HISTORY OF JAPANESE NATURAL PRODUCT RESEARCH

S. SUGASAWA

Tokyo Research Laboratory, Tanabe Seiyaku Co.,
Toda-machi, Saitama-ken, Japan

INTRODUCTION

It is a privilege and great honour to be invited to speak about our research on natural products at this symposium. To be honest, however, it was only after considerable hesitation that I made up my mind to accept the invitation, because I know that I am not well qualified to be the spokesman, considering my research career in the past. In other words, I was constrained to act as such.

Before entering into the main subject, I should like to tell you briefly, how organic chemistry has developed in this country, since I feel that such a summary might be conducive to your understanding of the present status of our natural product research.

The pioneer of organic chemistry in Japan was William Nagayoshi Nagai. At the age of twenty-five he was sent to Germany as a Government student to study organic chemistry. He stayed there for about fourteen years, during the latter part of which he worked as an assistant to the famous A. W. Hofmann. He returned home not only with a knowledge of organic chemistry, but also with a beautiful "deutsches Mädchen, namens Fräulein Schuhmacher" as Mrs Nagai, having been persuaded to do so by his Professor—a very good teacher, indeed.

After some time he became professor at the present School of Pharmacy, University of Tokyo, and remained there until his retirement in 1921 at the age of seventy-six. During these thirty odd years he firmly established the organization for organic chemical research, and taught and trained many young students, among whom the late Professor Kondo and Professor Asahina are especially to be remembered. He was also the founder of the Japanese Pharmaceutical Society and acted as its president for many years. Since his day organic chemical research has remained a main feature of Japanese pharmacy.

Dr Umetaro Suzuki is the next to be mentioned. After graduation from the present School of Agriculture, University of Tokyo, he went to Germany and studied with the famous Emil Fischer, under whose guidance he succeeded in synthesizing a certain tripeptide for the first time.

He returned home in 1906 and was appointed professor at his Alma Mater. His main interest was focused upon the problem of nutrition of the Japanese. Beri-beri was then a common disease among us, the white rice eating people. As far back as 1910 he had pointed out that besides common proteins, carbohydrates, fats and minerals, there must be something in the

diet, which is essential for the maintenance of good health in animals. He published this view in the Japanese language only, and hence unfortunately, but deservedly, his paper eluded the notice of foreign scholars. It was indeed in the following year, that Funk made known his famous vitamin theory.

Suzuki later proved his view by extracting rice bran to make what he called "orizanin", named after *Oryza sativa*, which produced a dramatic effect against beri-beri. As you know oryzanin is vitamin B_1 in the crude state. That a number of famous vitamin chemists have since appeared in the agricultural chemical field has been due entirely to the influence of Suzuki.

Now comes Riko Majima. He trained at the present School of Chemistry, University of Tokyo, where Sakurai, the famous physical chemist, was professor in charge. Since Majima, however, was so fascinated by organic chemistry he began working on his own, after graduation in 1899, on Japan lacquer. A few years later he also went to Germany and worked in the laboratory of Harries, University of Kiel, where he learned the technique of ozonization. He then shifted to Willstätter at Zürich and learned how to carry out catalytic hydrogenation of unsaturated compounds.

In 1911 a new School of Chemistry was established in Tohoku University, at Sendai, and he was appointed to the new chair, as befitted his popularity and reputation as an excellent teacher and researcher. Our present day boom in organic chemical research in the field of pure chemistry is due mainly to Majima.

I propose to call these people the three Japanese giants in organic chemistry of the past (*Table 1*). They made great contributions to the development of organic chemical research and have played important rôles in the prosperity of their respective scientific societies.

Table 1. Three Japanese giants in organic chemistry

(1)	William Nagayoshi Nagai (1845–1929) Prof. School of Pharmacy, Univ. of Tokyo
(2)	Umetaro Suzuki (1874–1943) Prof. School of Agriculture, Univ. of Tokyo
(3)	Riko Majima (1874–1962) Prof. School of Chemistry, Tohoku Univ., Sendai

Now I shall come back to the main subject and speak about some studies in these scientific fields, mostly up to around 1940. This is only because it is far beyond my ability to summarize in a single lecture the many investigations carried out in recent years, say since 1950, and moreover I suppose that most of you are more or less acquainted with these recent developments. During the intermediate ten years we lived through the chaos and devastation of the war and its aftermath, and mere survival was an urgent problem for every one of us.

THE AGRICULTURAL CHEMICAL FIELD

As mentioned earlier Suzuki was the pioneer of natural product research in this field, followed by Yabuta and Goto. The majority of our active workers today are descended from them.

Their investigations were extensive, and most of them were concerned

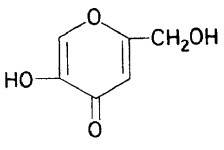
directly with the agricultural sciences and food stuffs. I shall mention just a few of them.

In 1913 Yabuta found kojic acid[1] in a kojic fermentation product, and in 1923 he established its structure as (I)[2].

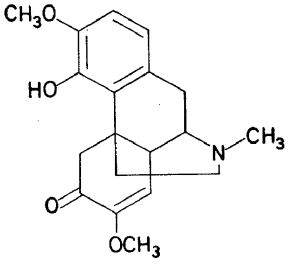
Yabuta's renowned work was the discovery of gibberellin. It was Kurosawa, who found in 1926 that the filtered fermentation broth of *Gibberella fujikuroi* causes elongation of the rice plant making it unfruitful, but he could not isolate the effective constituent. In 1938 Yabuta and Sumiki[3] succeeded in the isolation of what they thought to be the pure component, "gibberellin", and in collaboration with Aso and Tamura they devoted themselves to its structural elucidation. By 1940 they had established the presence of the fluorene nucleus. After the war this compound aroused the interest of foreign scientists and in the meantime I.C.I of England had succeeded in mass-producing it by fermentation. It is of interest that today this compound is being used as an agricultural chemical. It then became known that Yabuta's original compound was a mixture of several related substances which have now been separated and their constitutions established.

Goto is the sole exponent of alkaloid chemistry in this field. He started working on an alkaloid sinomenine in 1923 and devoted the remainder of his life to its study. This is the main alkaloid of *Sinomenium acutum* Rehder and Wilson, which was also investigated quite independently at about the same time by the late Kondo, and Ochiai.

Thanks to the intense efforts of these two teams it was shown that this base has structure (II) and belongs to the morphinan group of alkaloids, but with the opposite configuration to that of morphin.



(I)

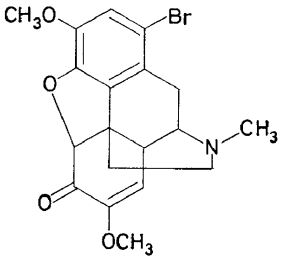


(II)

Based on this discovery Goto *et al.* succeeded in preparing more than ten compounds of the sinomenine group, which represented antipodes of the corresponding morphins, and showed that these two groups of alkaloid manifest quite different physiological properties.

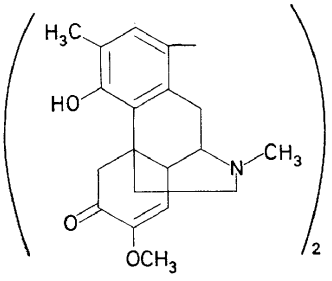
On the other hand Goto prepared a number of specific derivatives of sinomenine and studied their structures and reactions. As an example the bromination of sinomenine will be mentioned. One of the non-phenolic products obtained by treating sinomenine with bromine, followed by alkali was later found by Schöpf[4] to be 1-bromosinomeneine (III), in the light of his bromination study of dihydrothebainone. Thus Goto incidentally

succeeded in forming an oxide bridge between the 4 and 5 positions, and this method was later utilized to convert sinomenine into (+)-morphin, one of his brilliant achievements.



(III)

Besides sinomenine Goto also isolated several minor alkaloids, disinomenine, sinactine and tuduranine, and established their structures as (IV), (V) and (VI).



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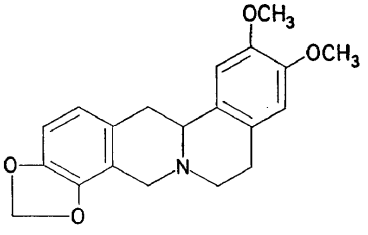

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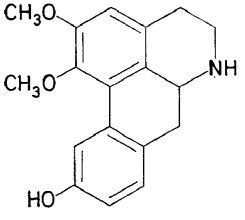


(VI)

The scope of his work on the chemistry of sinomenine is too extensive to be treated fully here, and for details, I advise you to consult his recent book *Sinomenine*, which he has recently compiled, and I am told, will be presented with the author's compliments to any of the participants of the Kyoto Symposium who is interested in this alkaloid. His address is as follows:—

Dr Kakuji Goto,

No. 235, Wakabayashi-cho, Setagaya-ku, Tokyo, Japan.

Several other studies are summarized in *Table 2*.

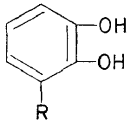
Table 2

K. Takahashi *et al.*[5]	Vitamin A
S. Hamano[6]	Vitamin A β-Naphthoate
	Vitamin A β-Anthraquinonecarboxylate
A. Ichiba, K. Michi[7]	Vitamin B_6
S. Takei, S. Miyajima[8, 9]	Rotenone
R. Yamamoto[10]	Pyrethrin
K. Mori[11]	Adenylthiomethylpentose
M. Onuki[12]	Stachyose
Z. Nikuni[13]	α- and β-Sorinin (*Rhamnus jap.* Maxim)
E. Nishikawa[14]	Mellein (*Asper. melleus* Yukawa)
M. Tsujimura[15]	Teacathechin II
Y. Oshima[16]	(+)-Casuarin (*Casuarina equisetifolia*)

THE PURE CHEMISTRY FIELD

The majority of those who were, or are, actively engaged with natural product research in this field belong directly or indirectly to the Majima school.

In the chemistry laboratories of Tohoku University, Majima, with several of his students, resumed the study on Japan lacquer. Thus urushiol, the main constituent of *Lacca japonica* obtained from *Rhus verniciflua* Stokes, was found to comprise 2,3-dihydroxy-1-pentadecenylbenzene (VIIa) and its dihydro- (VII*b*) and dehydro- (VII*c*, *d*, *e*) derivatives, of which the first forms the main component[17]. The techniques of ozonization and catalytic hydrogenation which he brought back from abroad did good service in this research. This achievement made Majima famous and many talented young students flocked to work with him, including Dr Kotake, who is acting as chairman of this symposium.



(VII)

a: R= $-(CH_2)_7-CH=CH-(CH_2)_5-CH_3$

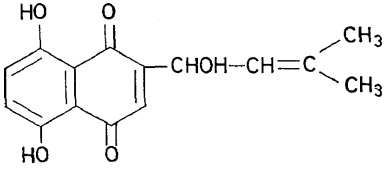
b: $-(CH_2)_{14}-CH_3$

c: $-(CH_2)_7-(CH=CH-CH_2)_2-C_2H_5$

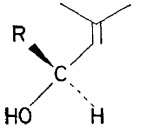
d: $-(CH_2)_7-CH=CH-(CH_2)_4-CH=CH_2$

e: $-(CH_2)_7-CH=CH-CH_2-(CH=CH)_2-CH_3$

Apart from her work on the pigment of the sea-urchin, Dr Kuroda carried out chemical investigations under Majima's guidance on two pigments known from olden days, which were extracted from roots of "Murasaki" (*Lipospermum erythrorhizon* Siebold and Zuccarini), and from



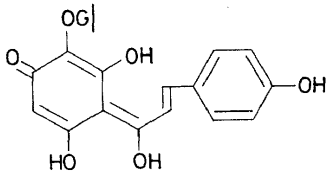
(VIII)



(VIII′)

flowers of "Benibana" (*Carthamus tinctorius* Linné). They were called shikonin[18a] and carthamin [18b] respectively. She put forward the expression (VIII) for the former, of which the absolute configuration (VIII') of the secondary alcohol group was recently worked out by Nakazaki *et al.*[19]

For carthamin she had put forward the formula (IX). Recently, Seshadri[20] proposed that the term carthamin should be given to the yellow precursor, which turns to the red pigment, Kuroda's carthamine, by the agency of polyphenoloxidase. He proposed to call the red pigmant carthamone, to which he gave the revised structure (X) as compared to (IX) by Kuroda. Carthamin-Seshadri is therefore (XI).



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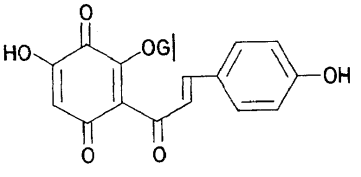
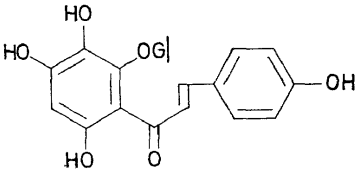


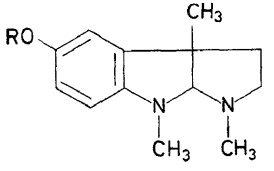
(X)



(XI)

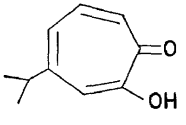
Around 1920 Majima, Ono and Unno[21] succeeded in the preparation on a laboratory scale of indole by passing a mixture of aniline vapour and acetylene through porcelain tubing heated in an oven. Though the yield of indole was by no means good, they thus succeeded in obtaining indole in hundred gramme quantities from easily accessible materials.

Majima and Hoshino then made an extensive study of the Grignard reaction with indole and its derivatives and established methods for preparing β-substituted indoles and indolenines. Independently Hoshino then ingeniously extended this work to the synthesis of eserine. In 1935 he, with his associate Kobayashi[22], succeeded in the synthesis of ($\pm$)-eserethole (XII)-methiodide from 5-ethoxytryptamine, and in its optical resolution, in providing synthetic support for Sir Robert Robinson's revision (XIII) to the structure of eserine proposed by the Polonowskis of France in 1923.



(XII): R = C_2H_5

(XIII): =—OC—NHCH$_3$



(XIV)

His success in the synthesis of bufotenine[23], and his establishment of the structure of abrine[24], may be regarded as "by-products" of the above achievement.

Hirao isolated hinokitin from the essential oil of *Chamaecyparis taiwaensis* Masamune and Suzuki, which was supposed to be the red pigment of the heart-wood. In 1936 Nozoe, the successor to the chair of Majima, but in Formosa at the time, found that hinokitin is a iron complex of what he termed hinokitiol, and after elaborate investigation he established that hinokitiol is an isopropyltropolone (XIV)[25]. After the termination of the war it was revealed that Erdtman of Sweden had also isolated three compounds of this type, α-, β- and γ-thujaplicin from Swedish *Thuja plicata*, of which the β-isomer was found to be identical with hinokitiol.

Among many other works from the Majima school several are listed in *Table 3.*

Table 3

H. Nomura[26]	Gingerone (*Zingiber officinalis* Roscoe)
S. Kawai[27]	Egonol (*Styrax jap.* Sieb and Zucc.)
S. Fujise[28]	Matteuchinol, Desmethoxymatteuchinol (*Matteuchia orientalis* Trev.)
M. Murahashi[29]	Matsutakealcohol
H. Suginome[30]	Aconitum alkaloids
M. Kotake[31]	Strychnine
S. Akabori[32]	Methionol

THE PHARMACEUTICAL FIELD

The Nagai-Kondo school and the Asahina school were the main academic groups in the Japanese pharmaceutical field engaged on natural product research.

Nagai [1845–1929]–Kondo [1877–1963] school

Nagai was born in the Tokushima prefecture, where natural indigo has long been produced. He made some contributions to the promotion of this industry, but his main interest was directed towards chinese drugs, their extraction and the chemical and pharmaceutical study of their constituents.

For instance root bark of *Paeonia moutan* Ait. was long known for its analgesic and spasmolytic activity. He isolated a crystalline substance named paeonol from its ethereal extract and proposed the structure 2-hydroxy-4-methoxyacetophenone. Confirmation of this structure by synthesis was provided by Tahara, one of his early students, and constitutes the first example in Japan of the use of synthesis to establish the structure of a natural product.

I can not speak about Nagai without mentioning his work on ephedrine, the effective constituent of the Chinese drug "Ma-Huang" (*Ephedra vulgaris*), which he isolated in 1885 and showed to be α-hydroxy-β-methylamino-n-propyl-benzene. This was proved by his synthesis starting from benzaldehyde and nitroethane, followed by optical resolution.

From "Ma-Huang" he also isolated norephedrine, norisoephedrine, methylephedrine and methylisoephedrine, whose structures were all

elucidated. He also discovered the isomerization between the ephedrines and the corresponding iso-bases.

At his request the late Professors Miura and Takahashi, both at the School of Medicine, University of Tokyo, studied its pharmacological properties and found its mydriatic action. It was in 1924, only five years prior to Nagai's death, when Chen and Schmidt discovered its sympathomimetic activity and thus this alkaloid became widely used therapeutically as Ephedrine-Nagai to treat asthma in this country.

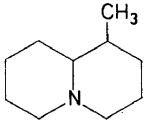
In 1927 Nagai visited Germany for the third time and delivered a lecture on ephedrine at the German Chemical Society meeting held at "Hofmann-Haus" Berlin, and in 1929 he and Kanao, his most competent assistant, published their paper "Über die Synthesen isomeren Ephedrine und ihrer Homologe"[33].

Sophora flavescens Ait., a well-known domestic medicine of bitter taste, is a wild herb growing on the hills and in the fields of this country. In 1885 Nagai isolated from its dried root a water-soluble dextrorotatory liquid base, which he named matrine. Its correct analysis was given by him and Kondo in 1903 but their efforts to elucidate its structure met with little success, and the work was suspended.

In 1918 the late Professor Kondo, who was the leading alkaloid chemist in Japan and successor to Nagai's chair in the university, embarked on its structural study in collaboration with Ochiai and Tsuda. They recognized its lactam nature and succeeded in cleaving the ring with potassium hydroxide to form potassium matrinate, which became a key intermediate for further study.

Thus on zinc dust distillation the hydrochloride salt of matrinic acid afforded a liquid base, which, as was suggested by Schöpf, was found to be identical with his β-lupanine with the established structure (XV), suggesting the presence of a quinolicine ring system in matrine.

When potassium matrinate was distilled with soda-lime, two basic decomposition products, α- and β-matrinidine were produced. The α-compound was considered to be either (XVI) or (XVII).



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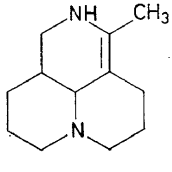
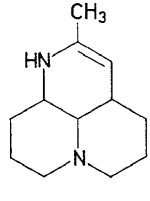


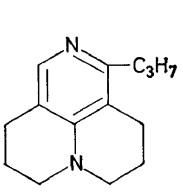
(XVI)



(XVII)

Tsuda then succeeded in extending the *N*-α-methyl side-chain of tetradehydro-α-matrinidine to the corresponding *N*-α-n-propyl derivative (XVIII or XIX), which was proved to be identical with dehydro-decarbonylmatrinane derivable from matrine, whose n-propyl side-chain very probably arose from fission of the lactam ring. Based on these data matrine could now be expressed by either (XX) or (XXI). Kondo and Tsuda

preferred the former because of the fact that in none of the lupinane type of alkaloid is the second nitrogen atom directly attached to the quinolicine ring[34].



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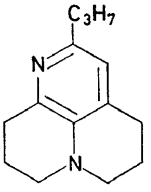

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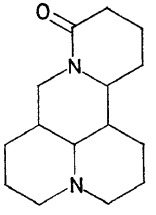

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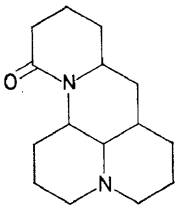
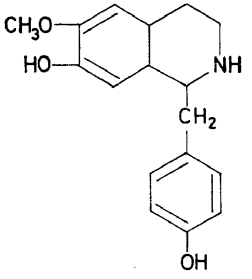


(XXI)

It was in later years that Tsuda *et al.* provided synthetic support for the above view through their total synthesis of matridine, and they elucidated the stereochemistry of matrine, matridine and the corresponding allo-compounds. Very recently a total synthesis of (±)-matrine was described by Mandell *et al.*

Among Kondo's studies of menispermaceous alkaloids, those on biscoclaurines[35] and on lycorine[36] are most important.

In 1929 the late H. Kondo and the late T. Kondo isolated an alkaloid named coclaurine from *Cocculus laurifolius* D. C. indigenous to the southern part of Kyushu island, Japan. Since then its structure has been established as (XXII). This base forms an important key compound which throws light on the biosynthesis of the biscoclaurine alkaloids.



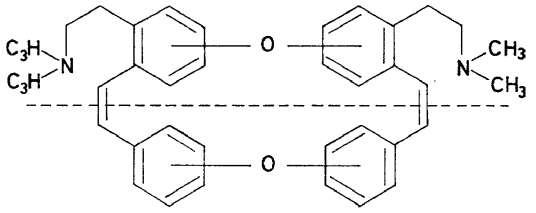
(XXII)

Kondo and his collaborators had further isolated many biscoclaurine bases, for instance trilobine, isotrilobine, dauricine and tetrandrine, and found that they all furnish one and the same 2-methoxydiphenylether-3, 4'-dicarboxylic acid on being oxidized.

During his structural study of oxyacanthine, another biscoclaurine alkaloid, Bruchhausen in 1931–1933 achieved the "horizontal" degradation with ozone of the methine base of the alkaloid, firmly establishing its structure as schematically shown in (XXIII).

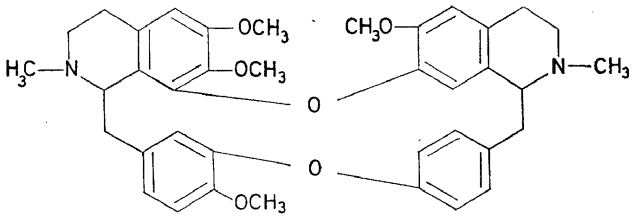
Kondo *et al.* applied Bruchhausen's method to their own studies, and structures of all biscoclaurine bases under investigation were thus made clear. For instance the following expression (XXIV) represents tetrandrine.

It was in later years (1949–1960) that Tomita and his collaborators succeeded in cleaving the diphenylether linkage with metallic sodium and



(XXIII)

liquid ammonia, and in establishing the stereochemistry at the asymmetric centres of the original bases. They are currently engaged in the total synthesis of these biscoclaurine bases.



(XXIV)

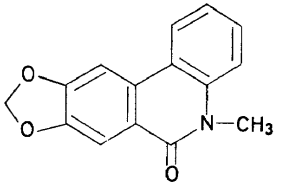
Lycoris radiata Herb., an amaryllidaceous herb, is indigenous to warm districts of Japan. It was the late Professor Morishima who first isolated a crystalline base termed lycorine from tubers of this herb. Its correct analysis, $C_{16}H_{17}O_4N$, was given by Asahina and Sugii.

Kondo and Uyeo started the structural study of lycorine and, after Späth, obtained phenanthridine by zinc dust distillation. Thus the presence of the phenanthridine skeleton in lycorine became probable.

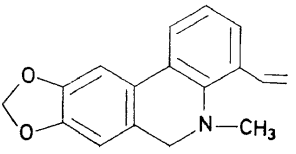
They further carried out the Hofmann degradation of lycorine and obtained a methine base with simultaneous loss of two molar equivalents of water. The product, "lycorineanhydromethine", afforded a phenanthridone derivative (XXV) after oxidation and decarboxylation. The structure of (XXV) was confirmed by synthesis.

On being distilled with zinc dust the dihydromethine furnished 1-methyl and 1-ethylphenanthridine. Thus the structure of lycorineanhydromethine was established as (XXVI), and hence the nitrogen atom of lycorine must be common to two rings. This led to the partial formula (XXVII) for

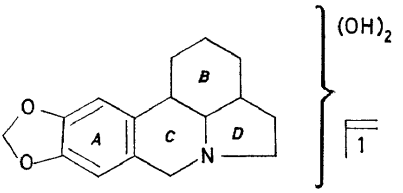
lycorine, since the latter has two hydroxyl groups and one readily reducible double bond.



(XXV)

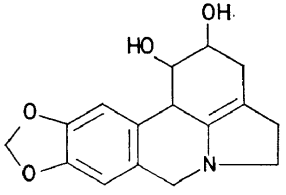


(XXVI)

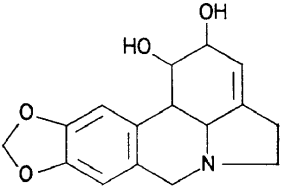


(XXVII)

Kondo and Katsura have further shown that the two hydroxyl groups are vicinal. Considering the easy aromatization of the *B*-ring of lycorine during the Hofmann degradation reaction, they provisionally put forward formula (XXVIII) for lycorine, as compared with the present one (XXIX), taking into account the u.v. data that the double bond is not conjugated with the aromatic *A*-ring.



(XXVIII)



(XXIX)

Uyeo and Takeda have carried on Kondo's work and established the the structure and stereochemistry of no less than fifteen alkaloids of *Lycoris radiata* during the last ten years.

Asahina school

No one will contradict me if I say that Professor Asahina is the greatest natural product chemist we have had since the introduction of organic chemistry in this country. He was born in Tokyo in 1881 and is still going strong. Today at the age of eighty-three the microscope is still his favourite daily companion.

He graduated from the present School of Pharmacy, University of Tokyo in 1905 and started his research career as an assistant to Shimoyama. A few years later he visited Willstätter and worked on chlorophyll and haemin.

In 1912 he returned home and succeeded to the chair of his professor, who died at the beginning of the same year, first as assistant professor and then as full professor, a post which he occupied until April, 1941, when he retired.

During these years he first worked on Chinese drugs with conspicuous success. It was around 1925, when he first started working on taxonomy and the chemical investigation of the constituents of various lichens, a study which developed into his life's work. He still continues this work as his hobby.

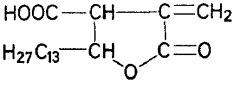
The scope of his work is extensive, involving studies of essential oils, flavones and allied compounds, alkaloids and lichen substances. For the sake of brevity studies on the lichen substances only will be described here.

Before he began work on the lichen substances in 1925, *Die Flechtenstoffe* written by Zopf in 1907 and some of Hesse's papers on lichen substances appearing in *Journal für praktische Chemie* up to 1913, were the only publications describing lichens and lichen substances. Thus a number of lichen substances had already been recorded, but their chemical structures had been left almost untouched. Today some ninety-five lichen substances with established chemical structures are known, of which fifty-three were worked out by Asahina, the late Professor Asano, one of his early students, and their collaborators. Their investigations revealed the biogenetic rules in the structure of lichen substances. Moreover, the microchemical method developed by Asahina became an important means for the classification of lichens.

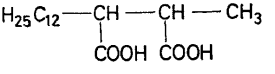
For the sake of brevity the compounds studied by them will be classified according to their structures into several groups, each of which is illustrated by two representative compounds, in *Table 4*[73].

Table 4. Lichen substances

Group 1: Fatty acids and their lactones

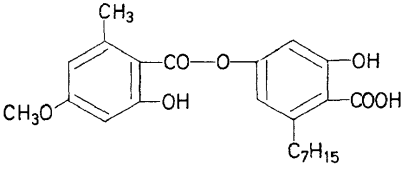


(XXX)
Protolichesteric acid
(*Cetraria islandica* Ach.)
M. Asano (1927)

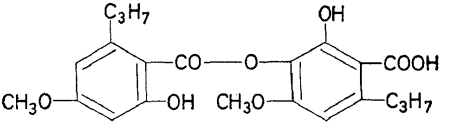


(XXXI)
Roccellic acid
(*Roccella tinctoria* L.)
M. Asano *et al.* (1939)

Group 2: Depsides
Orcinol type



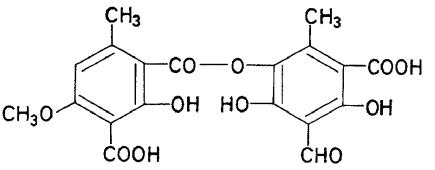
(XXXII)
Sphaerophorin
(*Spaerophorus fragilis* Pers.)
Asahina, Hashimoto (1936)



(XXXIII)
Sekikaic acid
(*Ramalina geniculata* Hook and Tayl.)
Asahina, Nonomura (1933)

Table 4—contd.

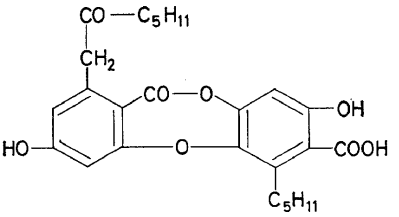
Group 2—contd
β-Orcinol type



(XXXIV)

Thamnolic acid
(*Thamnolia vermicularis* (Sw.) Schaer.)
Asahina, Hiraiwa (1936–1939)

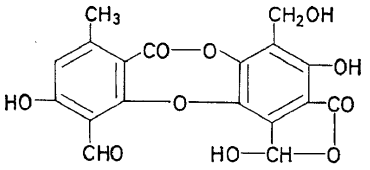
Group 3: Depsidones
Orcinol type



(XXXV)

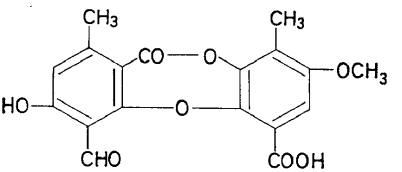
Physodic acid
(*Parmelia physodes* Ach.)
Asahina, Nogami (1935)

β-Orcinol type



(XXXVI)

Salazinic acid
(*Parmelia cetrata* Ach.)
Asahina, J. Asano (1933)

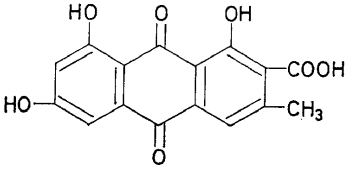


(XXXVII)

Psoromic acid
(*Alectoria sulcata* Nyl.)
Asahina, Shibata (1939)

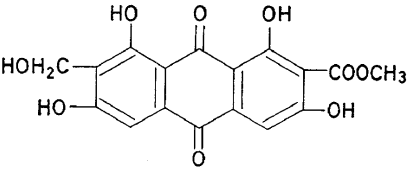
Table 4—contd

Group 4: Anthraquinones, xanthones and benzofurans



(XXXVIII)

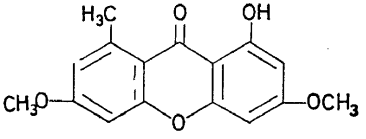
Endocrocin
(*Nephromopsis endocrocea* Asahina)
Asahina, Fuzikawa (1935)



(XXXIX)

Rhodocladonic acid
(*Cladonia spp.*)
Shibata (1941)

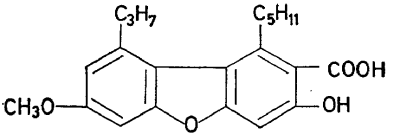
Xanthone



(XL)

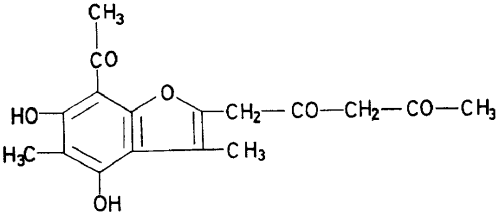
Lichexanthone
(*Parmelia formosana* Zahlbr.)
Asahina, Nogami (1942)

Benzofurans



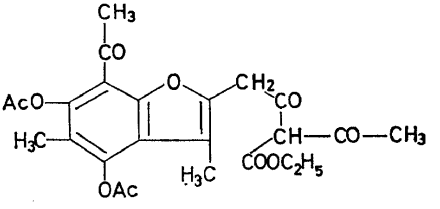
(XLI)

Didymic acid
(*Cladonia floerkeana* (Fr.))
Shibata (1944)



(XLII)

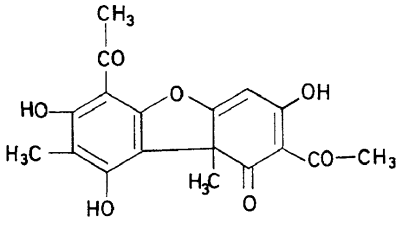
Decarbousnic acid



(XLIII)

O-Diacetylusnic acid
ethoxide
Asahina, Yanagita, Maeda, Okazaki (1937–43)

Table 4—contd



(XLIV)

Usnic acid
Robertson *et al.* (1937)
Schöpf *et al.* (1938–41)
Barton *et al.* (1956) (Synthesis).

There has been a long dispute over the structure of usnic acid, and several formulae have been advanced by various workers. However, Barton's brilliant synthesis of this compound settled the problem in favour of the expression (XLIV) due to Robertson *et al.* and Schöpf *et al.*, whose proposal of this formula rested partly upon the structures of two degradation products of usnic acid, *i.e.* decarbousnic acid and *O*-diacetylusnic acid ethoxide, the structures of which were established by Asahina *et al.* as (XLII) and (XLIII) respectively.

MISCELLANEOUS STUDIES

Since olden days we have eaten "Kombu" (*Laminaria japonica*), a kind of seaweed, which has also been used extensively to make stock. In 1909 Ikeda (1864–1936), of the School of Chemistry, University of Tokyo, attempted to uncover the secret of its delicious taste and eventually he succeeded in isolating a solid, which he thought to be responsible, together with large amounts of mannitol. This solid was found to be (+)-glutamic acid[38] and this discovery was the inception of the commercial production of M.S.G. under the trade-name of "Ajinomoto", which developed into one of the greatest enterprises in Japan. A large quantity of its preparation is exported all over the world.

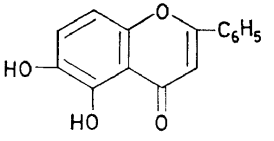
Apart from his structural study of domestine, an alkaloid of *Nandina domestica* Thunb., Kitazato[39] isolated a triterpenoid hederagenin from *Spindus mukurosi* Gartner. After elaborate study he put forward a tentative formula, and also one for oleanolic acid which he was investigating at the same time. These studies are worth mentioning as being pioneering work in Japan in this field, though the formulae he advanced underwent some revision afterwards.

Oyamada[40] isolated fustin from *Rhus succendanea* Linne *var. japonica* Engler and established its structure as 3,7,3′,4′-tetrahydroxyflavanone. His one-step synthesis of 3-hydroxyflavones from chalcones by the agency of alkaline hydrogen peroxide, a method which was also found independently by J. Algar *et al.*, is well known as the Alger-Flynn-Oyamada method.

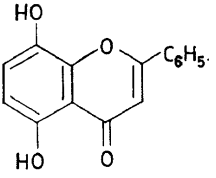
Apart from his work on wogonin, Hattori, Professor Emeritus of botany at Tokyo, isolated primetin in a state of purity from *Primura farinosa* L. *var.*

modesta Makino. This product had been obtained from the same plant previously, but in a crude state, by the late Professor Shibata *et al.* Based on degradation studies and u.v. spectral data, Hattori *et al.* designated it as 5,6-dihydroxyflavone (XLV)[41]. I attempted its synthesis, starting from hemipinic acid, and obtained a compound which by analysis, was a monomethyl ether of a dihydroxyflavone but was not identical with primetin-monomethyl ether. Consequently, I assumed this compound to be 5-hydroxy-8-methoxyflavone, in that primetin was 5,6-dihydroxyflavone[42].

Some year later Baker pointed out that the compound I synthesized was a 5,6-dihydroxyflavone derivative, and that primetin is in reality 5,8-dihydroxyflavone (XLVI), a conclusion which was confirmed by his synthesis of 5-hydroxy-8-methoxyflavone[43]. 5,8-Dihydroxyflavone was synthesized later by two groups of Japanese workers, Nakazawa *et al.*[44], and Horii *et al.*[45] at about the same time, but quite independently, providing further support for Baker's view.

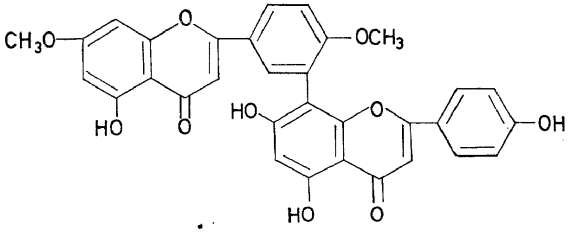


(XLV)



(XLVI)

In the 1932s, Furukawa[46] isolated a flavonoid pigment, which was afterwards named ginkgetin by Baker, from the yellowed leaves of *Ginkgo biloba* L. and erroneously assumed it to be 5,8-dihydroxy-4′-methoxyflavone. Later in 1941 Nakazawa obtained the pigment in a pure state by means of its sparingly soluble potassium salt, and established the formula $C_{32}H_{22}O_{11}$. From degradation experiments he assumed it to be bisgenkwanin[47]. Though his assignment was not correct, this was the first description of a biflavone



(XLVII)

in the literature. Baker began the structural study of this pigment in 1946, and in 1959 put forward the expression (XLVII)[48], which was later supported by Nakazawa's total synthesis[49].

Some more biflavones, *e.g.* hinoki-, kaya, sotetsu- and ametoflavone were

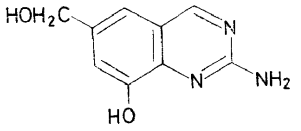
found in leaves of various conifers by Kariyone, the first discoverer of eburicoic acid in *Formes officinalis*, and Kawano[50]. These biflavones, except hinoki-flavone, have the same skeleton as ginkgetin, since, when completely methylated, they all give one and the same compound. From the viewpoint of chemotaxonomy the discovery of these biflavones are not without interest.

NATURAL PRODUCTS FROM ANIMALS

The natural products so far described have all been plant products. Though those from the animal kingdom are comparatively rare, I cannot omit them altogether in this review.

First to be mentioned is surely tetrodotoxin, which was isolated from the ovary of globe fish and studied by Tahara[51] (1855–1935) in 1884. The toxin he isolated was, however, so highly impure, that his structural study was fruitless. In 1952 Tsuda and Kawamura[52a], and also Yokoo[52b], succeeded in obtaining this toxin in a pure, crystalline state, which made it possible to determine the correct composition. Arakawa, Nagai and Hirata obtained one and the same toxin from various globe fish.

By alkaline hydrolysis Tsuda *et al.* obtained a base, $C_9H_9O_2N_3$, together with a large quantity of oxalic acid. This base was shown to be (XLVIII), a conclusion which was confirmed by synthesis[53], rendering the existence of the quinazoline ring system in tetrodotoxin highly probable. Hirata *et al.* have also independently made an extensive study of this toxin, and the recent results worked out by these two research groups will be reported at this symposium.



(XLVIII)

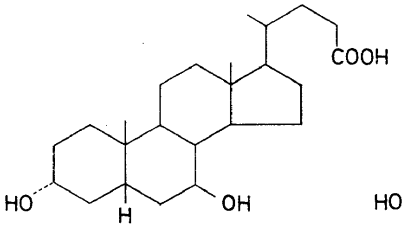
Apart from his discovery of the strong digestive enzyme, Taka-diastase, from *Aspergillus oryzae* in 1894, Takamine's (1854–1922) name became immortal when with Uenaka he succeeded in 1900 in the isolation of adrenalin from the adrenal gland in the pure crystalline state[54]. This was the first hormone obtained in a pure crystalline state. He lived in the States for many years and died in 1922 in New York at the age of sixty-seven. He did much to promote friendship between America and Japan.

It is also to be remembered that in 1916 Tsujimoto discovered and isolated squalene for the first time from shark liver oil[55].

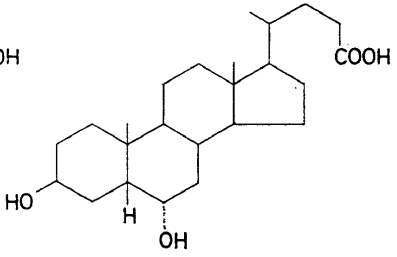
Sh'an Su (or Toad-cake), a well-known Chinese drug prepared from the secretion of a kind of toad, is said to act as cardiotonic. Kotake and Kuwata[56] isolated two components, cinobufagin and cinobufotalin. They also obtained gamabufotalin from *Bufo vulgaris formosus* and showed that they are all steroidal compounds, and advanced tentative formulae for them.

The late Shimizu (1889–1958), Professor of Biochemistry at the School of Medicine, Okayama, worked on bile acids under the late Professor Wieland during 1920–23. He continued this work after coming home and for thirty-five years until his sudden death in 1958 he with his associates isolated and

characterized many new bile acids from various animals, of which ursodeoxycholic acid (XLIX)[57] and β-hyodeoxycholic acid (L)[58], isolated from bear and pig respectively are the two first bile acids having a β-oriented hydroxyl



(XLIX)



(L)

group in the molecule. His work is being carried on by Kazuno of the School of Medicine, Hiroshima, and by Yamazaki of the School of Medicine, Tottori.

I am very much afraid that I might have omitted some important studies which should have been included in this review, and I apologize to the authors concerned.

Finally, I have to thank my friends and colleagues who helped me in preparing this review.

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