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<td>Authors</td>
<td>Fujita, Eiichi</td>
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The Chemistry on Diterpenoids of *Isodon* Species

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Received July 4, 1968

This review deals with the chemical works on diterpenoids of *Isodon* species mainly carried out in our laboratory.

The leaves of *Isodon trichocarpus* Kudo and *Isodon japonicus* Hara (labiatae) have been used as common household medicine for gastrointestinal disorder in Japan. Japanese name of this medicine is “enmeiso” which means an effective grass for prolongation of one’s life. Isolation of enmein, a main diterpenoid bitter principle of the leaves, was reported in 1958 independently and simultaneously by three groups in Japan, and the name “enmein” came from the Japanese name of the plant medicine.

The structure and absolute configuration of enmein have been elucidated as formula 1 on the basis of chemical evidences and X-ray analysis of dihydroenmein-3-acetate-6-bromoacetate.

As one of the chemical evidences, a chemical conversion of enmein into (-)-kaurane was attempted and carried out by us.

Enmein may be biogenetically regarded as a product derived from a diterpene hydrocarbon, (-)-kaurene, by the oxidative cleavage of the ring B and recyclization. (Scheme 1)

\[ (-)-I \rightarrow HO \rightarrow HO \rightarrow HO \]

\[ (-)-Kaurene \]

Hence, the conversion of enmein into (-)-kaurane (2), whose absolute configuration has been established, without any changes of the stereochemistry of the asymmetric centers would supply a chemical evidence for the absolute configuration of enmein. Moreover, this chemical interconversion would constitute a chemical recyclization of the biosynthetically cleaved ring B. These interests prompted us to carry out the conversion.

I. THE CHEMICAL CONVERSION OF ENMEIN INTO (-)-KAURANE

As a key reaction of this series, the acyloin condensation was chosen, and a

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compound 3, which has no oxygen function except useful lactone and ester, was adopted as the material for the reaction.

Bisdehydrodihydroenmein (5), an oxidation product of dihydroenmein (4), was subjected to alkaline hydrolysis to give dihydroenmeinenonoic acid (6) accompanied by minor products 7 and 8. The methyl ester of the enonoic acid on hydrogenation gave diketolactone ester 9, which on treatment with ethanedithiol and boron trifluoride gave monoethylene dithioketal 10 as a major product and bisethylenedithioketal 11 as a minor product. The spectral data confirmed these structures. Monoethylenedithioketal 10 was desulfurized with Raney nickel in ethanol to give a ketolactone ester 12, while bisethylenedithioketal 11 was treated in the same way to give an isopropyl derivative 13. Further thioketalization followed by desulfurization of compound 12 led to the cleavage of the D-ring to give 13. (Scheme 2)

Thus, the conversion of the diketolactone ester 9 into the desired lactone ester 3 resulted in failure, so attention was turned to an attempt for the first reduction
of the carbonyl group at C-15 to methylene.

Dihydroenmein diacetate 14 was subjected to a partial hydrolysis with oxalic acid to give dihydroenmein-3-acetate (15), which on chromic acid oxidation yielded dehydrodihydroenmein-3-acetate (16). The latter was also yielded from dihydroenmein diacetate (14) by direct partial oxidation with chromic acid in aqueous acetic acid. The acetate 16 on hydrolysis with an equivalent methanolic potassium hydroxide solution gave dehydrodihydroenmein (17). The thioketalizations of dehydrodihydroenmein and its 3-acetate followed by desulfurization of the thioke-tals with Raney nickel afforded deoxo compounds, 18 and 19. Deoxo derivative 18 was also obtained by hydrolysis of 19. Compounds 17 and 18 on acetylation gave acetates 16 and 19, respectively. (Scheme 3)

The following steps which led to the key material for the acyloin condensation consisted of ring opening of the δ-lactone and subsequent removing of the oxygen function at C-3. Dehydrodeoxodihydroenmein 18 was successfully converted into the desired ester 3 as shown in the Scheme 4.

Now, we carried out acyloin condensation of the lactone ester with sodium in liquid ammonia, and got four products. A substance which has largest R<sub>f</sub> value on thin layer chromatogram was shown to have the molecular formula of C<sub>20</sub>H<sub>20</sub>O. The IR and NMR spectral analyses led to an ether structure 21 and a chemical evidence, that this substance was identical with the ether which was derived from kaurane-6β, 20-diol (22) by treatment with p-toluenesulfonyl chloride in pyridine, supported the structure.

The diol 22 which gave second largest R<sub>f</sub> value on thin layer chromatogram was yielded rather abundantly in a suitable condition. In the NMR spectrum of diacetate 23, the methylene protons on C-20 appeared as AB type at δ 4.32 and 4.59 ppm (J=12.0 c/s) and a proton on C-6 as an octet at δ 5.27 ppm, the coupling constant value (J=5.0, 9.5, and 11.0 c/s) of which enabled the assignment of
equatorial bond to the hydroxy group at C-6.

6-Hemiketal product had molecular formula C_{20}H_{32}O_{3} and its NMR spectrum exhibited singlet signals of C-20 methylene protons at \( \delta \) 3.89 and of C-7 at \( \delta \) 3.30 ppm. The treatment with deuteroxide showed the presence of two hydroxy groups in the molecule in its NMR investigation. The compound on acetylation gave monoacetate 25, whose IR spectrum still showed the presence of one hydroxy group, which was also recognized by disappearance of the corresponding signal in the NMR spectrum when treated with deuteroxide. The C-7 singlet signal at \( \delta \) 3.30 ppm of the original alcohol caused a paramagnetic shift to \( \delta \) 4.69 ppm, but the two protons signal at \( \delta \) 3.89 ppm (C-20 H2) did not change the chemical shift. These data confirmed 6-hemiketal structure 24 of the product.

Finally, the main product, 7-hemiketal compound had the same molecular formula C_{20}H_{32}O_{3} as the foregoing product and its NMR spectrum in pyridine showed AB type quartet assignable to C-20 methylene protons at \( \delta \) 3.90 and 4.11 ppm, the coupling constant of which was 11.0 c/s. A doublet assignable to C-6 proton was also observed at \( \delta \) 4.17 ppm (J=4.0 c/s). Acetylation of the compound
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gave monoacetate 27 which kept still one hydroxy group. The doublet signal of C-6 proton appeared at δ 5.01 ppm splitting with coupling constant of 4.5 c/s. From these data the structure 26 of 7-hemiketal-6-ol was reasonably assigned to the main product. The B-ring can exist only as a boat form, so the stereochemistry of the C-6 hydroxy group was reasonably estimated as β from NMR spectrum.

Kaurane-6, 20-diol (22) on oxidation with chromic acid-pyridine complex easily gave a keto aldehyde 28, but the subsequent Wolff-Kishner reduction was unsuccessful; the small scale preliminary tests with the keto-aldehyde 28 of the methods of Djerassi *et al.* and of Nagata *et al.* gave a mixture of many kinds of undesired products, provided that only a small peak, the retention time of which was identical with that of (−)-kaurane (2), appeared in the vapor-phase chromatogram of the hydrocarbons from the reaction product in the latter case.* (Scheme 5)

So, we gave up the route from diol and chose 7-hemiketal-6-ol compound 26, the major acyloin product, as the material to (−)-kaurane.

The material 26 was heated with 98.5 % hydrazine prepared by Kusama’s method and anhydrous ethanol in a sealed tube at 170–180°, then sodium ethoxide was added and heated again to decompose the hydrazone. The reaction gave the expected kaur-6-en-20-ol (29) as crystals. The kaurenol 29 and its acetate 30 on catalytic hydrogenation gave kauran-20-ol (31) and its acetate 32, respectively. Acetate 32 on hydrolysis gave alcohol 31. The oxidation of the saturated alcohol with chromic acid-pyridine complex under nitrogen afforded a corresponding aldehyde 33. The heating of a mixture of aldehyde and 98.5 % hydrazine in anhydrous ethanol which was sealed in a tube for 42 hours at 170–180°, subsequent decomposition of the resulting hydrazone by heating for two days with added potassium hydroxide, and column chromatography of the reaction products on alumina followed by recrystallization gave needles of a hydrocarbon, m. p. 87.5–88.5°, [α]D −28.7°.

The compound was identified with (−)-kaurane (2) by the mixture melting point determination, IR spectra, vapor phase chromatograms, mass spectra and ORD curves comparisons. Thus, the conversion of enmein into (−)-kaurane was

* Recently, we tried Nagata’s modification of Wolff-Kishner reduction on isokaurene-6, 20-dione and got (−)-kaurane in a moderate yield. (Unpublished.)
accomplished, and the absolute configuration of enmein was chemically established\(^1\). (Scheme 6)

This chemical conversion was also carried out independently by Professor Okamoto and co-workers\(^{11}\) of University of Tokyo. Their method is almost same with our's. But the route of the synthesis of lactone ester 3 is different from ours. The route is shown in Scheme 7.

Another different point from us is that their acyloin condensation was carried out by heating the material with sodium in xylene.

**II. OTHER DITERPENOID COMPONENTS**

As the chemical conversion of enmein into \((-\))-kaurane was accomplished, the crude extract from which enmein was isolated was investigated to check the other components.

The previous investigations of *Isodon trichocarpus* KUDO and *Isodon japonicus* HARA in Japan reported only the isolation of some crystalline compounds, but no detailed investigations were carried out.

Now, we isolated ten kinds of diterpenoids including enmein. Table 1 shows their physical constants and the other data.

Hitherto, enmein has been isolated from *Isodon trichocarpus* and always contaminated with some dihydroenmein. We isolated very pure enmein from the leaves of *Isodon japonicus*\(^{12}\).

Enmein-3-acetate (35) has been derived from enmein in the early investigation.
**Table 1**

<table>
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<tr>
<th>name</th>
<th>mol. formula</th>
<th>m. p.</th>
<th>((\alpha)_{D}^{17})</th>
<th>source*</th>
</tr>
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<tr>
<td>enmein (1)</td>
<td>(C_{20}H_{30}O_{6})</td>
<td>308-312°, dec.</td>
<td>-136°</td>
<td>t, j</td>
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<tr>
<td>enmein-3-acetate (35)</td>
<td>(C_{22}H_{28}O_{7})</td>
<td>267-271°, dec.</td>
<td>-112°</td>
<td>j</td>
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<td>isodocarpin (36)</td>
<td>(C_{22}H_{28}O_{8})</td>
<td>270-273°, dec.</td>
<td>-172°</td>
<td>t, j</td>
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<td>nodosin (37)</td>
<td>(C_{20}H_{26}O_{6})</td>
<td>275-280°, dec.</td>
<td>-203°</td>
<td>t, j</td>
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<tr>
<td>isodotricin (44)</td>
<td>(C_{21}H_{30}O_{7})</td>
<td>240-245°, dec.</td>
<td>-114°</td>
<td>t, j</td>
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<td>trichodonin (90)</td>
<td>(C_{22}H_{26}O_{7})</td>
<td>234-237°, dec.</td>
<td>+32°</td>
<td>t</td>
</tr>
<tr>
<td>ponicidin</td>
<td>(C_{20}H_{28}O_{6})</td>
<td>238-241°, dec.</td>
<td>-118°</td>
<td>j</td>
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<tr>
<td>trichokaurin (45)</td>
<td>(C_{22}H_{32}O_{7})</td>
<td>184-185°, dec.</td>
<td>-93°</td>
<td>t</td>
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<tr>
<td>oridonin (73)</td>
<td>(C_{20}H_{26}O_{6})</td>
<td>248-250°, dec.</td>
<td>-46°</td>
<td>t, j</td>
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<td>trichodin</td>
<td>(C_{20}H_{26}O_{6})</td>
<td>&gt;300°</td>
<td></td>
<td>t</td>
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* t: *Isodon trichocarpus* KUO; j: *I. japonicus* HARA

The molecular formula of isodocarpin has one less oxygen than enmein, that is, it corresponds to des-0-enmein. The spectral investigation of isodocarpin led to an assumption that it must be 3-deoxyenmein (36), which was proved to be correct by chemical evidence shown in Scheme 8.13,14)

Nodosin (37) has the same molecular formula as that of enmein. The spectral data suggested an enmein-type structure, that is, nodosin contains a \(\delta\)-lactone, an exomethylene, a five-membered ring ketone and a five-membered ring hemiacetal. Moreover, another secondary hydroxy group was assumed to be present, because of the IR spectrum and a triplet proton signal at \(\delta\) 5.16 ppm.
assignable to a proton on a hydroxylated carbon.

Nodosin was hydrogenated to give dihydronodosin (38) and tetrahydronodosin (39). Dihydronodosin on acetylation yielded a crystalline 6-monooacetate (40), in which the singlet signal at $\delta$ 5.79 ppm in dihydronodosin caused a paramagnetic shift to $\delta$ 6.46 ppm. Another secondary hydroxy group was hardly acetylated, so acetylation over a period of 16 days did not accomplish the reaction. In the case of enmein, C-3 axial hydroxy group was easily acetylated on standing overnight under the same condition. This is a big contrast. (Scheme 9)

Oxidation of dihydronodosin monoacetate (40) with chromic acid-pyridine complex afforded a crystalline keto-derivative 41, in which the unidentified secondary alcohol was oxidized, as a major product, and a crystalline keto-tertiary alcohol, as a minor product. The major keto-compound on thio-ketalization and subsequent desulfurization with Raney nickel in ethanol yielded an acetal 42. This acetal proved to be identical with the compound which was prepared from dihydro-enmeinone acetate (43). (Scheme 10)
This interconversion confirmed that nodosin is an isomer of enmein differing in the location of a secondary hydroxy group, that is, nodosin corresponds to a hydroxyisodocarpin. Since the unidentified secondary hydroxy group in nodosin is much more hardly acetylated than the $\beta$-axial hydroxy group at C-3 in enmein, it must be located in a more hindered position than the $\beta$-axial C-3 position. An investigation of such a position resulted in the selection of $\alpha$-axial at C-2, $\beta$-quasiaxial at C-11, $\alpha$-quasiaxial at C-12 or $\beta$-quasiaxial conformation at C-14. NMR and mass spectral data led to a conclusion that the secondary hydroxy group is located in C-11. The coupling constants reasonably explain the assignment of a $\beta$-quasiaxial conformation to this hydroxy group. In the NMR spectrum of keto-acetate 41, two sharp singlet signals were observed at $\delta$ 3.13 and 3.02 ppm. One of them was assigned to the proton on the carbon adjacent to the carbonyl group, while the other to the proton at C-5. The abnormal paramagnetic shift of the proton signal at C-5 in this keto-acetate is due to the anisotropic effect of the C-11 carbonyl group. In the NMR spectra of dihydronodosin (38), 6-monoacetate 40 and diacetate 41, a one proton doublet appeared at $\delta$ 3.87, 3.78 and 3.14 ppm, respectively. The coupling constants were in the range of 11.0–12.0 c/s. On the basis of the spin decoupling experiments on the proton signal at $\delta$ 3.87 and 3.78 ppm, these signals could be assigned to a $\beta$-proton at C-14. This proton is deshielded by the effect of the $\beta$-hydroxy group at C-11. Thus, the structure and absolute configuration of nodosin were elucidated as 37. The stereochemistry of the D-ring of tetrahydronodosin was revised to 39 from the previous assignment.

Isodotricin (44) has a structure of the methanol adduct which was derived from enmein by addition of one mole methanol to the exocyclic methylene of the D-ring. The structure was deduced from several spectral data and was supported from the chemical evidence as shown in Scheme 11.

The substituent on C-16 was first given the thermodynamically more stable $\beta$-configuration, but hitherto some data to support $\alpha$-configuration have been obtained.

Subsequently, the structure and stereochemistry of trichokaurin (45) will be mentioned. The IR spectrum of trichokaurin shows the presence of hydroxy

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The following experiments suggested the presence of one secondary hydroxy group and one tertiary hydroxy group. Trichokaurin itself contains two acetoxy groups, that is, IR spectrum showed the absorption band at 1730 cm⁻¹ and the NMR spectrum exhibited acetyl methyl protons singlet signals at 6 2.19 and 2.06 ppm. The proton signals on the acetylated carbons also appeared as a doublet splitted with coupling constant of 7.0 c/s at 6 5.21 ppm, and as a triplet splitted with coupling constant of 2.0 c/s at 6 5.62 ppm.

Trichokaurin on acetylation gave an acetate 46, whose NMR spectrum exhibited singlet signals at 6 2.18, 2.09 and 2.06 ppm indicating the presence of three acetoxy groups. The one proton signal which was recognized at 6 3.58 ppm in the NMR spectrum of trichokaurin caused a paramagnetic shift to 6 4.64 ppm by acetylation. Chromic acid oxidation of trichokaurin yielded a monoketo-derivative 47 (IR absorption at 1700 cm⁻¹). These facts suggested the presence of a secondary hydroxy group in the diterpenoid.

In the NMR spectrum of the foregoing acetate 46, a proton signal due to a hydroxy group appeared at 6 3.76 ppm. In the IR spectrum of the same compound, an absorption band at 3500 cm⁻¹ due to a hydroxy group was observed. The presence of a hydroxy group also in the foregoing keto-derivative 47 was shown by the NMR signal at 6 3.38 ppm and IR absorption at 3400 cm⁻¹. Accordingly, a tertiary hydroxy group is present in trichokaurin. (Scheme 12)

Thus, six oxygens in trichokaurin were characterized. Subsequently, the remaining one was shown to be an ether-type oxygen, because a singlet signal of two protons due to an ether-type methylene group was observed at 6 3.93 ppm in the NMR spectrum of trichokaurin.

The IR absorption at 1660 cm⁻¹ and NMR signals at 6 5.04 and 4.91 ppm suggested an exocyclic methylene group in trichokaurin. As couplings of each of exocyclic methylene protons to the proton at 6 5.62 ppm were recognized, the partial structure 48 (D-ring) was proposed.

It is very characteristic and different from enmein-type that trichokaurin contains neither a five-membered ring hemiacetal nor a δ-lactone ring, but does bear
a tertiary hydroxy group. From its molecular formula the number of site of unsaturation is calculated as 8. Since no other unsaturated bonds than one exomethylene and two carbonyls in acetoxy groups were found, trichokaurin must have five rings. Trichokaurin was also shown to have two tertiary methyl groups from the NMR spectrum. Moreover, the proton at δ 5.21 ppm appeared as a doublet with a coupling (J=7.0 c/s) to the proton at δ 1.93 ppm.

The foregoing data and a biogenetic consideration led to an assumption that trichokaurin might have a kaurene-type 7-hemiketal structure 49, provided that the location of the secondary hydroxy group was not known.

An alkaline hydrolysis of trichokaurin was tried in order to get tetraol, but only a low yield of the desired product was obtained. The major product was an unsaturated aldehyde 51, which was yielded by the cleavage of the D-ring. A satisfactory yield of tetraol 50 was achieved by the treatment of trichokaurin with lithium aluminum hydride. The acetate of trichokaurin on treatment with the same reagent also gave the tetraol in good yield. (Scheme 13)

The tetraol 50 in methanol was allowed to react with periodate at room temperature for three days to afford an enmein-type hemiacetal lactone 52 as a major product and a lactone aldehyde 53 as a minor product. The latter on treatment with a weak acid was easily converted into the former. This product 52 on hydrogenation using Adams' catalyst followed by oxidation with Jones' reagent
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gave a crystalline keto-dilactone, which was proved to be identical with 3-deoxy-1-epi-dehydrodihydroenmein (54), a product prepared from 1-epi-bisddehydrodihydroenmein (7) by thioketalization followed by desulfurization.

Accordingly, the unidentified hydroxy group was proved to be located in C-1 and to have axial β-orientation; the R-configuration of C-1 was thus established. (Scheme 14)

\[ \text{Scheme 14} \]

The tetraol 50 on acetylation yielded a crystalline diacetate 54 and an oily 6-monoacetate 55. The fact suggests that the C-6 hydroxy group in this tetraol has β-configuration, because α-hydroxy group at C-6 would be more hardly acetylated than β-hydroxy group at C-1. Thus, the β-configuration is assigned to the acetoxy group at C-6 in trichokaurin. (Scheme 15)

\[ \text{Scheme 15} \]

1-Keto-derivative 47, a chromic acid oxidation product of trichokaurin, was subjected to thioketalization followed by desulfurization with Raney nickel. The crude product was subjected to catalytic hydrogenation on Adams' catalyst, then to treatment with lithium aluminum hydride to yield a saturated triol 56. The trans relationship between C-15 and C-16 hydrogens in the triol was recognized based on the coupling constant of 5.0 c/s in the NMR spectrum, hence the C-15 hydroxy and the C-16 methyl groups are trans each other. Accordingly to the usual examples of hydrogenation on the exomethylene at the D-ring in the series of compounds, we supposed β-configuration of the methyl group at C-16. On the
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basis of the assumption, we first gave an assignment of \( \alpha \)-configuration to the C-15 acetoxy group in trichokaurin, but we reached the conclusion that the assignment was incorrect from the evidence which will be mentioned below. The correct structure 56 is shown in Scheme 16.

The methanesulfonate 57 of trichokaurin on oxidation with Lemieux-Johnson's reagent gave a ketone 58, which was also obtained from trichokaurin by Lemieux-Johnson's oxidation followed by mesylation. The ketone was heated in dimethylsulfoxide\(^{18}\) at 150° for three hours to afford an unsaturated ketone 59, which on catalytic hydrogenation gave a saturated ketone 60. (Scheme 17)

The ketone 60 was treated with lithium aluminum hydride to afford a tetraol 61, which was converted into diacetate 62. In the NMR spectrum of this compound, a quartet splitted with the coupling constants of 3.5 and 9.0 c/s at \( \delta \) 4.26 ppm assignable to the C-15 proton and a quartet splitted with the coupling constants of 6.5 and 9.0 c/s at \( \delta \) 4.97 ppm assignable to the C-16 proton were observed. On the basis of the investigation on the stereomodel, only a steric configuration shown in formula, in which the C-15 and C-16 hydrogens are \( \alpha \)-cis oriented, can provide a reasonable interpretation for the NMR data. Hence, the configuration of the C-15 acetoxy group in trichokaurin must be \( \beta \), that is, the asymmetric center C-15 must have the R-configuration. (Scheme 18)
Chemical evidences were also provided to support this assignment. Dehydrotrichokaurin (47) on treatment with lithium aluminum hydride gave an epimeric tetraol 63, whose periodate oxidation resulted in the formation of an enmein-type product. The structure and absolute configuration of the product were proved to be shown in formula 64, because the derivative prepared by a partial acetylation followed by the catalytic hydrogenation was shown to be identical with tetrahydroisodocarpin-6-acetate (65) by IR and NMR spectral comparisons and the mixture melting point determination. Moreover, the identity was reconfirmed by the comparison of the oxidation product, with the sample of the known dehydrodihydroisodocarpin (66)\textsuperscript{19}. The C-15 proton in tetrahydroisodocarpin-6-acetate (65) being coupled to C-16 proton with splitting of 10.0 c/s, gives rise to a doublet at $\delta$ 4.93 ppm. Thus, the C-15 hydroxy group has cis-relationship with $\alpha$-oriented methyl group at C-16 as shown in formula 65, that is, the absolute configuration of C-15 must be R. (Scheme 19)

Another evidence supported this conclusion; the foregoing tetraol 63 on treatment with 15% hydrochloric acid yielded a saturated ketone 67 quantitatively. This fact shows an easy migration of C-15 hydride due to a convenient steric environment\textsuperscript{19}, that is, the $\beta$-configuration of C-15 hydroxy group in this tetraol. Hence, the original acetoxy group of C-15 in trichokaurin must have a $\beta$-configuration.

The ketone on periodate oxidation gave dihydroisodocarpin 68, which confirmed
the structure and absolute configuration 67 of the ketone. An unusual IR absorption of cyclopentanone at 1715 cm\(^{-1}\) of this compound can be attributed to the hydrogen bonding with the C-6 hydroxy group. This fact again supported the \(\beta\)-assignment of the C-6 acetoxy group in trichokaurin, that is, the asymmetric center C-6 must have the S-configuration. (Scheme 20)

Thus, the chemical structure and absolute configuration of trichokaurin were established as 45.

Subsequently, we carried out the chemical conversion\(^{20}\) of trichokaurin into \((-\)\)kaurene and diterpene alkaloids.

The ketone 60 on hydrogenolysis with calcium in liquid ammonia gave a ketone 69 and a triol 70. The structure of both compounds was confirmed on the basis of the spectral data of their acetates. The triol 70 was subjected to Nagata’s modification\(^9\) of Wolff-Kishner reduction, then to catalytic hydrogenation on Adams’ catalyst to give diol 71, which was oxidized with Jones’ reagent to afford a keto-carboxylic acid. The product was proved to be identical with the sample of \((-\)\)16-keto-10-carboxy-17, 20-bisnorkaurane (72)\(^{21}\) by the mixture melting point determination and IR and mass spectral comparisons. Since this compound has already been converted into \((-\)\)kaurene,\(^{21,22}\) atisine,\(^{23,24}\) garryine,\(^{25,26}\) and veatchine,\(^{25,27}\) this transformation constitutes the accomplishment of the chemical conversion of trichokaurin into \((-\)\)kaurene and these diterpene alkaloids. (Scheme 21)

The next problem is concerned with the structure of oridonin\(^{28}\).

Oridonin was first isolated from the leaves of Isodon japonicus, and later also from the leaves and stems of Isodon trichocarpus.\(^{29}\) Isodon japonicus is called as Orido in Kochi prefecture where we collected the plant, so we gave the diterpenoid the name “oridonin”. The molecular formula corresponds to C\(_{20}\)H\(_{28}\)O\(_8\). Its UV (\(\lambda_{\text{max}}\ 238\text{ m\(\mu\)} \ (\varepsilon 10600)) and IR spectra (1705 and 1645 cm\(^{-1}\)) suggested the presence of a conjugated ketone. The infrared spectrum also suggested the presence of the hydroxy groups. The NMR spectrum showed the presence of three secondary hydroxy groups, that is, the proton signals on the hydroxylated car-
bons were observed at $\delta$ 3.65 as triplet ($J=8.0$ c/s), at $\delta$ 4.29 as quartet ($J=10.0$ and 7.0 c/s), and at $\delta$ 5.35 ppm as singlet. Exocyclic methylene was recognized as NMR singlet signals at $\delta$ 6.31 and 5.53 ppm. On catalytic hydrogenation it was converted into a secondary methyl group. In addition, one ether-type methylene group was observed at $\delta$ 4.41 and 4.77 ppm as AB quartet and two tertiary methyl protons signals were observed at $\delta$ 1.20 and 1.14 ppm as singlets. The remaining unidentified oxygen was clarified to belong to a tertiary hydroxy group as follows: oridonin on Jones' oxidation followed by acetylation gave a ketoacetate 74, whose NMR spectrum showed a hydroxy proton signal at $\delta$ 4.29 ppm as a singlet. Oridonin on sodium borohydride reduction followed by acetylation gave a triacetate 75, whose NMR spectrum also exhibited a singlet signal due to a tertiary hydroxy proton at $\delta$ 4.41 ppm. (Scheme 22)

Oridonin contains neither a five-membered ring hemiacetal, nor lactone ring, but it does a tertiary hydroxy group. From these facts and investigation of number of site of unsaturation, a kaurene-type structure which resembles trichokaurin was deduced. The carbon skeleton and the functional groups in oridonin

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were established by conversion of the diterpenoid into dehydrotetrahydroisodocarpin. That is, oridonin on periodate oxidation gave an ennein-type hemiacetal δ-lactone, whose spectral data reasonably explained the structure 76. The hemiacetal was treated with acetic acid to give monoacetate 77. The hemiacetal was oxidized with Jones' reagent to give a ρ-dilactone 78, which was subjected to catalytic hydrogenation to afford dihydro-derivative 79. Compound 79 was converted into mesylate. (Scheme 23)

The mesylate 80 on reduction using Raney nickel gave dilactone alcohol 81, which proved to be identical with dehydro-tetrahydroisocarpin 81 derived from isodocarpin (36) by hydrogenation, chromic acid oxidation and sodium borohydride reduction. (Scheme 24)
From these facts, oridonin can be represented as 73, provided that the stereochemistry of the C-6 hydroxy group and the location of one secondary hydroxy group remained unsolved.

Oridonin on treatment with anhydrous acetic acid in pyridine at room temperature for 1 hour gave monoacetate 82 and diacetate 83. The diacetate was treated with oxalic acid solution to give another partially hydrolyzed monoacetate 84. The preceding monoacetate 82 on treatment with periodate gave an enmein-type hemiacetal-lactone monoacetate 86, while the latter monoacetate 84 on the same treatment gave an aldehyde 87. (Scheme 25)

Generally in the UV spectra of enmein-type derivatives the α, β-unsaturated five-membered ring ketone has the maximum absorption at about 230 mµ, for instance, 232.5 mµ in enmein, 230 mµ in 76, and 231 mµ in 86, while oridonin has the absorption at 238 mµ. In addition, enmein has IR adsorption at 1745~1755 cm⁻¹, the compound 76 at 1745 cm⁻¹, the compound 86 at 1750 cm⁻¹, and aldehyde 87 at 1738 cm⁻¹, respectively, due to α, β-unsaturated five-membered ring ketone, that is, these absorption bands are in considerably higher wave number, while orido-
nin has IR absorption due to the α, β-unsaturated ketone at 1705 cm⁻¹, 82 at 1710 cm⁻¹, and 84 at 1725 cm⁻¹, which means that these oridonin-type compounds have adsorption bands at considerably lower wave number region compared with enmein-type compounds. The characteristic shift to the lower wave-numbers of the oridonin-type is due to the hydrogen bonding between C-6 hydroxy group and the ketone of the D-ring, accordingly, the hydroxy group at C-6 is β-oriented, that is, the C-6 asymmetric center has the S-configuration.

Finally, unidentified secondary hydroxy group was determined to be located in C-14 and β-oriented because of the following facts; (i) The proton signal of the hydrogen on the hydroxylated carbon always appeared as singlet, that is, oridnin has a singlet signal at δ 5.35 ppm, and the other many derivatives have also singlet signal. The location and stereochemistry which satisfied the foregoing facts were sought for using a stereo-model. Consequently, only when a hydroxy group is located in C-14 and β-oriented, the dihedral angle between α-hydrogen at C-14 and α-hydrogen at C-13 is about 90°, and C-14 α hydrogen proton signal may appear as a singlet. (ii) Dihydrooridonin 88 on treatment with 3% potassium hydroxide gave a γ-lactone 89. (Scheme 26)

From these evidences, the structure and absolute configuration were established as 73.

Next diterpenoid is trichodoninⱾ. This compound was first isolated by a Japanese group and we gave it the name trichodonin. From the spectral investigation of trichodonin and its several derivatives, we assumed the presence of a five-membered ring ketone conjugated with an exomethylene, a δ-lactone, an aldehyde group, a secondary alcohol, a primary acetoxy group, and two tertiary methyl groups. The environment of the secondary alchol was deduced from NMR comparison with the oxidized keto-compound. These data and biogenetic consideration led to an assumption that the structure of trichodonin may be represented as formula 90. Recently, professor Kubota and co-workers in the Osaka City University proved our proposed structure to be correct by a chemical methodⱾⱾ. In addition to these diterpenoids, we isolated ponicidine and trichodin from the leaves of Isodon species. Ponicidin was contained as very minor component and yet remained unsolved. Trichodin was supposed to have a γ-lactone, a δ-lactone, a five-membered ring ketone, a secondary methyl group, and a secondary hydroxy group presumably at C-11, and a structure was tentatively assumed, but the detail is now being investigated.
Subsequently, we tried to investigate the components of the stems of *Isodon trichocarpus* Kudo. The dried stems were extracted with ether and in addition to some steroids and triterpenoids, enmein and oridonin were isolated as diterpenoids.

### III. CHEMICAL CONVERSION OF ENMEIN INTO ENANTIOABIE TANE AND TOTAL SYNTHESIS OF ABIETANE

The lactone ester 13 described in section I was used as the material for synthesis of enantioabietane. But the yield of this isopropyl derivative was not good according to the method shown in Scheme 2, so the investigation for better yield was carried out; the keto lactone ester 12 was subjected to reduction with sodium borohydride to yield alcohol 34, which on treatment with sodium hydride in tetrahydrofuran gave aldehyde 91 in a satisfactory yield through a retroaldol-type reaction. Or the alcohol was heated at reflux for ten minutes in ethylene glycol gave a very good yield of the aldehyde. The aldehyde on thioketalization followed by desulfurization afforded the desired material 13 in a good yield. (Scheme 27)

![Scheme 27](image)

An ethereal solution of the material was added to a solution of metallic sodium in liquid ammonia under vigorous stirring. The reaction using 1.2 to 1.6 equivalent amount of sodium gave 6-hemiketal-7-ol compound 92 as a major product and 7-hemiketal-6-ol derivative 93 as a minor product. The use of a large
excess of sodium resulted in the formation of \(6\beta, 7\alpha, 20\)-triol 94 and diol 95 accompanied by \(6\alpha, 7\alpha, 20\)-triol 96, which was also obtained by sodium borohydride reduction of the foregoing \(6\)-hemiketal 92 in tetrahydrofuran. This cis-triol on acetylation gave first \(7, 20\)-diacetate, which was converted into triacetate under vigorous conditions, while \(6\beta\)-triol 94 on acetylation easily afforded triacetate. These experimental results and spectral data allowed the reasonable assignment of these products. In this acyloin condensation, primary alcohol 97 was also found as a minor product.

A mixture of hemiketal acyloin products was subjected to Nagata's modification of Wolff-Kishner reduction to yield the expected crystalline unsaturated alcohol 98, which on hydrogenation with Adams' catalyst gave a dextrorotatory saturated alcohol 99 in a crystalline form. The alcohol on oxidation with Jones' reagent at \(0^\circ\) yielded a crystalline aldehyde 100 which was again subjected to the modified Wolff-Kishner reduction to afford a dextrorotatory hydrocarbon 101. It was shown to be homogeneous on a vapor phase chromatogram. (Scheme 28)

Commercial abietic acid was purified through diisooamylamine salt and then subjected to hydrogenation on Adams' catalyst in acetic acid to give all-trans-tetrahydroabietic acid 102.33 On similar catalytic hydrogenation dihydroabietic acid 103 also gave all-trans-tetrahydroabietic acid. The methyl ester 104 on reduction with lithium aluminum hydride gave a crystalline alcohol 105, which was oxidized with Jones' reagent at \(0^\circ\) to yield an oily aldehyde 106. Finally, the aldehyde was subjected to a modified Wolff-Kishner reduction to afford a crystalline hydrocarbon 107 having m. p. 37–38° and \([\alpha]\) -5°. The analysis and mass spectrum confirmed the molecular formula \(C_{20}H_{36}\) for the hydrocarbon, whose ORD showed \((-\)) -plain curve. (Scheme 29)

The foregoing hydrocarbon 101 which was derived from enmein had \([\alpha]\) +5° and the same m. p. 38°, and exhibited \((+\)) -plain ORD curve. Its IR and mass spectra coincided with those of the hydrocarbon 107, and its retention time on vapor phase chromatogram was the same with that of 107. These facts
established that these hydrocarbons were enantiomeric.

Since it is the first time that these hydrocarbons were synthesized, we propose the name "abietane" for 107, hence "enantioabietane" for 101. The conversion of abietic acid into abietane constitutes the total synthesis of the latter, because (−)-abietic acid has already been synthesized by Wenkert et al.\(^3\)

The research on the diterpenoids of *Isodon* species is still being in progress. Prof. Uyeo et al., Prof. Kubota et al., and Prof. Okamoto et al. published several interesting papers recently. I regret to omit the introduction of their valuable works\(^4\) (31) (32) (35).

**REFERENCES**

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