California in Berkeley as a post-doctorate where he spent one year. He was appointed an associate professor in the newly founded Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo in 1956, and became a full professor the following year. He worked on the chemistry and synthesis of indole alkaloids and other bioactive substances such as antibiotics and anti-tumor agents for many years until his retirement from the university in 1985. He published more than 200 scientific papers in well-known international journals. Nearly 200 students, including three foreign students, grew up from his laboratory, and most of them are now working actively in the field of pharmaceutical sciences not only in academic institutions but also in pharmaceutical industries and hospitals. During his Hokkaido University days he was very active in both research and administrative works. He served twice as the dean of the faculty (1966-1970, 1978-1981).

After retirement from Hokkaido University, he was nominated a professor of the graduate course in the Faculty of Pharmaceutical Sciences, Toho University (1985-1987). He was elected President of Hokkaido University in 1987 and served in this capacity until 1991. He was the first president elected from the pharmaceutical field among the big seven national universities in Japan.

His research activities have been highly evaluated worldwide and he was invited to many international meetings as a plenary lecturer such as Gordon

Conference (1965, 1974, and 1975), IUPAC Natural Products Symposium (1972), International Congress of Heterocyclic Chemistry (1975), IUPAC Congress (1981), IUPAC Symposium on Organometallic Chemistry Directed Toward Organic Synthesis (1981), etc.

He received numerous honors for his research, but only a few are listed here: The Pharmaceutical Society of Japan Award (1963) "The synthesis and their stereochemistry of indole alkaloids"; Japan Academy Prize (1984) "Synthesis of indole alkaloids"; Special Award in Synthetic Organic Chemistry (1992, from the Society of Synthetic Organic Chemistry, Japan).

On his death, Professor Ban was decorated with The First Order of Merit from the Emperor for his brilliant scientific achievements and leading activities in educational administration.

Professor Ban leaves his wife (Miwa), daughter (Yumiko) and son (Takashi).

Scientific Activity

I Before Hokkaido University (1945-1956)

Prof. Ban started his research activity in the Faculty of Pharmaceutical Sciences, University of Tokyo, in 1945 under the guidance of Prof. Shigehiko Sugasawa. Synthesis of sulfamerazine was his first project. The key step in the synthesis was the condensation of sulfaguanidine with formylacetone acetal to form a pyrimidine ring. This success encouraged young Ban to continue his synthetic work although research facilities were extremely poor. The next project was the synthesis of emetine whose structure had been revised in 1948 by R. Robinson. He completed the synthesis of rubremetinium salt which was obtained by the oxidation of emetine in 1955. The starting material was vanillin from which he prepared homoveratrylamine by a unique route including electrochemical (electrolytic) reduction. He utilized the ultraviolet and infrared spectroscopy effectively in the identification of the final product. At that time, it was rarely the case that these machines were used for this purpose. He received his Ph. D. degree for this work. He had another new experience when he was a post doctorate fellow in Prof. W. G. Dauben's lab, Berkeley, California. Although he stayed only for one year there, 1955-1956, he carried out biosynthetic studies of eburicoic acid, a triterpene incorporating

^{14}C-labeled compounds. The use of radioactive compounds was almost impossible in Japan.

II Hokkaido University: Early period (1956-1965)

Research activity of Prof. Ban's group in Hokkaido University started in 1956 with establishment of the stereochemistry of emetine. He clarified the *trans*-quinolizidine structure in emetine and further determined α-configuration of 11*bH* in emetine by the molecular rotation method. Then his research work moved to the determination of absolute configurations of indole alkaloids, yohimbin and reserpine, by the chemical method, because his previous conclusion on the stereochemistry of emetine was based on the configuration of these indole alkaloids. Application of the Prelog asymmetric synthesis to yohimbin and reserpine derivatives and the subsequent chemical correlation of yohimbin to corynantheine whose absolute configuration had been determined already clarified the absolute configuration of these indole alkaloids.

Another brilliant contribution in this period was the discovery of a new method for the simple synthesis of indolo[2,3-a]quinolizines. He found that the indoloquinolizine ring system could be obtained by simply heating 3-indolylethyl bromide with 2-halopyridines. By this method he synthesized indole alkaloids such as flavoperirine, sempervirin, and alstoniline. This method was used by other researchers such as Professors G. Büchi and F. E. Ziegler.

Then, Prof. Ban's research field gradually moved to the total synthesis of indole alkaloids.

III Hokkaido University: Total synthesis of polycyclic indole alkaloids containing quaternary carbon atom (1961-1985)

His synthetic strategy towards aspidospermine was to initially synthesize the tricyclic ketone, a non-tryptamine moiety of aspidospermine, and then subject it to the Fischer indolization. In fact, when the tricyclic ketone was heated with formic acid, the stereoisomer of aspidospermine along with a small amount of natural aspidospermine was obtained. Before he completed this work, the synthesis of the same alkaloid from the stereoisomeric tricyclic ketone had been reported by G. Stork et al. Professor Ban and his coworkers scrutinized the stereochemistry of the tricyclic ketones prepared by the two groups through physicochemical methods, and concluded that the stereochemistry of Ban's tricyclic ketone did not correspond to that of natural alkaloid, while the stereochemistry of Stork's ketone was the same as that of the

natural product. Thus, Professor Ban exerted his efforts to the development of a more straightforward synthetic strategy and later established a general method for the synthesis of Aspidosperma alkaloids based on the conversion of oxindoles to indolines. This strategy was successfully applied to the synthesis of a series of important indole alkaloids, ibogamine, tabernamine, and ibogaine, using Fischer indolization in the final step.

Oxindole alkaloids having a unique 3,3-disubstituted oxindole structure were also chosen as synthetic targets. Prof. Ban developed a new method for the preparation of 3,3-disubstituted oxindoles by the condensation of oxytryptamine with aldehydes. His research group synthesized the aldehyde having two vicinal chiral centers with established stereochemistry. The condensation of this aldehyde with oxytryptamine gave the spiro-oxindole having four rings whose stereochemistry at 15 and 20 was *trans*. The isomeric spiro-oxindoles were also synthesized from the diastereomeric aldehyde to confirm the *trans* stereochemistry of rhyncophilline. Utilizing a series of the same reaction sequences, the natural and its iso-form of formosanine and mitraphilline were synthesized, respectively.

Condensation of the inactive lactam carbonyl group present in 3,3-disubstituted oxindole derivatives with carbanions to produce 2,3,3-trisubstituted indolines could be achieved successfully when the lactam moiety was converted to the reactive imino ether with Meerwein reagent. Based on this unique reaction, a general and unprecedented method for the synthesis of a wide variety of Aspidosperma and related alkaloids was established. Syntheses of 1-acetylaspidospermine, deoxyaspidospermine, aspidofractinine, fendleridine as well as vindoline, an important part of antitumor agent vinblastine, were accomplished.

During the study of the photochemistry of 1-acylindole derivatives, it was found that the acyl group migrated mainly to the 3-position to form 3-acylindolenine. Using this photochemical reaction azoninoindoles having 9-membered lactam ring were prepared, which proved to be a versatile intermediate in the synthesis of various types of aspidosperma and strychnos alkaloids. For example, dihydroaspidospermidine, quebrachamine, condyfoline, tubifoline, and others were synthesized from this azoninoindole intermediate.

IV Hokkaido University: Synthesis of biologically active nitrogen heterocycles based upon newly developed methods (1970-1983)

As described above, Professor Ban made brilliant contributions to the total synthesis of polycyclic indole alkaloids. Nevertheless, his interests spread further to

the development of new versatile synthetic methods and the synthetic targets extended to other biologically active nitrogen heterocycles.

The first example was the "crisscross annelation"; a double ring closure of a cyclic amidoketone to form a pyrrolizidine or indolizine system. The benzopyrrolizidine ring system involved in an antibiotic mitomycin was synthesized by this crisscross annelation of 2-(2-aminophenyl)cyclopenta-1,3-dione. A modification of this reaction effected a simple synthesis of the benzoazocine ring system from which they synthesized mitomycin analogs.

The second example was the CO insertion reaction between the nitrogen atom and the aromatic ring via an organopalladium intermediate. This was an early example of the formation of nitrogen heterocycles using organometallic compounds. Various benzolactams have been synthesized based on this method. This strategy was applied to the synthesis of various anthramycin antibiotics such as dehydrocyclopeptine, anthramycin SEN-215, and cyclopenine. Using vinyl halides instead of aryl halides, benzolactams as well as ß-lacams can be prepared by this method.

The third example was the utilization of electrolytic oxidation to the synthesis of alkaloids. Professor Ban used the electrolytic reduction at an early stage of his research career. Furthermore, he had been interested in electronics since he was young. These experiences undoubtedly facilitated access to electro-organic chemistry. Thus, various alkaloids such as lupinine, vincamine, and ebrunamonine were synthesized. An electrolytic oxidation of N-alkyl lactams to α-hydroxylactams has been involved in the early stage of these syntheses.

V Hokkaido University: Synthesis of Terpenes and Macrolides

Professor Ban extended his research field to the synthesis of terpenes and macrolides in the latter period of his Hokkaido University tenure. The acyloin condensation of esters was improved by carrying out the reaction in the presence of trimethylsilyl chloride. The bis-silylenol ether thus obtained is a masked acyl anion and can be converted to 1,2-enediols by methyllithium and alkylating agents. These 1,2-enediols have been utilized for the synthesis of terpenes such as dihydrojasmone and *cis*-jasmone.

A method of preparation of 10-membered lactones such as decan-9-olide from bis-silyl derivative of cyclohexenediol was developed and, based on these strategies, various macrolides such as diplodialide, pyrenophorin, vermiculine and colletanol were synthesized.

These contributions were summarized by Prof. Ban in the following three review articles.

1. Review of early research: Synthesis [gousei], the Memorial Issue of Professor Shigehiko Sugasawa on the Occasion of his 75th Birhtday (Edited by S. Yamada), 1972, Hirokawa Publisher, Tokyo (in Japanese).
2. The Memoirs and Dreams of One Organic Chemist, Organic Synthesis in Japan. Past, Present, and Future (Editor-in-Chief, R. Noyori), 1992, Tokyo Kagaku Dozin, 3-7.
3. Total Synthesis of Natural Products; From Alkaloids to Terpenes, J. Synthetic Organic Chemistry , 1993, 51, 111-127 (in Japanese), [Memorial article when he got a Special Prize from the Society of Synthetic Organic Chemistry of Japan, 1992]

Other reviews are included in the complete list of publications of Professor Ban in this issue.

Activities in Scientific Society

He was a very important member of the Pharmaceutical Society of Japan; Chairman of organizing committee of the annual meeting (1970), Vice president (1972-1973, 1974-1975), President (1981-1983), and honorary member of the Society (1986-). He was also a very active member in the International Society of Heterocyclic Chemistry; Chairman of the 3rd (1971, Sendai) and 9th (1983, Tokyo) International Congress; President (1988-1989). He was also a key person in the French-Japanese Symposium on Medicinal and Fine Chemistry, which started in 1981 and has been held every one and a half years.

He was very active in promoting international scientific exchange. He invited two Nobel prize winners, R. B. Woodward and H. C. Brown, to the Annual Meeting of Pharmaceutical Society as plenary lecturers in 1970. This was actually an epoch-making affair at that time. Another of his major international contributions was the initiation of the Japan-United States Congress of Pharmaceutical Sciences. The first congress was held at Hawaii in 1985 under his outstanding leadership.

As mentioned above he was truly a pioneer in introducing organic chemistry in pharmaceutical fields in Japan to the chemical communities of the world. He had many friends abroad. He invited many prominent organic chemists to Japan, mostly under the JSPS program. By his efforts, many foreign scientists became familiar with Japanese organic chemists and their research work.

He was a reliable person and many people not only scientists but also administrative people, respected him for his honesty and enthusiasm. He was the first organic chemist to organize a big "special research project" supported by the

Ministry of Education, Science, and Culture in the form of Grant-in-Aid for Scientific Research. This research project, Chemical Research in Development and Utilization of Nitrogen-Organic Resources (1978-1980), accelerated and stimulated the research activity of many organic chemists in Japan. Since then, such kind of big research projects in organic chemistry field has been undertaken from the time to time, and the number of such projects is increasing gradually.

In addition to the publication of this memorial issue, there will be a symposium on September 2, 1995, at Nagai Hall of the Pharmaceutical Society of Japan, Tokyo, in the memory of Professor Ban.

The death of Professor Yoshio Ban is a great loss to the field of synthetic organic chemistry and natural product chemistry. We express deepest condolences on the passing of Professor Ban.

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