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LABORATORY OF PHYSIOLOGICAL ACTIVITY

Head: Dr. Eiichi Fujita

This laboratory was established on 21st. December, 1962, and the official name of the laboratory was settled as shown on 25th February, 1964. In April, 1968, the laboratory moved from an old building at Takatsuki to a new building on Uji campus.

In 1967, Dr. Tetsuro Fujita was appointed Assistant Professor in this laboratory. Dr. Kiyoshi Bessho was transferred to Assistant Professor of College of Liberal Arts, Kyoto University. In 1973, Dr. T. Fujita was promoted to Professor of Tokushima University, and also Dr. Masayuki Shibuya to Assistant Professor of Tokushima University. Dr. Kaoru Fuji was appointed Assistant Professor in this laboratory. In the present time (August, 1976), the staff members are as follows: Dr. Eiichi Fujita, Dr. Kaoru Fuji, Dr. Yoshimitsu Nagao, Dr. Manabu Node, and Mr. Masahito Ochiai (M. Pharm. Sci.).

Main subjects of research have been concerned with the physiologically active organic natural products. Works carried out since 1967 are classified and summarised.

I. Aklaloids

Systematic separation of the alkaloids from *Lythrum anceps* Makino (Lythraceae) utilizing a combination of treatment with McIlvaine's buffer and chromatography on a silicic acid column resulted in isolation of 13 alkaloids of the lythranine group and lythrancine-lythrancepine group. The structures of all of these new alkaloids *i.e.* lythranine, lythranidine, lythramine, lythrancine-I, -II, -III, -IV, -V, -VI, and -VII, and lythrancepine-I, -II, and III, including their absolute configuration were elucidated on the basis of the chemical and physical evidence. They were unique and novel type, which had never been found. Lythranine group has a biphenyl part, a piperidine ring, and a 17-membered ring in their molecule, while lythrancine-lythrancepine group has a biphenyl part, a quinolizidine ring, and a 13-membered ring. Lythrancepine-II was chemically transformed into a lythranidine derivative and the antipodal stereochemistry of the four asymmetric centres between two related groups of alkaloids (lythranine group and lythrancine-lythrancepine group) was indicated.

A review on the Lythraceous alkaloids was very recently published by E. Fujita and K. Fuji.

Total synthesis of the optically active natural O-methylthalicberine whose structure had been presented by E. Fujita *et al.* was accomplished.

II. Diterpenoids

After accomplishment of the chemical conversion of enmein, a major bitter diterpenoid isolated from *Isodon trichocarpus* Kudo, into *ent*-kaurane in 1966, many kinds of

diterpenoids were isolated from *I. trichocarpus* and *I. japonicus* Hara and their structures were elucidated. They are trichokaurin, isodocarpin, nodosin, isodotricin, oridonin, and trichodonin.

A formal chemical conversion of trichokaurin into *ent*-16-kaurene, atisine, garryine, and veatchine, the chemical conversion of enmein into *ent*-abietane, and the total synthesis of abietane were accomplished. An interesting epimerisation of enmein derivatives under mild alkaline conditions was studied.

The foregoing studies were summarised as a review by E. Fujita in 1968.

Several other minor diterpenoids were isolated from *I. japonicus* and their structures were clarified. They are epinodosinol, sodoponin, isodoacetal, and odonicin, besides the known isodonal and epinodosin. In addition, the stereochemistry of C-16 in isodotricin and the structure of ponicidin, another minor diterpenoid isolated from *I. japonicus,* were elucidated on the basis of the chemical and spectroscopic evidence.

Four new diterpenoids, lasiokaurin, lasiodonin, lasiokaurinol, and lasiokaurinin were isolated from *I. lasiocarpus* (Hayata) Kudo and their structures were determined.

A biogenetic classification of all diterpenoids isolated from the *Isodon* plants was suggested.

A formal chemical conversion of enmein into *ent*-16-kaurene, atisine, garryine, and veatchine, chemical conversions of enmein into *ent*-15-kaurene, *ent*-16-kaurene, and enmelol, of oridonin, enmein, nodosin, and trichokaurin into isodocarpin, of lasiodonin into epinodosin, and of sodoponin into epinodosinol were carried out and published.

Epimerisation of the enmein derivatives was investigated, and a retro-aldol type mechanism in which a common stereoelectronic requirement was satisfied in the transition state was suggested.

The total synthesis of a tumour inhibitor, enmein, and the plant hormons, gibberellin A_{15} and gibberellin A_{37} were attempted and carried out successfully. In the former total synthesis, an interesting intramolecular participation of the hydroxy groups in the Birch reduction of a 5-methoxy-tetralin derivative was observed. The δ-lactonisation from a 6,7-secokaurene material to an enmein-type skeleton proceeded very smoothly, which was reasonably explained by a transition state satisfying the stereoelectronic requirement. In the synthesis of gibberellins, an excellent demethylation agent was developed and the methoxy group was effectively used for the protection of an alcoholic hydroxy group. For the oxidation of the C-19 methyl group of the material, the hypoiodite reaction was successfully applied. The ring B contraction from the kaurane-type into gibberellane-type compound was investigated in detail. As the result of the preliminary experiments, the best material for this rearrangement was found, and it was converted into a key intermediate *i.e.* a norgibberellane aldehyde quantitatively.

Enmein and oridonin have been thought to be biosynthesised through the pathway similar to that of general cyclic diterpenes. After examination of changes in the quantity of major diterpenoids during growth of *I. trichocarpus* by gas chromatography and combined gas chromatography-mass spectrometry as a preliminary experiment, tracer experiments with the C-17 labelled several kaurene derivatives were carried out.

Thus, it was clarified that *ent*-16-kaurene was an important precursor to the diterpenes of *I. japonicus*, and a triplet oxygen was related to oxygenation at the allylic 15-position of *ent*-kaurene. Now, the tracer experiments with the radioactive kaurene derivatives having an oxygen function at C-7, -6, or -20 as well as having two oxygen functions, for instance, at C-7 and C-15, have been carried out or are being attempted.

The antitumour activity of some available diterpenoids and their derivatives against Ehrlich ascites carcinoma was investigated by their i.p. injection of 5–40 mg/Kg every 24 hours after tumour inoculation to mice for 7 days, followed by observation for 33 days. As the result, oridonin and lasiokaurin showed a significant activity. Enmein and its 3-acetate were also shown to be active. The relationship between activity and structure was analysed.

Subsequently, the antibacterial test was carried out, and oridonin, lasiokaurin, enmein, and enmein 3-acetate were shown to have activity against gram-positive bacteria.

The investigation on diterpenoids of Labiatae in this laboratory was extended from the *Isodon* to the *Teucrium* genus. Two new norditerpenes, teucvin and teucvidin, were isolated from *Teucrium viscidum* Blume *var. Miquelianum* (Maxim.) Hara, and their structures were elucidated. They were found to be diastereomers each other. The antibacterial activity of these norditerpenes were recognized.

The review series "The Chemistry on Diterpenoids" were published for 1967 to 1975 Part I (from 1964 on).

III. Miscellaneous

Harman, friedelin, and β-sitosterol were isolated from *Ophiorrhiza japonica* Bl. The structure and absolute configuration of calliterpenone was established, and the formula suggested previously by Chatterjee *et al.* was revised.

An improved method for methoxymethylation of alcohols under mild acidic conditions was developed. This is an acid-catalysed acetal exchange reaction using methylal and phosphorus pentoxide in chloroform.

New reactions with thallium (III) trinitrate (TTN) were developed. In the reactions of both *ent*-16-kaurene and *ent*-15-kaurene with TTN, allylic nitrates were formed, and [3,3]-sigmatropic rearrangement between them was observed. α-(3,4-dimethoxyphenyl)-β-nitroethylthioethane on treatment with 1.2 mol. equiv. of TTN in several alcohols at room temperature afforded α-(3,4-dimethoxyphenyl)-β-nitroethoxyalkanes in good yields. Thus, a new transformation of thioethers into ethers was achieved. Several thioacetals were dethioacetalised by the treatment with TTN under mild conditions for a short time to recover the parent carbonyl compounds in good yields.

A new method for a carbon-carbon bond formation at the β-position of 3,4-dimethoxy-*E*-β-nitrostyrene was developed. Thus, a selective synthesis of a sole geometric *E*-isomer of 3,4-dimethoxy-β-substituted-β-nitrostyrene was accomplished starting from 3,4-dimethoxy-*E*-β-nitrostyrene, *via* a Michael-type reaction with α-(3,4-dimethoxyphenyl)-β-nitroethylthioethane which was derived from the starting material by addition of ethane thiol and subsequent stereoselective elimination.

Publications

(* indicates an article published in Japanese)

I. Alkaloids

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II. Diterpenoids

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IV. Reviews

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