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By Toshi Irie

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BROMO COMPOUNDS FROM MARINE ALGAE

/p.1179/

Toshi IRIE*1

(Received July 10, 1969)

Seven new compounds containing bromine were isolated from red algae (the family Rhodomelaceae) and their chemical structures were elucidated. Those new compounds are as follows: two bromic phenols, 2,3-dibromo-4,5-dihydroxybenzaldehyde [2] and 3,4-dibromo-5-(methoxymethyl) catechol [3]; two bromine-containing sesquiterpenoids, laurinterol [14], $C_{15}H_{19}OBr$, and laurenisol [17], $C_{15}H_{19}OBr$; and three bromine-containing cyclic ethers, laurencin [18], $C_{17}H_{23}O_3Br$, laureatin [19], $C_{15}H_{20}O_2Br_2$, and isolaureatin [20], $C_{15}H_{20}O_2Br_2$. Also, some other new substances related to these bromine-containing compounds such as laurene [9], $C_{15}H_{20}$, and debromolaurinterol [15], $C_{15}H_{20}O$, were isolated from the algae. Furthermore, aplysin [11], aplysinol [12], and debromoaplysin [13] were found as components of the algae. Lastly, a tentative idea concerning the biosynthesis of these bromic compounds was proposed.

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1. INTRODUCTION

1.1. Preface

It is known for long that marine algae contain bromine.[1] According to the results of analyses by Kylin,[2] Ochi and Takahashi,[3] and others, bromine is usually contained in a large quantity in red algae, especially the algae of the genera Itogusa (Polysiphonia), Fujimatsumo (Rhodomela) and Nokogirihiba (Odonthalia), while it is contained in brown and green algae in a comparatively small quantity.

Bromine in the sea-water is said to exist mainly as Br^- ion, and its content is only about 63.8 ppm, though larger than that of I^-. How marine algae take bromine into their body and in what form they preserve it are very interesting questions. Yet, there have been only a very few studies of the bromine-containing compounds in marine algae. In 1949, Mastaglin and Augier[4] isolated a substance having the composition of $C_6Br_2(SO_3K)_2(OH)(COOH)$ from a species of a red alga Itogusa (Polysiphonia), but they did not elucidate its structure. Then, in 1955, Saitō and Andō[5] isolated 5-bromo-3,4-dihydroxybenzaldehyde [1] from Moroitogusa (Polysiphonia morrowii), a species of the red alga family Fujimatsumo (Rhodomelaceae). This is the first bromic compound

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1) For general information on the components of marine algae, see:
   a) R. A. Lewin, Physiology and Biochemistry of Algae, Academic Press, New York (1962).
   b) Yasuhiko Tsuchiya, Suisan-Kagaku /Chemistry of Marine Products/, Vol. 2, Kōseisha, Kōseikaku (1962).
   c) Yatarō Obata, Kagaku /Chemistry/, **15**, 403 (1960).

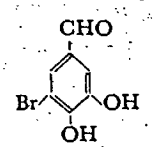
2) H. Kylin, Z. Physiol. Chem., **83**, 171 (1913).

3) Shuichirō Ochi and Takeo Takahashi, Tōkōshi, **28**, 1 (1933).

4) P. Mastaglin and J. Augier, Compt. Rend., **229**, 775 (1949).

5) Tsuneyuki Saitō and Yoshiaki Andō, Nikka /Jap. Chem./, **76**, 478 (1955).

that was isolated from marine algae and whose structure was also elucidated.



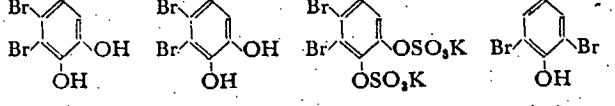
〔1〕

In the laboratory of the present author and his associates, organic chemical researches have been made into the composition of marine algae for several years, and some information has been obtained on the bromine-containing organic compounds in marine algae. The present paper describes its details.*2

The bromine-containing organic compounds in marine algae that are known at present can be distinguished into the following three groups: 1) Phenolic compounds, 2) terpenic compounds, and 3) cyclic ethereal compounds.

1.2. Phenolic Bromic Compounds

As mentioned above, Saitō and Andō isolated 5-bromo-3,4-dihydroxybenzaldehyde 〔1〕 from Moroitogusa (Polysiphonia morrowii). Thereafter, the present author and his associates investigated some other species of the same algal family and succeeded in isolating 2,3-dibromo-4,5-dihydroxybenzaldehyde 〔2〕 and 3,4-dibromo-5-(methoxymethyl) catechol 〔3〕 from Fujimatsumo (Rhodomela larix).[6] The latter corresponded to the one isolated by Matsumoto and Kagawa[7] from Hakesakinokogirihiba (Odonthalia corymbifera).



〔2〕 〔3〕 〔4〕 〔5〕

*2 The results of their researches are outlined here on the basis of their data that have been already published elsewhere together with their some unpublished data.

6) N. Katsui, Y. Suzuki, S. Kitamura, and T. Irie, Tetrahedron, 23, 1185 (1967).

7) Cf. Takeshi Matsumoto and Shohei Kagawa, Abstracts of the presentations at the 17th annual meeting of the Chemical Society of Japan (1964), p. 278; Private communication.

Craigie and others[8] isolated 1,2-disulfuric acid hydrogen ester di- /p.1180/ potassium salt [4] of 3,4-dibromo-5-(hydroxymethyl) catechol from Polysiphonia lanosa and clarified its structure. It seems that this compound probably has a close relationship with the carboxylic acid which had been previously isolated by Mastaglin and his associate. Craigie and others[9] also isolated 3,5-dibromo-4-hydroxybenzylalcohol [5] from Odonthalia dentata and Rhodomela confervoides. These dibromo-phenols have structures which are very closely related to each other. They are also closely related to [1] which was isolated by Saitō and Andō. However, nothing has yet been known about the biosynthetic mechanism of these bromic compounds of hydroxybenzaldehyde or benzylalcohol and its methyl ether.

1.3. Bromine-containing Sesquiterpenoids

The presence of terpene in marine algae was pointed out by Heilbron and his associates[10] in 1934 with reference to a brown alga Fucus vesiculosus.*3 Then, in 1951, Takaoka and Andō[11] isolated cadinene and a type of sesquiterpene alcohol (which was named "dictyol") from a brown alga Ezoyahazu (Dictyopteris divaricata). Thereafter, Andō[12] reported the presence of sesquiterpene and

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8) J. S. Craigie, Proc. Can. Soc. Plant Physiol., 6, 16 (1965); J. H. Hodgkin, J. S. Craigie, and A. G. McInnes, Can. J. Chem., 44, 74 (1966).

9) J. S. Craigie and D. E. Gruenig, Science (London), 157, 1058 (1967).

10) I. M. Heilbron, P. F. Phipers, and H. R. Wright, J. Chem. Soc., 1934, 1572.

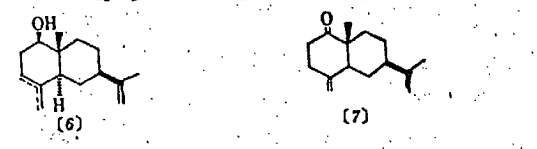
*3 For monoterpene in marine algae, there are Katayama's broad studies of brown algae.[1a] Teruhisa Katayama, Nissuisan [Jap. Fish. Industry], 24, 925 (1959); 27, 75 (1961); and his many other reports.

11) Michio Takaoka and Yoshiaki Andō, Nikka [Jap. Chem.], 72, 999 (1951).

12) Yoshiaki Andō, Nissuisan, 19, 713 (1953).

sesquiterpene alcohol in the neutral fraction of the essential oil from Amiji-gusa (Dictyota dichotoma). Also, Obata and Fukuse[13] reported the presence of sesquiterpene and sesquiterpene alcohol in a red alga Oosozo (Laurencia glandulifera). However, the chemical structures of these compounds were not elucidated.

The present author and his associates[14)15)] investigated the sesquiterpene of Ezoyahazu (Dictyopteris divaricata), from which they isolated (-)-δ-cadinol, (-)-γ_1-cadinene, (+)-β-elemene, and (-)-cubebene.*4 They also isolated a new sesquiterpene alcohol, dictyopterol [6], and a corresponding sesquiterpene, ketonic dictyopterone [7]. Then, they determined the chemical structures of these compounds. Compounds [6] and [7] were 1-hydroxy and 1-oxygenated selinenes, respectively, which were supposed to be formed from a germacrane-type precursor [8] through anti-parallel oxidative cyclization.



Furthermore, the author and his associates[16] isolated from Oosozo

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13) Yatarō Obata, and Shunichi Fukushi, Nōka [Agric. Chem.], 27, 331 (1953).

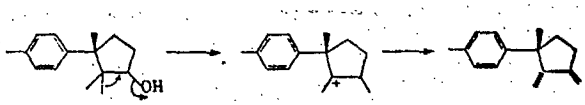
14) T. Irie, K. Yamamoto, and T. Masamune, Bull. Chem. Soc. Japan, 37, 1053 (1964).

15) E. Kurosawa, M. Isawa, K. Yamamoto, T. Masamune, and T. Irie, ibid., 39, 2509 (1966).

*4 The sesquiterpene which the author and his associates had previously reported as (-)-copaene turned out to be (-)-cubebene. It is so corrected here.

16) a) T. Irie, Y. Yasunari, I. Suzuki, N. Imai, E. Kurosawa, and T. Masamune, Tetrahedron Letters, 1965, 3619.
b) T. Irie, T. Suzuki, Y. Yasunari, E. Kurosawa, and T. Masamune, Tetrahedron, 25, 459 (1969).

(Laurencia glandulifera) a new sesquiterpene hydrocarbon, laurene [9], together with the bromine-containing compound laurencin which will be described later, and then elucidated its structure. Laurene was supposed to be formed from a cuparene-type precursor [10] by the 1,2-shift of methyl group.[17] *5



(10) (9)

Bromine-containing sesquiterpenes are known by the aplysin [11] and aplysinol [12] which were isolated from a marine animal Amefurashi (Aplysia kurodai) by Yamamura and Hirata.[18] Recently, these compounds were also found in a red alga Mitsudesozo (Laurencia Okamurai) collected in the Seto Inland-Sea.[19] This is a very interesting finding because the Amefurashi lives on the Sozo (Laurencia) alage.

(11) X=Br, Y=H
(12) X=Br, Y=OH
(13) X=Y=H

(14) X=Br, R=H
(15) X=R=H

Besides, debromoaplysin [13] was found in both Amefurashi and Mitsudesozo.[18][19]

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17) Cf. W. Parker, J. S. Roberts, R. Ramage, Quart. Rev. (London), 21, 331 (1967).

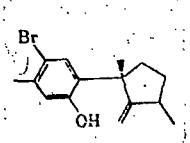
*5 As will be discussed later (3.1), formation of a cyclopropane type intermediate may be conceivable here.

18) S. Yamamura, and Y. Hirata, Tetrahedron, 19, 1485 (1963).

19) T. Irie, M. Suzuki, and Y. Hayakawa, Bull. Chem. Soc. Japan, 42, 843 (1969).

Laurinterol [14], a new bromine containing sesquiterpene having a bicyclo [3.1.0] hexane ring isolated from Kurosozo (L. intermedia) and Mitsudesozo, and its debrominated derivative, debromolaurinterol [15],[20] were found to have a chemical structure which is very closely related to aplysin. Also, isolaurinterol [16], an isomer of laurinterol, has been found as a micro-component of Kurosozo.[21]

As a sesquiterpene containing bromine atoms besides benzene nucleus, laurenisol [17] was found in Urasozo (L. nipponica).[22] Its structure was found to be related to laurene, and a vinyl bromide type structure was conceived for it. /p.1181/



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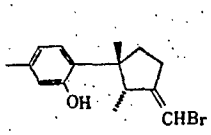

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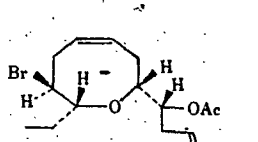

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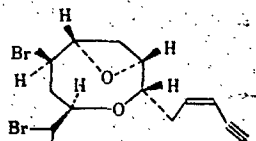

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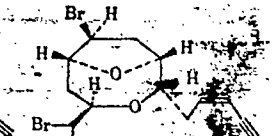

(20)

1.4. Cyclic Ethereal Compounds Containing Bromine

The author and his associates found out a cyclic ethereal compound containing bromine, laurencin [18],[23] in Oosozo (Laurencia glandulifera). Furthermore, they isolated from Urasozo (L. nipponica) laureatin [19][24)25] and isolaureatin [20][25)26] which have structures closely related to laurencin.

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20) T. Irie, M. Suzuki, and T. Masamune, Tetrahedron Letters, 1966, 1837.

21) Toshi Irie, and Minoru Suzuki, unpublished.

22) T. Irie, A. Fukuzawa, M. Izawa, and E. Kurosawa, Tetrahedron Letters, 1969, 1343.

23) a) T. Irie, M. Suzuki, and T. Masamune, Tetrahedron Letters, 1965, 1901.
b) T. Irie, M. Suzuki, and T. Masamune, Tetrahedron, 24, 4193 (1968).

24) T. Irie, M. Izawa, and E. Kurosawa, Tetrahedron Letters, 1968, 2091.

25) T. Irie, M. Izawa, and E. Kurosawa, Tetrahedron, in press.

26) T. Irie, M. Izawa, and E. Kurosawa, Tetrahedron Letters, 1968, 2735.

Then, they elucidated the structures of these compounds.

These compounds were supposed to be formed probably via epoxide from a common precursor, hexadeca-4,7,10,13-tetraenoic acid [21] which is an unsaturated fatty acid found in marine algae.[26)27)]

$$CH_3\text{-}CH_2\text{-}(CH{=}CH\text{-}CH_2)_4\text{-}CH_2\text{-}COOH$$

[21]

As described above, the bromic compounds in marine algae that are known today are not many as yet. The bromine atoms in the particles of these compounds, including those into which structural researches are in progress in the laboratory of the author and his associates, seem to be explicable if it may be supposed that they are introduced in a form of bromohydrine via the position in which the phenolic particles can easily be brominated, or via epoxide from double bonds.

In the following chapters, some main bromic compounds of those that have been briefly described above will be discussed in reference to their isolation and structural determination.

2. PHENOLIC COMPOUNDS CONTAINING BROMINE[6)]

Through the treatment as outlined in Table 1, two types of new bromophenols (A, B) were isolated in a crystallized form from 8 kg of air-dried specimen of the Fujimatsumo (Rhodomela larix (Turner) C. Agardh) collected in Hakodate Bay in June.

Bromophenol-A[2], $C_7H_4O_3Br_2$, mp 203~205°C (yield, 1.2 g) turned dark green with iron chloride (III) and was readily soluble in a sodium carbonate

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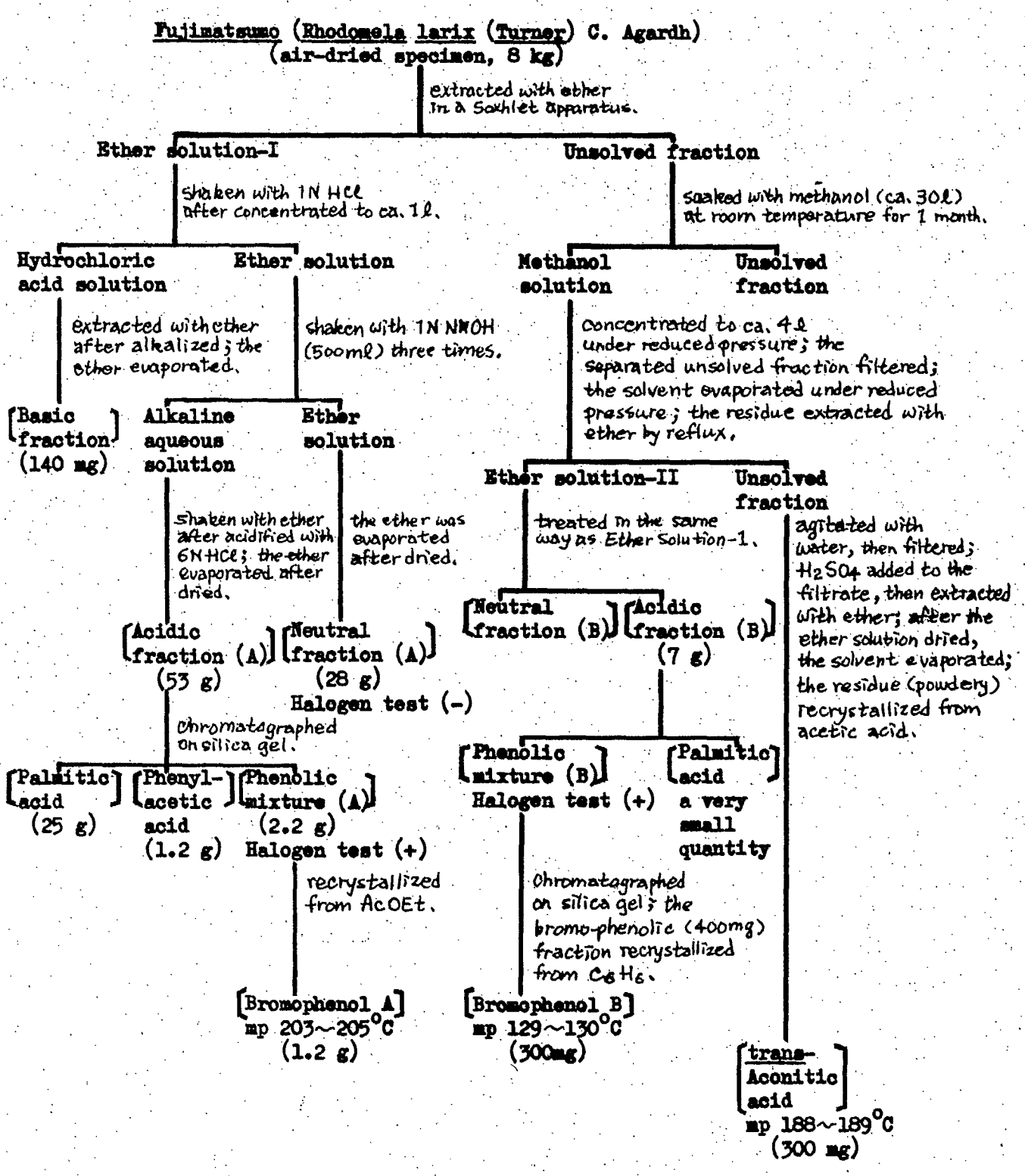
[27)] Professor Sir Ewart Jones, Private communication; Cf. Chemistry in Britain, 2, 6 (1966).

Table 1:


Fujimatsumo (Rhodomela larix (Turner) C. Agardh)
(air-dried specimen, 8 kg)
extracted with ether in a Soxhlet apparatus.
Ether solution-I
Unsolved fraction
shaken with 1N HCl after concentrated to ca. 1 l.
soaked with methanol (ca. 30 l) at room temperature for 1 month.
Hydrochloric acid solution
Ether solution
Methanol solution
Unsolved fraction
extracted with ether after alkalized; the ether evaporated.
shaken with 1N NaOH (500ml) three times.
concentrated to ca. 4 l under reduced pressure; the separated unsolved fraction filtered; the solvent evaporated under reduced pressure; the residue extracted with ether by reflux.
Basic fraction (140 mg)
Alkaline aqueous solution
Ether solution
Ether solution-II
Unsolved fraction
shaken with ether after acidified with 6N HCl; the ether evaporated after dried.
the ether was evaporated after dried.
treated in the same way as Ether Solution-1.
agitated with water, then filtered; H2SO4 added to the filtrate, then extracted with ether; after the ether solution dried, the solvent evaporated; the residue (powdery) recrystallized from acetic acid.
Neutral fraction (B)
Acidic fraction (B) (7 g)
Acidic fraction (A) (53 g)
Neutral fraction (A) (28 g)
Halogen test (-)
chromatographed on silica gel.
Palmitic acid (25 g)
Phenyl-acetic acid (1.2 g)
Phenolic mixture (A) (2.2 g)
Halogen test (+)
Phenolic mixture (B)
Halogen test (+)
Palmitic acid a very small quantity
recrystallized from AcOEt.
chromatographed on silica gel; the bromo-phenolic (400mg) fraction recrystallized from C6H6.
Bromophenol A
mp 203~205°C
(1.2 g)
Bromophenol B
mp 129~130°C
(300mg)
trans-Aconitic acid
mp 188~189°C
(300 mg)

aqueous solution. Its color reaction to Tollens' reagent and to 2,3,5-triphenyltetrasodium chloride was positive. From its UV [λ_{max} (EtOH) mμ (ε): 332 (6400), 294 (8400), 240 (26800); λ_{max} (0.1N NaOH-EtOH): 404 (14400), 274 (10800)] and IR spectra [ν_{max} (nujol): 3300 (OH), 1645 (CO), 1595, 1574, 1503, 876 cm^{-1} (benzene nucleous)], it was inferred to be dibromoprotocatechualdehyde. This inference was supported by the fact that a formyl group forms acetal with methanol, but not fluorescing ketazine with hydrazine. The position of the two bromines was then determined as 2,3-dibromo-4,5- /p.1182/ dihydroxybenzaldehyde (5,6-dibromoprotocatechualdehyde) by directly comparing its dimethyl ether, mp 128~129°C [NMR: one H signal due to an aromatic ring at τ 6.15, 6.13 (each 3H, s)] with its synthetic product.

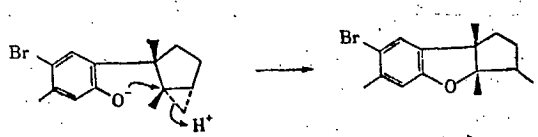
Bromophenol-B [3], $C_8H_8O_3Br_2$, mp 129~130°C (yield, about 300 mg) was isolated from the acidic fraction of the methanol extracts of the alga. From its UV [λ_{max} mμ (ε): 292 (3500), 230 (12000); λ_{max} (0.1N NaOH-EtOH) 303 (7300), 269 (10300)] and IR spectra [ν_{max} 3485, 1608, 1575, 1428, 1167, 920, 878 cm^{-1}], it was inferred to be 3,4-dibromo-5-(methoxymethyl) catechol, the same substance as Matsumoto and Kagawa[7] had previously isolated from Hakesakinokogirihiba (Odonthalia corymbifera). It was identified as such by directly comparing its dimethyl derivative, mp 71~72°C, afforded upon methylation with dimethyl sulfate, with its synthetic product.

3. LAURINTEROL, DEBROMOLAURINTEROL, AND LAURENISOL

3.1. Laurinterol and Debromolaurinterol[20]

Air-dried specimen of the Kurosozo (L. intermedia Yamada) collected in August in Oshoro Bay, Hokkaidō, was soaked in methanol at room temperature for 20 days. Then, the extracted liquid was filtered, and the filtrate was concentrated under reduced pressure. The brown syrupy residue was then taken

into ether, and the ethereal solution was dried after washed successively with a dilute sodium hydroxide solution, dilute hydrochloric acid, and water. The neutral fraction of the brown oily residue after the removal of the ether was then chromatographed on silica gel, and the effluent with n-hexane-benzene (1:1) was collected and purified by similar chromatography for several times. Thus, laurinterol [14], $C_{15}H_{19}OBr$ (M^+ 296, 294), mp 54~55°C, $[\alpha]_D$ +13.3°, was obtained; the yield was about 0.22% of the air-dried specimen. Its UV, IR, and NMR spectra (Figure 1) supposedly indicated the presence of a trisubstituted phenol group [λ_{max} (EtOH) mμ (ε): 225 (7100), 283 (2200), 289 (2100); ν_{max} ($CHCl_3$): 3600, 1610, 1495, 1152 cm^{-1}; τ5.14 (1H, s), 3.58 (1H, s), 2.53 (1H, s)], an aromatic methyl group [τ7.78 (3H, s)], two tertiary methyl groups [τ8.66, 8.71 (each 3H, s)], and a cyclopropane ring [ν_{max} 3060, 1025 cm^{-1}; τ9.48 (2H, d, J = 6.5 cps), about 8.9 (1H, m)]. Besides, taking into consideration the result of analysis of its mass spectrum, it was supposed that laurinterol may have a structure similar to that of aplysia [11],[18] except its possession of a phenolic hydroxyl group and a cyclopropane ring. For the purpose of finding the relationship between laurinterol and aplysin, therefore, laurinterol acetate was treated with p-toluenesulfonic acid in acetic acid at 50°C for 24 hours. Then, aplysin, $C_{15}H_{19}OBr$, mp 95°C, $[\alpha]_D$ -86.1°, was afforded a good yield.



(11)

Consequently, the structure of laurinterol [14] was clarified, and a hint was gained for finding the process of the biosynthesis of aplysin. As to the stereochemistry of laurinterol, even its absolute configuration has been

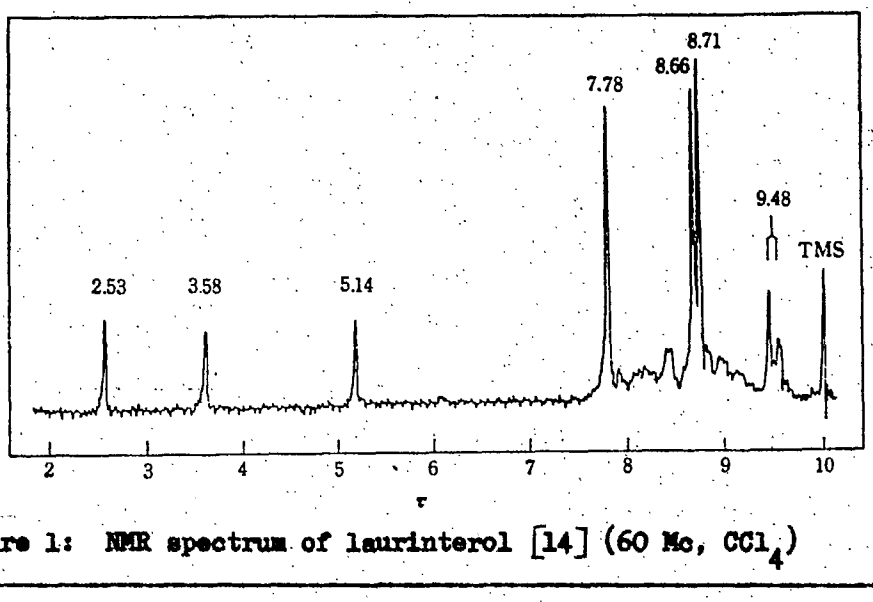


Figure 1: NMR spectrum of laurinterol [14] (60 Mc, CCl_4)

determined by Robertson and his associates[28] as a result of their X-ray analysis of laurinterol acetate, $C_{17}H_{21}O_2Br$, mp 93~93.5°C, $[\alpha]_D$+11.1° (monoclinic system) (Figure 2). According to this, the methyl group at C-1 and the methyl group at C-2 are cis to each other so as to be β, while the aromatic ring and the cyclopropane ring become α.

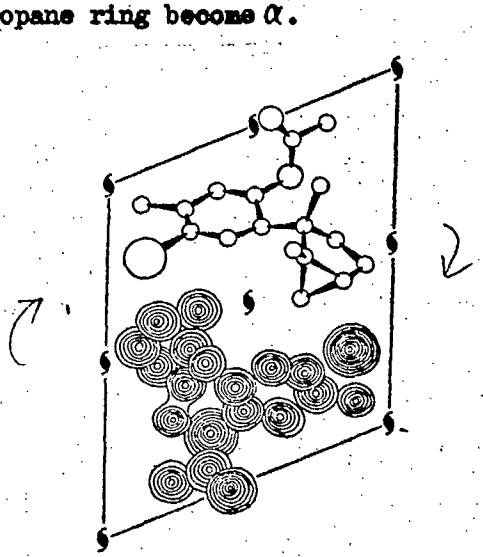


Figure 2: X-ray analysis of laurinterol acetate[28]

[28] A. F. Cameron, G. Ferguson, J. M Robertson, Chem. Commun., 1967, 271.

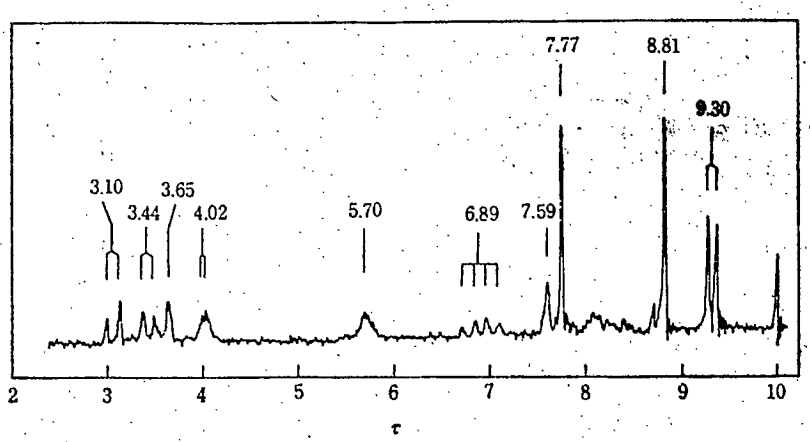
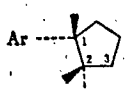


Figure 3: NMR spectrum of laurenisol [17] (60 Mc, CCl_4)

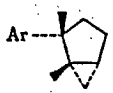
Together with laurinterol, a new phenolic sesquiterpene containing no bromine, debromolaurinterol [15], $C_{15}H_{20}O$, $[\alpha]_D$ -12.2°, was isolated from the neutral fraction of the Kurosozo specimen. For this isolation, the product by acetylation of a crude sample of laurinterol was carefully chromatographed on silica gel, so as to lead to the isolation of two kinds of acetates, i.e., laurinterol acetate and debromolaurinterol acetate. Then, hydrolysis of the latter acetate readily afforded debromolaurinterol [15], which has a phenolic hydroxyl group (ν 3680, 3060, 1185 cm^{-1}). Its spectrum was similar to that of laurinterol [14] in the higher magnetic field region. In the low magnetic field region, however, the former showed signals due to three aromatic protons appeared at τ 3.70 (1H, br. s), 3.51 (1H, br. d, J = 7.5 cps), and 2.77 (1H, d, J = 7.5 cps), instead of two singlets (each 1H) at τ 3.58 and 2.53 in the latter. This spectral pattern of [15] was then attributed to 1,2,4-trisubstituted benzene ring. From these results, it was inferred that this phenolic compound must be a debrominated substance of laurinterol. This inference was substantiated by the reduction of laurinterol to debromolaurinterol in a good yield with lithium aluminium hydride. Also, as in the case

of laurinterol, the treatment of debromolaurinterol with p-toluenesulfonic acid in acetic acid afforded debromoaplysin [13].[19]

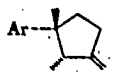
The bicyclic [3.1.0] hexane ring observed in laurinterol [14] and debromolaurinterol [15] is not only noticed as a form of precursor in the biosynthesis toward the aplysin type as mentioned above, but also it is very interesting for its conceivable role as an intermediate in the biosynthesis from the cuparene type to the laurene type.



Cuparene type



Laurinterol type



Laurene type

The absolute configuration of the methyl group at C-1 in cuparene was determined by Enzell and Erdtman[29] by relating it to (+)-camphor. The absolute configuration of the methyl group at C-1 in laurene was determined by relating laurene to cuparene.[16b)30] Also, the absolute configuration of the methyl group at C-1 in laurinterol was determined on the basis of the result of X-ray analysis as mentioned above,[28] so that it was shown that the methyl group has the same stereo-configuration as the methyl groups at C-1 in cuparene and laurene. However, the stereo-configuration of the methyl group at C-2 was found in cis with that at C-1 in laurinterol, whereas in trans in the case of laurene.[16b)30]

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29) C. Enzell and H. Erdtman, Tetrahedron, 4, 361 (1958).

30) T. Irie, T. Suzuki, S. Itō, and E. Kurosawa, Tetrahedron Letters, 1967, 3187.

3.2. Laurenisol[22)]

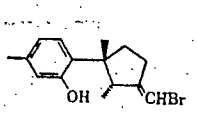
Together with lauren, laureatin, and isolaureatin, a new bromine-containing sesquiterpenoid, laurenisol, was isolated in a crystallized form from the neutral fraction of the methanol extracts from Urasozo (Laurencia nipponica Yamada) in ca. 0.001% yield.

From its UV [λ_{max} 278, 285 mμ (ε 2600, 2600)] and IR spectra [ν_{max} 3610, 3340, 3070, 1640, 1620, 1583, 1513, 1418, 1254, 1156, 1133, 1119, 953, 850, 810 cm^{-1}], it was inferred that laurenisol [17], $C_{15}H_{19}OBr$, $[\alpha]_D$+85.9°, has a double bond with a 2,5-disubstituted phenol group. Its NMR spectrum (Figure 3) showed signals due to a secondary methyl, a tertiary methyl, and an aromatic methyl group at τ9.30 (d, J = 7 cps), 8.81 (s), and 7.77 (s), respectively, and three aromatic protons at τ3.65 (br. s), 3.44 (br. d, J = 8 cps), 3.10 (d, J = 8 cps). Furthermore, the NMR spectrum showed three one-proton signals at τ6.89 (q, J = 7, 7, 7 cps), 5.70 (br. s), and 4.02 (finely splitted doublet, J = 2 cps), which were attributed to the proton of >CH-CH_3, that of phenolic OH, and that of >C=CHBr, respectively. The upfield shift of the secondary methyl signal was attributed to an anisotropic effect of the aromatic nucleus, as in the case of laurene.[16)] Therefore, it was inferred that the aromatic ring and the methyl group must be in cis to each other.

Laurenisol is unstable in normal temperature and so easily changeable as will be described below, whereas its acetate, $C_{17}H_{21}O_2Br$ (M^+ 338, 336), mp 102.5~103°C, is stable. In the NMR spectrum of this acetate, the signal due to the proton of >C=CHBr (finely splitted doublet, J = 2 cps) was also shown at τ4.00. The crystals of laurenisol changed into an oily mixture after placed overnight in a desiccator at room temperature under reduced pressure. Purification of this mixture by chromatography afforded two types

of bromo-ethers [22] and [23] as its principal components. Compound [22], $C_{15}H_{19}OBr$ (M^+ 296, 294), $[\alpha]_D$+22.2°, showed in its UV [λ_{max} 278, 287 mμ (ε 3400, 3500)] and IR [ν_{max} 1622, 1577, 1504, 1411, 1252, 1240, 1167, 1084, 1019, 966, 866, 811, 767 cm^{-1}] spectra the presence of an aromatic ether group and the absence of both hydroxyl and carbonyl groups. In its NMR spectrum, on the other hand, it showed the presence of a secondary methyl (τ 9.27, d, J = 7 cps), a tertiary methyl (τ 8.66, s), an aromatic methyl (τ 7.77, s), and three aromatic protons (τ 3.57, br. s; 3.51, br. d, J = 8 cps; and τ 3.16, d, J = 8 cps). The NMR spectrum also showed AB-quartets (2H, J = 10 cps) at τ6.59 and 6.49, which were attributable to the methylene protons of $-\overset{|}{C}-CH_2Br$. The other bromo-ether [23], an isomer of [22], showed in its spectrum at τ4.97 a signal (finely splitted doublet, J = 14 cps) attributable to the proton at the root of the bromine in $>CH-\overset{|}{C}HBr$, instead of the AB-quartets. /p.1184/

Treatment of the bromo-ether [22] with zinc and acetic acid followed by acetylation afforded a phenol acetate [24] having an exocyclicmethylene group [ν 1656, 879 cm^{-1}; 5.24 (1H, br. s), 5.15 (1H, br. s)]. Upon treatment of this phenol acetate with acid, the exo-methylene moved into the ring, so that the acetate changed into an isomer [25] (τ 8.69, 8.38, each 3H, s) having a tetrasubstituted double bond. This relationship is similar to that between lauren and isolauren.[16] The isomeric cyclopentene [25] was then treated with p-toluensulfonic acid in acetic acid at 50°C for 24 hours to afford debromo-aplysin [13]. According to these chemical and spectral data, the formula [17] was given for laurenisol.



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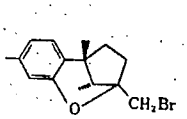

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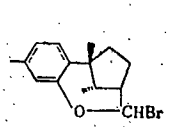
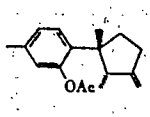


(23)



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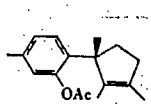

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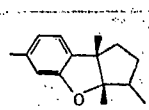
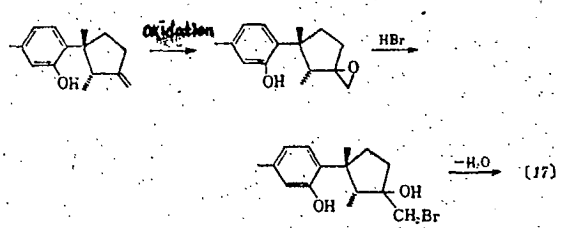


(13)

The structure of laurenisol [17] was observed to be closely related to those of lauren [9] and laurinterol [14]. Also, the characteristic >C=CHBr grouping in [17] was found in natural matters for the first time. These observations are very interesting from the point of view of biosynthesis. It was then suggested that the exo-methylene probably becomes a bromohydrine via epoxide, when dehydration occurs to form this grouping.



This supposition was supported by the fact that eupatorin acetate having an exocyclic epoxide structure and its corresponding eupachlorine acetate of chlorhydrine were found in the same plant.[31]

As mentioned earlier, aplysin [11], debromoaplysin [13], and aplysinol [12] were isolated from a marine animal Amefurashi (Aplysia kurodai) and also their structures were determined by Yamamura and Hirata.[18] It is interesting that they were isolated also from a red alga Mitsudesozo (Laurencia Okamurai).[19] Although the 20-aplysin [26] which was isolated also from the Amefurashi by Hirata and his asscciates[32] has not yet been isolated from marine algae, it is conceivable that either the aplysin itself or its precursor may be present in marine algae.

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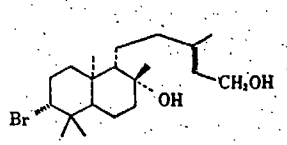
31) S. M. Kupchan, J. C. Hemingway, J. M. Cassady, J. R. Knox, A. T. McPhail, and G. A. Sim, J. Am. Chem. Soc., 89, 465 (1967); S. M. Kupchan, J. E. Kelsey, M. Maruyama, and J. M. Cassady, Tetrahedron Letters, 1968, 3517.

32) H. Matsuda, Y. Tomiie, S. Yamamura, and Y. Hirata, Chem. Commu., 1967, 898.



(26)

4. LAURENCIN, LAUREATIN, AND ISOLAUREATIN

The three types of cyclic ethereal bromic compounds that are related to each other structurally, laurencin [18],[23] laureatin [19],[24)25] and isolaureatin [20],[25)26] were found in the marine algae of the genus Sozo (Laurencia). Furthermore, there was found another type of bromine-containing compound that is closely related to these compounds, and researches into its structure has been also in progress. It must be noted here that, as will be described below, the NMR and NMDR were very useful for determining the structures of these compounds, and also that the prior isolation of laurencin and subsequent determination of its structure, though accidental, were convenient for proceeding the following experiments on the other compounds.

4.1. Laurencin[23]

Air-dried specimen (8.5 kg) of the Oosozo (Laurencia glandulifera Kützing) collected in Oshoro Bay, Hokkaidō, was soaked twice in methanol at room temperature for ten days. Then, the methanol solution was concentrated under reduced pressure, and the brown syrupy residue was taken into ether. The ethereal solution was then washed successively with 5% potassium hydroxide solution, 1N hydrochloric acid, and water to remove its acidic and basic components. After evaporation of the ether, a yellow oily neutral fraction

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33) Toshi Irie and Minoru Suzuki, unpublished.

(ca. 90 g) was obtained. This neutral fraction was then chromatographed on silica gel. First, the above-mentioned sesquiterpene hydrocarbon, lauren [9], was isolated together with paraffin from the effluent with n-hexane. Then, a type of bromic sesquiterpene ketone, $C_{15}H_{23}OBr$,[33] was isolated from the effluent with n-hexane-benzene (ca. 9:1), and its structure is being investigated. From the effluent with n-hexane-benzene (ca. 5:1), then, laurencin 18 was isolated in a crystallized form. The yield was about 4.5 g. Also, cholesterol was isolated from the effluent with benzene.

Laurencin [18], $C_{17}H_{23}O_3Br$, was isolated as large rhombic crystals of mp 73~74°C, $[\alpha]_D$ +70.2°, by recrystallization from methanol. The IR and UV spectra of [18] indicated the presence of a terminal methyne (ν 3285, 2100 cm^{-1}), trans and cis double bonds (ν 3040, 950, 750 cm^{-1}), a conjugate diene or enyne (λ_{max} 224 mμ, ε 16400; λ_{infl} 232 mμ, ε 11000), and an acetoxyl group (ν 1735 cm^{-1}). The presence of these groups was then substantiated by the NMR spectrum (Figure 4). From the NMR spectrum, it also became clear that the presence of four olefinic protons is shown by the signals at τ 3.85 (1H, sex, J = 15, 7, 7 cps), τ 4.1 (2H, m), and τ 4.48 (1H, finely splitted doublet, J = 15 cps). These signals were given the symbols (A), (B), and (C), /p.1185/ respectively, so that the protons corresponding to them could be referred to accordingly in such a way as, for instance, the proton corresponding to (A) being referred to as H-A(as shown in Figure 4). From the values of the coupling constants of (A), (B), and (C), it was inferred that H-A and H-C are the protons in a trans double bond while H-B is the proton in a cis double bond, and that a methyl group is present next to the carbon with H-A. Furthermore, from the fact that H-C is finely splitted, this was attributed to a long-range coupling. These points were substantiated by the decoupling study which will

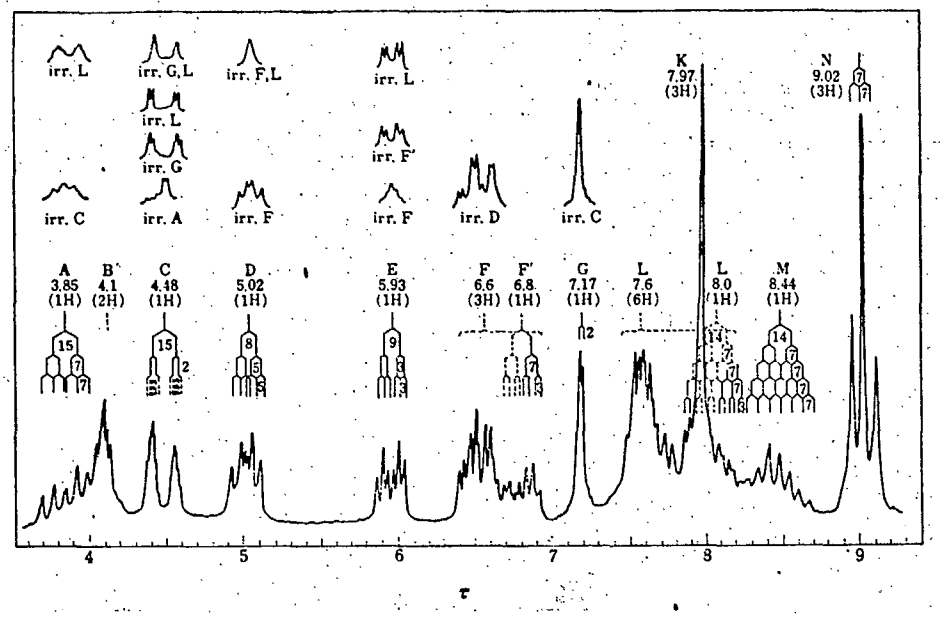

Figure 4: NMR and NMDR spectra of laurencin [18] (100 Mc, $CDCl_3$)

be described later. The 1H, doublet (J = 2 cps) at τ 7.17 (G) was supposed to indicate the proton of a terminal methyne; it disappeared by reduction as will be described later. The 3H, singlet at τ 7.97 (K) obviously indicated the methyl of acetoxyl, and the signal due to the proton at the root of its acetoxyl group appeared at τ 5.02 (D) as 1H, sextet (J = 8, 5, 5 cps). The similar 1H, sextet (J = 9, 3, 3 cps) at τ 5.93 (E) was supposed to indicate the proton at the root of bromine, but this will be discussed later. Taking into consideration the steep 3H, triplet (J = 7, 7 cps) at τ 9.02 (N), the 1H, heptad (J = 14, 7, 7, 7, 7 cps) at τ 8.44 (M), and the partly hidden 1H, decade (or dodecade) at τ 8.0 (L') altogether, this was inferred to be the proton of an ethyl group. This inference was also substantiated by the decoupling study which will be described below, and supported later by the isolation of propionaldehyde on ozonolysis of laurencin.

On mild hydrolysis*6 in a methanolic potassium hydroxide solution, laurencin [18] afforded deacetyllaurencin [27], $C_{15}H_{21}O_2Br$, which was uncrystallizable and reconverted into the original acetate [18] by treatment with acetic anhydride and pyridine. The NMR spectrum of [27] was not much different from that of [18]; in the former, however, the signal at τ 7.97 (K) had disappeared and the signal at τ 5.02 (D) was shifted to a higher field, 6.5 (1H, m). This substantiated that the above-mentioned signal at τ 5.02 (D) in the NMR spectrum of laurencin corresponds to the proton at the root of the acetoxyl group and, therefore, that the signal at τ 5.93 (E) corresponds to the proton at the root of the bromine.

Laurencin [18] became octahydrolaurencin [28], $C_{17}H_{31}O_3Br$, by consuming four moles of hydrogen when hydrogenated in acetic acid ethyl over Adams' catalyst. The UV spectrum of [28] showed only the terminal absorption, while its IR spectrum indicated the presence of an acetoxyl group (ν 1735, 1237 cm^{-1}). In the NMR spectrum of [28], the signals corresponding to those of (D), (E), and (K) in the spectrum of [18] were observed, though they were shifted to a slightly higher fields, τ 5.21, 6.13, and 8.02, respectively, while the signals due to the olefinic protons in (A), (B), and (C) and the signal in (G) in the spectrum of [18] had disappeared, thus proving the signal (G) to be due to the proton of terminal methyne. Also, corresponding to a complex signal (3H, (F) including (F')) at τ ca. 6.4~6.9 in the spectrum of [18], only a 2H, multiplet centered at τ ca. 6.5 was found in the spectrum of [28]. The disappeared signal (F') due to 1H was attributed to the proton at the allylic

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*6 The alkali treatment of laurencin under considerably strong conditions affords an allene-type compound (ν 1950 cm^{-1}).

position. This will be discussed later.

On hydrolysis, [28] afforded octahydrodeacetyllaurencin [29], $C_{15}H_{29}O_2Br$, $[\alpha]_D$+29.4. Its NMR spectrum showed signals due to two methyl groups (τ 9.06, br. t; 8.97, t, J = 8.8 cps), a secondary hydroxyl group (τ 7.76, 1H, s; τ about 6.3, 1H, m), and the proton at the root of bromine (τ about 6.0, 1H, m). Its acetylation recovered the original [28].

On the treatment with lithium aluminium hydride in thermo-tetrahydrofuran, [28] was debrominated and became hydroxyether [30], $C_{15}H_{30}O_2$, which was then acetylated by the ordinary method to give acetoxyether [31], $C_{17}H_{32}O_3$ [ν1740 cm^{-1}; τ6.48 (2H, m), 5.15 (1H, m)]. Compound [30], i.e., octahydrodeacetyldebromolaurencin, $[\alpha]_D$+21.5°, ν 3570, 3480, 1190, 1090 cm^{-1}, exhibited in its NMR spectrum two methyl groups (τ 9.06, 3H, br. t; τ 9.00, 3H, t), secondary hydroxyl groups (τ 7.64, 1H, br. s; τ 6.66, 1H, m), and two protons at the root of ether (τ about 6.7, m). Oxidation of this compound with chromic acid in acetic acid, afforded propionic acid, caproic acid, and adipin /p.1186/ acid. The propionic acid together with the above-mentioned propionic aldehyde afforded by the ozonolysis of laurencin indicated the presence of ethyl groups within the particles. The caproic acid indicated the presence of penthyl groups, and the adipin acid was supposed at least to indicate the presence of the group of $C-(CH_2)_4-C$.

In comparison of the NMR spectra of the above-mentioned laurencin and of its derivatives, the chemical shifts of their corresponding protons were as shown in Table 2. Within the range of τ 6.5~6.9, laurencin [8] and deacetyllaurencin [27] showed 3H, while all the octahydro-compounds [28], [29], [30] and [31] showed 2H. This 2H was attributed to the protons at the root of ether, while the 1H (F') at τ ca. 6.8 of the 3H in [18] was attributed to the proton at the

allylic position which had shifted to an unusually lower magnetic field. These (F') and (L') were examined further in terms of the results of their decoupling.

Table 2: NMR spectra (τ) of laurencin and its dirivatives

Compound	A	B	C	D	D'[c]	E	F	F'	G	K	K'[b]	L	L'	M	N	N'[c]
[18]	3.85	4.1	4.48	5.02	—	5.93	6.6	6.8	7.17	7.97	—	7.6	8.0	8.44	9.02	—
[27]	3.85	4.1	4.63	—	6.06	6.5	6.6	6.9	7.38	—	7.77	7.4~7.8	8.5	8.5	9.04	—
[28]	—	—	—	5.21	—	6.13	6.5	—	—	8.02	—	—	?	?	9.00	9.07
[29]	—	—	—	—	6.0	6.13	6.6	—	—	—	7.76	—	8.6	8.6	8.99	9.08
[30]	—	—	—	—	6.55	—	6.7	—	—	—	7.64	—	?	?	9.00	9.06
[31]	—	—	—	5.15	—	—	6.6	—	—	7.95	—	—	?	?	9.05	9.05

a) >CHOH. b) OH. c) $-(CH_2)_4CH_3$.

On the basis of the foregoing results, the following partial structural formula was given for laurencin [18]:

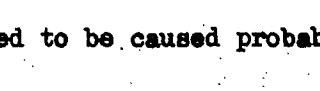
$C_{17}H_{23}O_3Br =$ { 3 $-CH_2-(C=C)$; $-C\equiv CH$; 2 $-CH=CH-$ (*cis* および *trans*); >$CHOCOCH_3$; >CHBr; >CH-O-CH< (あるいは $-CH_2-O-\overset{C}{\underset{C}{C}}-C$); $-CH_2-CH_3$ }

Examination of the decoupling results was helpful for formulating this partial structure. The decoupling data were as shown in Figure 4 and Table 3.

When (G) was irradiated, the fine splitting of (C) disappeared to become a simple doublet (J = 15 cps). When (C) was irradiated, the 2 cps coupling of (G) disappeared to become a singlet. This substantiated the conjugation of the trans double bond and the terminal acetylene bond. Also, the above-mentioned supposition of the presence of methylene group adjacent to H-A was substantiated by the result that (A) became a wide doublet (J = 15 cps) when (L) was irradiated. Thus, the following partial structure (i) became clear:

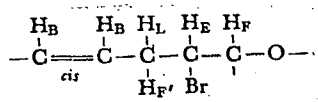
$$-\overset{H_L}{\underset{H_L}{C^*}}-\overset{H_A}{C}=\underset{H_C}{C}-C\equiv C-H_G \qquad (i)$$

Next, when (D), i.e., the proton at the root of the acetoxyl group, was irradiated, (F) and (L) showed significant change. On the other hand, when (F) and (L) was irradiated, (D) changed into a quartet (J = 8, 5 ops) and a wide doublet (J = 5 ops), respectively. Thus, the following partial structure (ii) became clear:



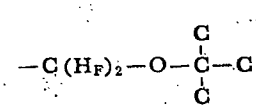
(ii)

Then, for the purpose of investigating the region around τ 5.93 (E), the proton at the root of bromine, (E) was irradiated. As the result, changes in (F), (F') and (L) were observed. On the other hand, (E) was decoupled respectively to a wide triplet (J = 3, 3 cps), a wide quartet (J = 9, 3 cps), and a quartet (J = 9, 3 cps) by the irradiation of (F), (F') and (L). The shift of H-F', the proton at the allylic position, to an unusually lower magnetic field was supposed to be caused probably by the bromine. Furthermore, when (F') and (L) were irradiated, changes occurred not only in their signals but also in (B). From these results, the following partial structure (iii) became clear:

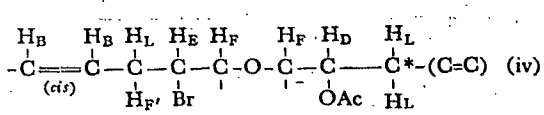


(iii)

Because both (D) and (E) were decoupled when the signal (F) due to the proton at the root of ether was irradiated, there was no posibility of the following partial structure:

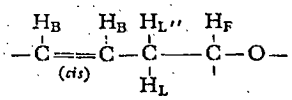


Therefore, (ii) and (iii) were combined into the following (iv):



(iv)

As mentioned above, when (B) was irradiated, changes occurred not only in (F') and (L) but also in the pattern around τ 7.8. Assuming its changing signal as (L"), this was supposed probably to be one of the Hs of the methylene at the allylic position adjacent to the cis double bond. This (L") was observed to be changed also by the irradiation of (F). Because (L") was overlapping with other signals so that the condition of its coupling was not clear, nothing decisive could be found. However, taking into consideration the foregoing results, the following (v) was conceivable as its skeleton:



(v)

The shifting of the H-L" signal, one of the Hs of the methylene at the allylic position, to a higher magnetic field, τ 7.8, must be attributed to a deshielding effect of the double bond. Since the cis double bond of (v) and the cis double bond at the left end of (iv) must be the same, (v) was supposed to link with the left end of (iv) while the right side of (v) was supposed to correspond to one of the carbons at the root of the ether of (iv). Also, the C* at the right end of (iv) was supposed to correspond to the C* at the left end of (i), and, accordingly, (i) was supposed to link to the right end of (iv).

Next, as mentioned above, the 1H, septet of (M) and the 1H, decade (or dodecade) of (L') were attributed to the methylene of ethyl group. This was substantiated by the results that both (M) and (L') became quartets by the irradiation of (N), while (N) was decoupled to a singlet when (M) and (L') were simultaneously irradiated. This means that these two methylenic hydrogens are magnetically unequivalent to each other. Besides, from the result that changes occurred in both (M) and (L') also by the irradiation of (F), this

/p.1187/

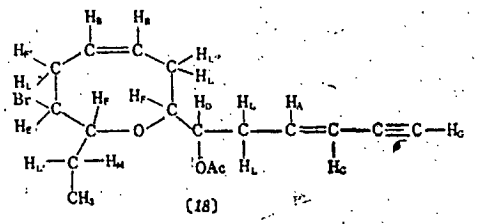
Table 3: NMR spin decoupling results of laurencin [18] (100 Mc, $CDCl_3$).

Run	Irradiated proton			Observed proton	Multiplicity change[a]	Splitting decoupled[b] (cps)
1	7.17 (G)	C-15	-C≡CH	4.48 (C)	dec→sex	2
2a	4.48 (C)	C-13	-CH=CH-	7.17 (G)	d→s	2
b			t	3.85 (A)	sex→t	15
c				7.6 (L)	(ch)	v. s.
3a	3.85 (A)	C-12	-CH=CH-	4.48 (C)	dec→s(br)	15
b			t	7.6 (L)	(ch)	
4a	5.02 (D)	C-10	-CH(OAc)-	6.6 (F)	(ch ?)	
b			t	7.6 (L)	(ch)	
5a	5.93 (E)	C-4	-CHBr-	6.6 (F)	(ch)	
b				6.8 (F')	(ch)	
c				7.6 (L)	(ch)	
6a	6.6 (F)	C-3	>CH-O-CH<	5.02 (D)	sex→q	5
b		and		5.93 (E)	sex→t(br)	9
c		C-9		8.03 (L')	dec→sex(?)	3
d				8.44 (M)	sep→sex	7
e				7.6 (L)	(ch)	
f				7.8 (L'')	(ch)	
7a	6.8 (F')	C-5	allylic	5.93 (E)	sex→q(?)	3
b			proton	4.1 (B)	(ch)	
c				7.6 (L)	(ch)	
8a	7.6 (L)	C-5,	allylic	3.85 (A)	sex→d	7, 7
b		C-8	protons	4.48 (C)	dec→q	1.5, 1.5
c		and		5.93 (E)	sex→q	3
d		C-11		5.02 (D)	sex→d(?)	5, 8
e				4.1 (B)	(ch)	
f				6.6 (F)	(ch)	
g				6.8 (F')	(ch)	
9a	4.1 (B)	C-6	-CH=CH-	6.8 (F')	oct(?)→q	7
b		and	c	7.6 (L)	(ch)	
c		C-7		7.8 (L'')	(ch)	
10a	9.02 (N)	C-1	$-CH_2-CH_3$	8.44 (M)	sep→q	7, 7, 7
b				8.03 (L')	dec→q	7, 7, 7
11	7.17 (G)	and 7.6 (L)		4.48 (C)	dec→d	2, 1.5, 1.5
12	6.6 (F)	and 7.6 (L)		5.02 (D)	sex→s(br)	5, 5, 8
13	8.44 (M)	and 8.03 (L')		9.02 (N)	t→s(br)	7, 7

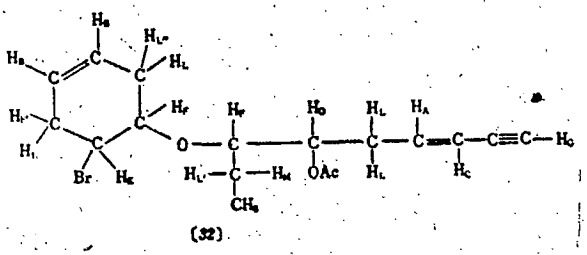
a) Abbr.: "s" means singlet; "d" doublet; "t" triplet; "q" quartet; "sex" sextet; "sep" septet; "oct" octet; "dec" decade; "br" broad; "ch" change; "?" means that the multiplicity is not clear.

b) Abbr.: "v.s." means "very small coupling constants". The error limits; $J \pm 0.5$ cps.

ethyl group was supposed to link with one of the carbons at the root of the ether. Taking account of all the foregoing results together, [18] and [32] remained as possible structures for laurencin.



(18)

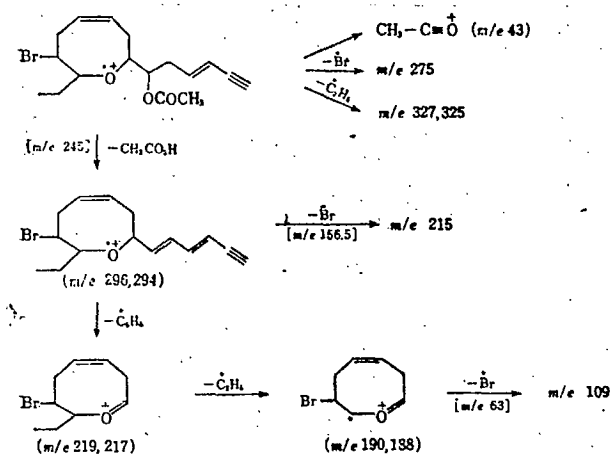


(32)

It was impossible by the above-mentioned method to determine the foregoing alternative, because there was no difference between the chemical shifts of the H-F protons. However, this problem was solved because their shifts in the solvent were different from each other. That is; because the chemical shifts of the two H-F were divided into two parts in the spectrum in benzene, τ 6.95 and 6.62, it turned out after decoupling of these that the former coupled with (D) while the latter with (E), (L') and (M). Accordingly, the formula [18] was given for laurencin.

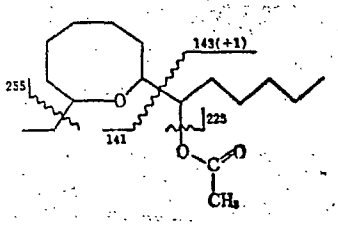
This structure of laurencin was supported also by its mass spectrum. That is; the main fragment ions of the mass spectrum of laurencin (Figure 5, A) may be shown as follows ([ ] shows metastable ions):

/p.1188/



Also, the mass spectrum (Figure 5, B) of octahydrodebromolaurencin [31] is explicable in terms of the following fragmentations:*7

*7 The strong peak at *m/e* 123 may be attributable to the loss of H_2O from *m/e* 141, as demonstrated by the appearance of a metastable ion peak at *m/e* 107.5.



Lastly, as to the stereochemistry of laurencin, the hydrogens at C-3 and C-4 were supposed from their coupling constants to be in trans position to each other, but the stereo-configurations at C-3 and C-4, and at C-9 and C-10, were not clear.

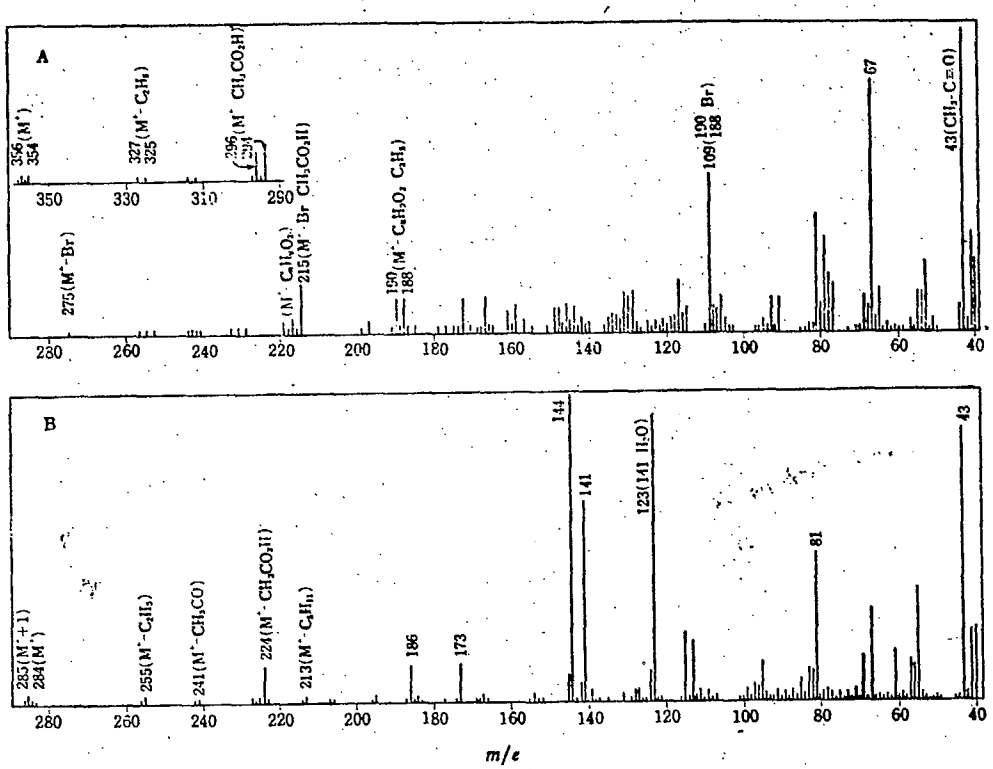
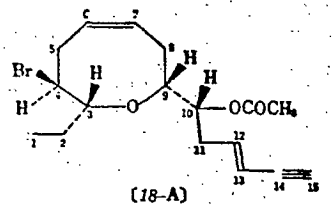


Figure 5: Mass spectra of (A) laurencin [18] and (B) octahydrolaurencin [31].

Soon after the publication of a preliminary report on the structure of laurencin by the author and his associates,[23a] X-ray analysis of laurencin was done by Prof. Robertson and his research associates. From its results, the plane structural formula proposed by the author and his associates proved

correct, and also the relative stereo-structure [18-A] was clarified.[34]



(18-A)

Therefore, if the absolute configuration of any one of the four asymmetric centers could be determined, the absolute structure of laurencin must accordingly be determinable. For this reason, the absolute configuration at C-10 was investigated by the following method, and it turned out to have a R-configuration. That is; octahydroacethyllaurencin [29] was changed by Prelog's method into phenylglyoxylic acid ether [33], which was acted on by methyl magnesium iodide and then hydrolyzed to afford levorotatory atrolactic acid [34]. Thus, it was determined that laurencin has the absolute structure shown by the foregoing [18-A].

Furthermore, the absolute structure of laurencin was recently investigated by means of three-dimentional X-ray analysis by Ferguson and his associates,[35] and the result also indicated that the asymmetric C at C-10 has a R-configuration, thus corresponding to the result obtained by the author and his associates by means of chemical method. /p.1189/

Laurencin is an 8-membered cyclic ether which had not been found in natural matters, having a peculiar structure with the side-chains of terminal

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34) A. F. Cameron, K. K. Cheung, G. Ferguson, and J. M. Robertson, Chem. Commun., 1965, 638.

35) Private communication from Dr. G. Ferguson.

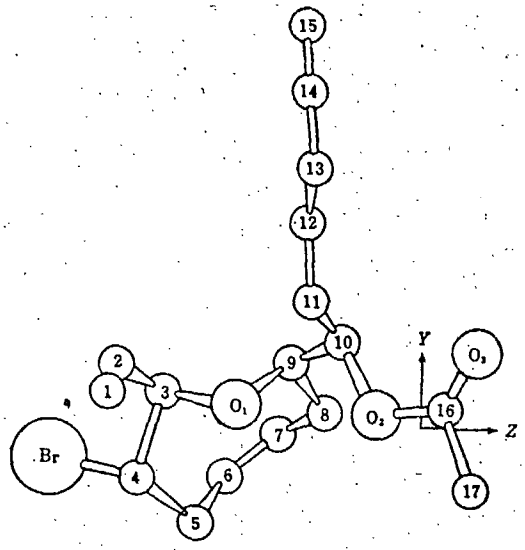
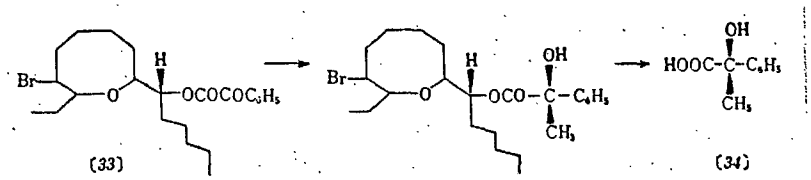


Figure 6: X-ray analysis of laurencin [18].[34]



conjugate enyne bonds. As mentioned above, this was supposed to be formed from hexadeca-4,7,10,13-tetraene acid via decarbonic acid and epoxidation of double bonds. This was more clarified through the examination of laureatin and isolaureatin.

4.2. Laureatin and Isolaureatin

On the supposition that there must be some other compounds related to laurencin [18], bromic components in the marine algae of mainly the genus Sozo (Laurencia) and its near genera were investigated. Then, as described earlier, laurinterol was found in the Kurosozo (L. intermedia) collected in Oshoro Bay, and also several bromine-containing sesquiterpenic compounds such as laurinterol, aplysin, and aplysinol were found in the Mitsudesozo (Laurencia Okamurai) collected in the Seto Inland-Sea. Yet, no bromic compounds related

to laurencin were than found out.[*8] Thereafter, two new bromine-containing compounds related to laurencin, i.e., laureatin and isolaureatin, were isolated from the Urasozo (L. nipponica Yamada) collected at the Mobeji Beach in Hakodate Bay. The method of isolation was almost the same as that in the case of laurencin. That is; the neutral fraction of the methanolic extracts was chromatographed and, after removing the effluents of paraffin, laurene [9], laurenisol [17], etc., a crudely crystallized substance which was positive to the halogen test was yielded from the effluent with n-hexane-benzene (1:2). This crystallized product was a mixture of two types of isomers having the composition of $C_{15}H_{20}O_2Br_2$, from which laureatin [19], mp 82~83°C, $[\alpha]_D$ +96°, and isolaureatin [20], mp 83~84°C, $[\alpha]_D$ +40°, were isolated in the yields of 0.05% and 0.02% (of the air-dried specimens), respectively, by carefully repeating recrystallization from the methanol.

The UV spectra of laureatin [19] and isolaureatin [20] were almost the same; λ_{max} 223, 229 mμ (ε 12400, 10300) and λ_{max} 223, 229 mμ (ε 12800, 10400), respectively. Their absorptions were very similar to those of laurencin [18]. Also, the presence of peculiar absorptions of the terminal methyne at ν 3,300, 2150 cm^{-1} and ν 3300, 2100 cm^{-1}, respectively, in their IR spectra was the same as in the case of laurencin. Furthermore, the NMR spectrum of laureatin (Figure 8) showed a 1H, sextet, (J = 11, 7, 7 cps) at τ3.97 (A), a 1H, finely splitted doublet (J = 11 cps) at τ 4.47 (B), and a 1H, doublet (J = 2 cps) at τ 6.94 (I). The NMR spectrum of isolaureatin also

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[*8] Aplin and his associates investigated the components of L. Pinnatifida collected on a coast of England, but they could not find any acethylenic compounds related to laurencin. Cf. R. T. Aplin, L. J. Durham, Y. Kanazawa, and S. Safe, J. Chem. Soc. (C), 1967, 1346; Private communication from Sir Ewart Jones.

showed almost the same signals, which also indicated the presence of the group of $-CH_2-CH_A=CH_B-C\equiv CH_I$ as in the case of laurencin. This was substantiated by their decoupling results. However, whether the double bond is cis or trans could not be determined because of J_{AB}= 11~12 cps and also because of the presence of other absorptions at the region around ν 950 cm^{-1} in the IR spectrum (Figure 7). Thereafter, the geometrical isomers of laureatin and isolaureatin whose respective J_{AB} is 16 cps were found in the same marine alga, though in a very small quantity,[36] so that the double bond can now be considered to be cis in the case of laureatin and isolaureatin. But the cause of the chemical shift of H-1 of the terminal methyne to a considerably lower magnetic field, τ 6.94, is not yet clear, although it may be attributable to the double bond being cis.

Because neither hydroxyl group nor carbonyl group were found in laureatin and isolaureatin (IR, NMR), their two oxygen atoms were supposed to be ethereal. This supposition was substantiated by their IR and NMR spectra. That is; the IR spectra showed absorptions of ν 1140, 1086, 1045, 975[*9] cm^{-1}, while the NMR spectra showed in the region of τ 5.0~6.5 the signals of 6H which were attributable to the protons at the root of ether and those at the root of bromine. Of these protons, if two were the protons at the root of bromine (>CHBr), the remaining 4H would then correspond to the protons at the root of ether. In the case of isolaureatin, these protons could not be analyzed because the signals of 4H of the 6H were overlapping one another in the NMR

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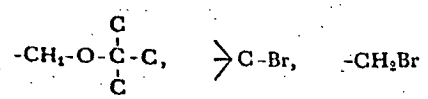
[36] Toshi Irie, Akio Fukuzawa, and Etsurō Kurosawa, unpublished.

[*9] The absorption of ν 975 cm^{-1} will be described later.

spectrum (Figure 11). In the case of laureatin, on the other hand, there were three 1H septets at τ 5.12 (C), 5.46 (D), and 5.87 (F), one bread 1H quartet at τ 5.62 (E), and two partially overlapping 1H multiplets centered at τ ca. 6.2 (G) and 6.35 (H). As will be described later, because the 15 carbon atoms of laureatin and of isolaureatin were combined together in a straight-chain form, the possibility of the following partial structure was excluded:



/p.1190/

Accordingly, those six protons were analyzed as follows: 2 >CH-O-CH< and 2 >CHBr.

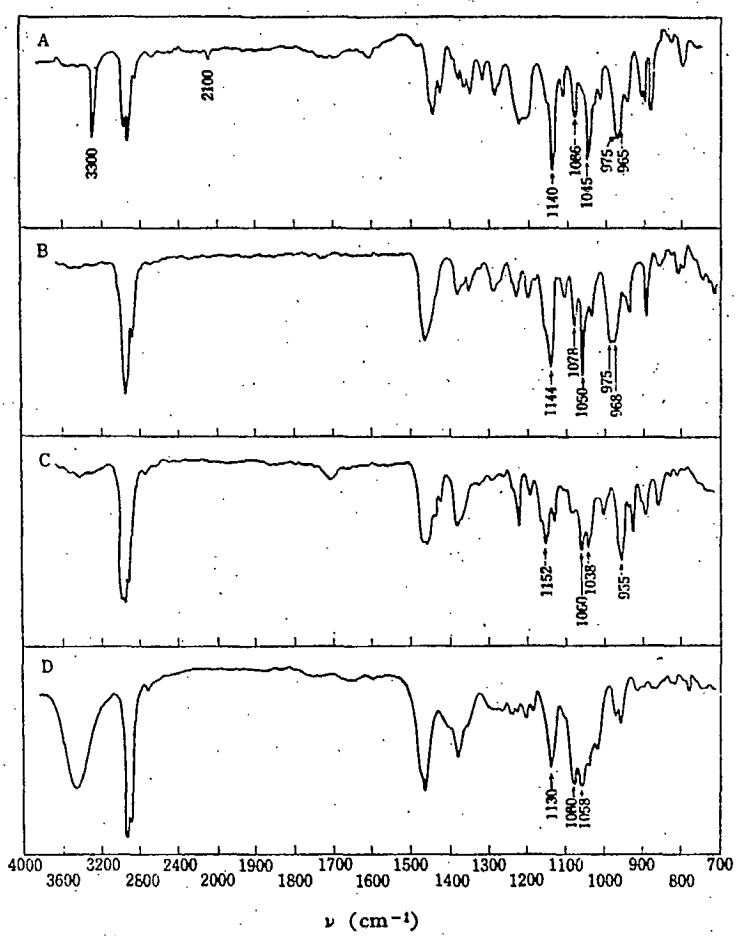


Figure 7: IR spectra of (A) laureatin [19], (B) hexahydrolaureatin [35], (C) hexahydrobisdebromolaureatin [43], and (D) hydroxyether [44].

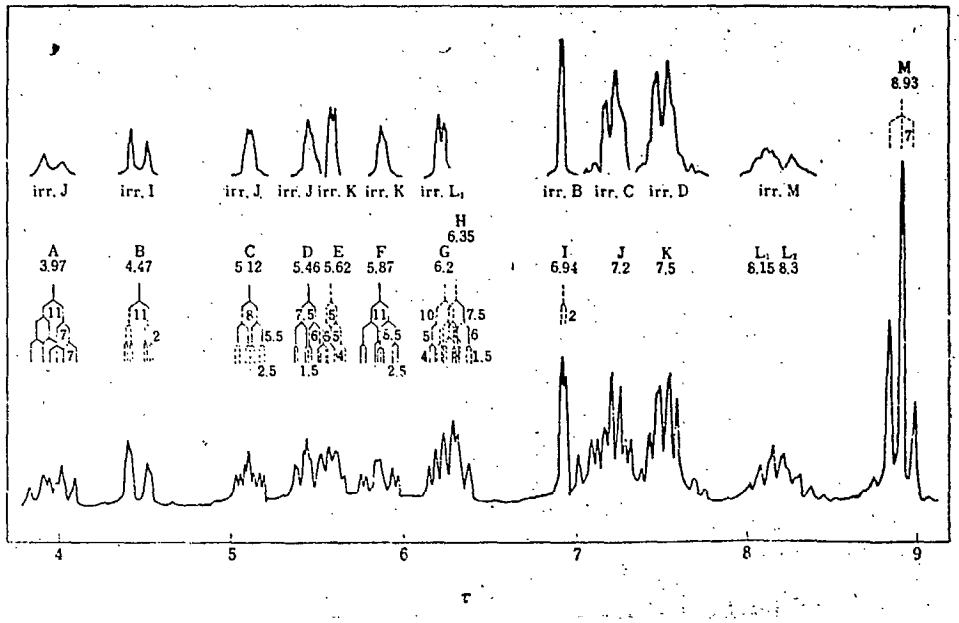


Figure 8: NMR and NMDR spectra of laureatin [19] (100 Mc).

Furthermore, in the NMR spectrum of laureatin, the 3H triplet at τ 8.93 (M), and the two 1H multiplets at τ ca. 8.15 (L_1) and 8.3 (L_2) were attributable to the protons of ether group, while the complex 3H multiplets at τ ca. 7.2 (J) and 7.5 (K) were attributable, as will be described later, to the protons of the two methylenic groups between the carbons bearing an ethereal oxygen and the carbons to which a bromine was attached and also to the two allylic protons.

Laureatin [19], when hydrogenated over Adams' catalyst, became hexahydrolaureatin [35], $C_{15}H_{26}O_2Br_2$, by consuming 3 moles of hydrogen. The IR spectrum (Figure 7) of [35] indicated the presence of oxyde groups (ν 1144, 1078, 1050, 975, 965 cm^{-1}). In its NMR spectrum (Figure 9), on the other hand, the signals corresponding to those of (A), (B), and (I) in the spectrum of laureatin disappeared, while a wide 3H triplet attributable to the methyl group at the end of alkyl group and a peak due to the methylenic protons (6H)

were shown at τ 9.05 (N) and τ 8.57 (P), respectively. Also, instead of the complex 3H signals at τ 7.2 (J) and 7.5 (K) in the spectrum of laureatin, signals of 2H multiplets appeared at τ 7.1 (J') and 7.3 (K'), so that 2H of the 6H in (J) and (K) were supposed to be corresponding to the protons at the allylic position and the remaining 4H to (J') and (K') of hexahydro compound. This observation will be further examined later. In the hexahydro compound [35], the signals in the region of τ 4.8~6.5, i.e., those due to the protons at the roots of bromine and ethereal oxygen, were divided into considerably clear independent signals (100 Mc). That is; the 1H signals corresponding respectively to those of (C) to (H) in the spectrum of laureatin were observed on the septet (J = 8, 5.5, 2.5 cps) at τ 4.97 (C), the septet (J = 7.5, 6, 1.5 cps) at τ 5.23 (D), the wide quartet (J = 5, 5, 4 cps) at τ 5.41 (E), the septet (J = 11, 8.5, 2.5 cps) at τ 5.74 (F), the quintet (J = 10, 5, 4 cps) at τ 6.15 (G), and the septet (J = 7.5, 6, 1.5 cps) at τ 6.39 (H). /p.1191/

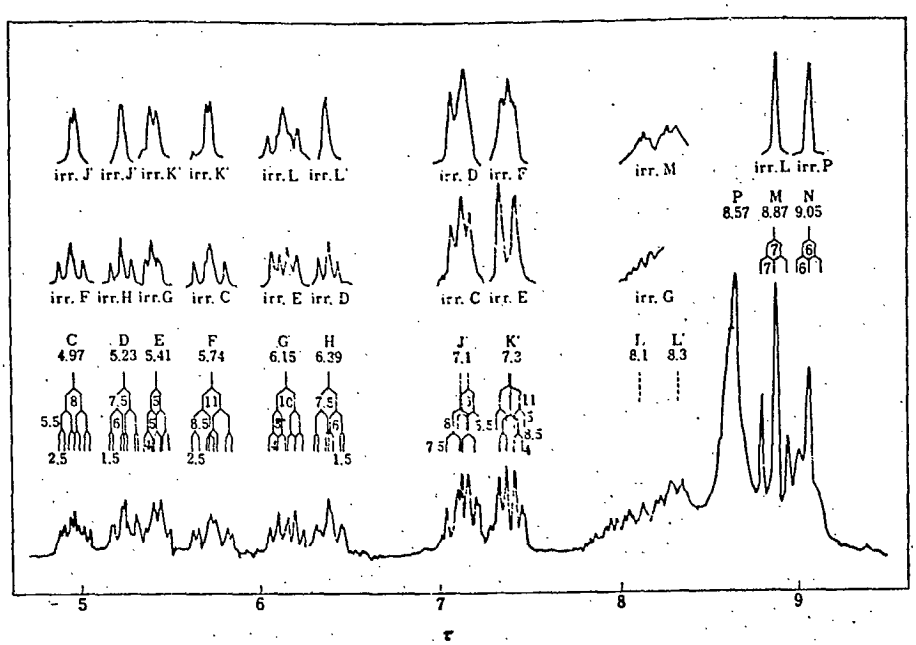


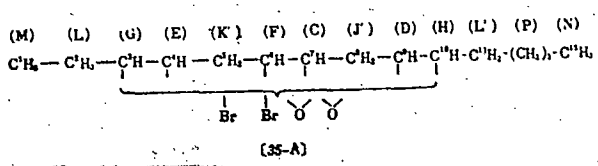
Figure 9: NMR and NMDR spectra of hexahydrolaureatin [35] (100 Mc)

Table 4: Spin decoupling of hexahydrolaureatin [35] (100 Mc, $CDCl_3$)

Irradiated proton		Observed proton	Multiplicity change[a]	Splitting decoupled (cps)
8.87(M)	C-1 $-CH_2-CH_3$	8.1 (L)	(ch)	7
8.1 (L)	C-2 $-CH_2-CH_3$	8.87(M)	t→s	7, 7
		6.15(G)	qui→t	10, 4
6.15(G)	C-3 H*[b]	8.1 (L)	(ch)	10, 4
		5.41(E)	q(br)→t(br)	5
5.41(E)	C-4 H*	6.15(G)	qui→q	5
		7.3 (K')	m→d(br)	5, 4
7.3 (K')	C-5 $-CH_2-$	5.41(E)	q(br)→d	5, 4
		5.74(F)	sep→d	11, 8.5
5.74(F)	C-6 H*	7.3 (K')	m→ds	11, 8.5
		4.97(C)	sep→t(br)	2.5
4.97(C)	C-7 H*	5.74(F)	sep→t(br)	2.5
		7.1 (J')	(ch)	8, 5.5
7.1 (J')	C-8 $-CH_2-$	4.97(C)	sep→d	8, 5.5
		5.23(D)	sep→s(br)	7.5, 6
5.23(D)	C-9 H*	7.1 (J')	m→ds	7.5, 6
		6.39(H)	sep→t(br)	1.5
6.39(H)	C-10 H*	5.23(D)	sep→t(br)	1.5
		8.3 (L')	(ch)	7.5, 6
8.3 (L)	C-11 $-CH_2-$	6.39(H)	sep→s(br)	7.5, 6
8.57(P)	$-CH_2-$	9.05(N)	t(br)→s	6, 6

a) For abbreviations, refer to the note of Table 3. "qui" means quintet; "ds" double doublet.
b) Proton on the carbon atom coupling with bromine or ethereal oxygen.

The results of the spin decoupling experiments on hexahydrolaureatin were as shown in Figure 9 and Table 4. In short, it became clear that hexahydrolaureatin [35] has a straight-chained carbon skeleton, and that two bromine atoms and two ethereal oxygens couple with some of the C-3, C-4, C-6, C-7, C-9, and C-10. Accordingly, the formula [35] can be expressed by the following formula [35-A]:*10

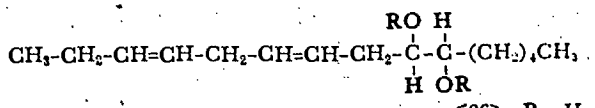


[35-A]

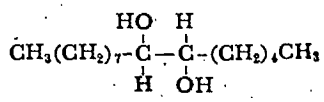
*10 For instance, (M) in the NMR spectrum indicates the signal corresponding to its proton.

(19)

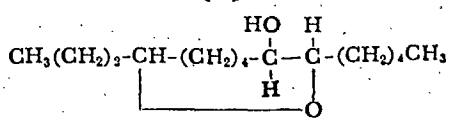
(35) X=Br
(43) X=H



(36) R=H
(37) R=Ac



(38)

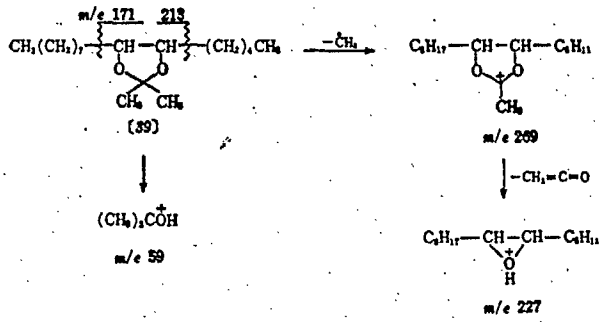


(44)

Then, in order to determine the coupling position of these bromines and ethereal exygens, the following experiments were conducted:

(i) The compound [35] was treated with zinc and acetic acid and then hydrogenated with dilute alkali, so that glycol [36], $C_{15}H_{28}O_2$(M^+ 240), was afforded. The multiplets at τ 6.61 (2H) and 4.54 (4H) in the NMR spectrum of [36] were attributed to the protons at the root of hydroxyl group and the olefinic protons, respectively. In the NMR spectrum of its diacetate [37], $C_{19}H_{32}O_4$(M^+ 324), the wide peak (2H) centered at τ 7.28 was attributed to the methylenic protons between two double bonds. Also, in the NMR spectrum, signals due to the four protons at the allylic position and to the two protons at the root of acetoxyl group were shown at τ 7.6~8.2 and at τ ca. 5.1, respectively. By contact catalytic reduction the unsaturated glycol [36] became /p.1192/ a saturated glycol [38], $C_{15}H_{32}O_2$(M^+ 244), mp 54~55°C, $[\alpha]_D$ -25.4°. The structure of [38] was inferred from the mass spectrum of its isopropylidene derivative [39], $[\alpha]_D$ -35°, and then determined by comparing it with the saturated glycol [40] that was derived from laurencin [18][23] by the method as

will be mentioned later. That is; the mass spectrum of [39] showed peculiar peaks at *m/e* 269, 227, 213, 171, and 59, corresponding to the following fragment ions:



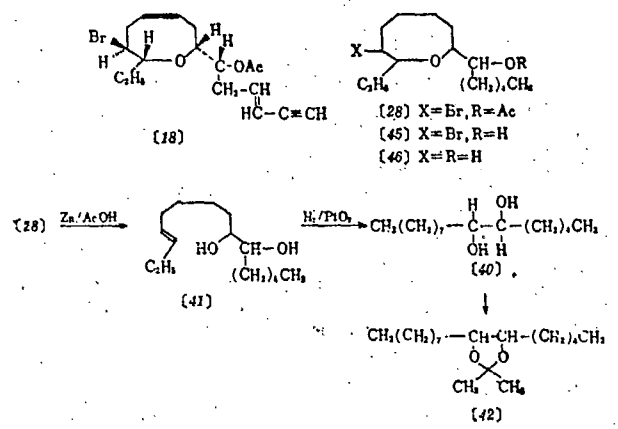
From the foregoing results, the formula [36] was determined for the unsaturated glycol. Another possible formula [36'] was ruled out on the basis of the data of the NMR spectrum of its acetate. That is; if the formula [36'] were given, its acetate was to have eight hydrogens at the allylic position, so that it would be inconsistent with the observed NMR spectrum.

$$CH_3\text{-}CH_2\text{-}CH{=}CH\text{-}CH_2\text{-}CH(OH)\text{-}CH(OH)\text{-}CH_2\text{-}CH{=}CH\text{-}(CH_2)_4CH_3$$

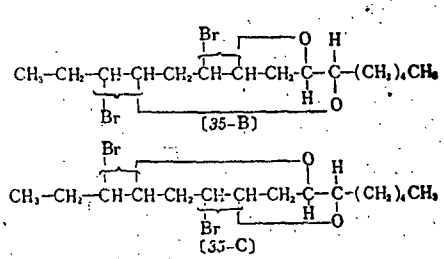
[36']

On the other hand, octahydrolaurencin [28], which was yielded from laurencin [18] by contact catalytic reduction, was treated with zinc and acetic acid and then hydrogenated with alkali, so that an unsaturated glycol [41] was afforded. The saturated glycol [40] derived from [41] by contact catalytic reduction, $C_{15}H_{28}O_2$(M^+ 240), mp 54~55°C, was then regarded as an antipode of [38], because its IR (in chloroform) and NMR spectra were $[\alpha]_D$+25.5°, corresponding completely to those of [38]. Also, the isopropylidene derivative [42] of [40] corresponded completely to [39] in the IR, NMR, and mass spectra, $[\alpha]_D$+34.5°, so that it was proved to be an antypode of [39]. As mentioned earlier, the prior determination of the absolute structure of laurencin led

to the determination of the structure of the glycol [40], and its two asymmetrical centers were then supposed to take a R-configuration respectively, so that those of [38] could be given a S-configuration respectively.

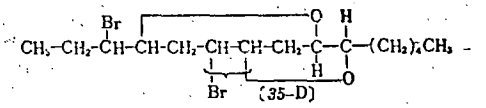


Considering from the structure of the unsaturated glycol [36], it was unconceivable that the two bromine atoms of hexahydrolaureatin [35] couple with their adjacent carbons. Therefore, the structure of hexahydrolaureatin was supposed to be either [35-B] or [35-C].

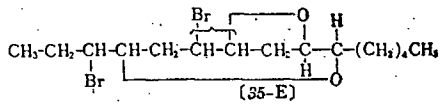


(ii) The hexahydrolaureatin [35] was treated with Raney nickel in alkaline ethanol, and two kinds of products were afforded. One of them was hexahydrobisbromolaureatin [43], $C_{15}H_{28}O_2$(M^+ 240), the IR spectrum (Figure 7-C) of which indicated the presence of oxyde groups (ν 1152, 1061, 1040, 955 cm^{-1}). The other was hydroxy ether [44], $C_{15}H_{30}O_2$(M^+ 242), the IR spectrum of which indicated the presence of a hydroxyl group (ν 3460 cm^{-1}) and oxyde groups (ν 1132, 1082, 1060 cm^{-1}). The mass spectra of [35] and [43]

revealed the presence of groups CH_3-CH_2-CHBr-(*m/e* 277 and 275 due to (M^+ - C_3H_6Br)) and CH_3-CH_2-CH_2-(*m/e* 197 due to (M^+ - C_3H_7)), respectively. In the mass spectra of octahydrolaurencin [28], octahydrodeacethyllaurencin [45], and octahydrodeacethyldebromolaurencin [46], on the other hand, the peaks due to (M^+ - C_2H_5) appeared, but no peaks corresponding to (M^+ - C_3H_6Br) or (M^+ - C_3H_7) were shown there. From these results, the structure of [35] must be either [35-D] or [35-E].



(35-D)



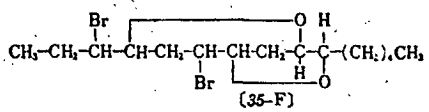
(35-E)

(iii) The NMR spectrum of hexahydrobisdebromolaureatin [43] exhibited a characteristic two-proton multiplet at τ ca. 7.4 (J') and four one-proton signals at τ 5.29 (C), 5.58 (D), 5.83 (E), and 6.72 (H). The latter four protons were assigned as those corresponding to (C), (D), (E), and (H) in the spectrum of [35].*11 This assignment was confirmed by the spin decoupling study. These results indicate that the bromine atom must be attached to C-6, and, therefore, the structure of [35] should be either [35-F] or [35-G].

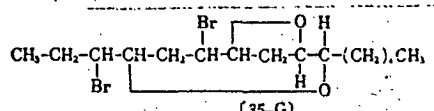
[35-F] has a structure of 7 membered-5 membered cyclic ether, while [35-G] has a structure of 8 membered-4 membered cyclic ether. Although these types of systems have so far been unknown, the 8 membered-4 membered structure [35-G] may be considered to be reasonable for [35] on the basis of the following reasons: (a) In the NMR spectra of laureatin [19], hexahydrolaureatin

*11 (C) and (E) changed into broad multiplets.

/p.1193/



(35-F)



(35-G)

[35], and hexahydrobisdebromolaureatin [43], the protons H-C and H-D were shifted to extraordinarily low magnetic fields as those at the root of ethereal oxygen. This downfield shift can be well explained by the assignment of those as α-protons of a 4-membered cyclic ether.[37] (b) The chemical shift of the signals due to the protons H-J' and its pattern in the NMR spectra of hexahydrobisdebromolaureatin [43] can also be well explained, if they are located on the β-position of the same 4-membered cyclic ether ring.[37a)37e)] This assuption was confirmed by the decoupling study (Figure 10). (c) The strong absorptions near ν 975 cm^{-1} in the IR spectra of [19], [35], and [43] are characteristic to C-O stretching vibrations in a 4-membered cyclic ether.[37b)37d)37e)38)] From the foregoing results, the formula [35-G] was given for hexahydrolaureatin. The mass spectrum of the derivative of laureatin which will be mentioned below can also be explained well by this formula.

Hexahydrolaureatin [35], when boiled with an ethanolic potassium hydroxide solution, afforded dehydrobromohexahydrolaureatin [47], $C_{15}H_{25}O_2Br$ (M^+

---

37) a) Cf. N. S. Bhacca, L. F. Johnson, J. N. Schoolery, NMR Spectra Catalog, Spectrum No. 33.
b) Cf. F. Piozzi, A. Quilico, T. Ajello, V. Sprio, A. Melera, Tetrahedron Letters, 1965, 1829.
c) R. C. Cookson, T. A. Crabl, J. J. Frankel, J. Hudec, Tetrahedron Suppl., No. 7, 335 (1966).
d) Cf. J. W. Hanifin, E. Cohen, Tetrahedron Letters, 1966, 5421.
e) Cf. Yukio Noichi, Nikka /Jap. Chem./, 88, 565 (1967).

38) Cf. G. M. Barrow, S. Searles, J. Am. Chem. Soc., 75, 1175 (1953).

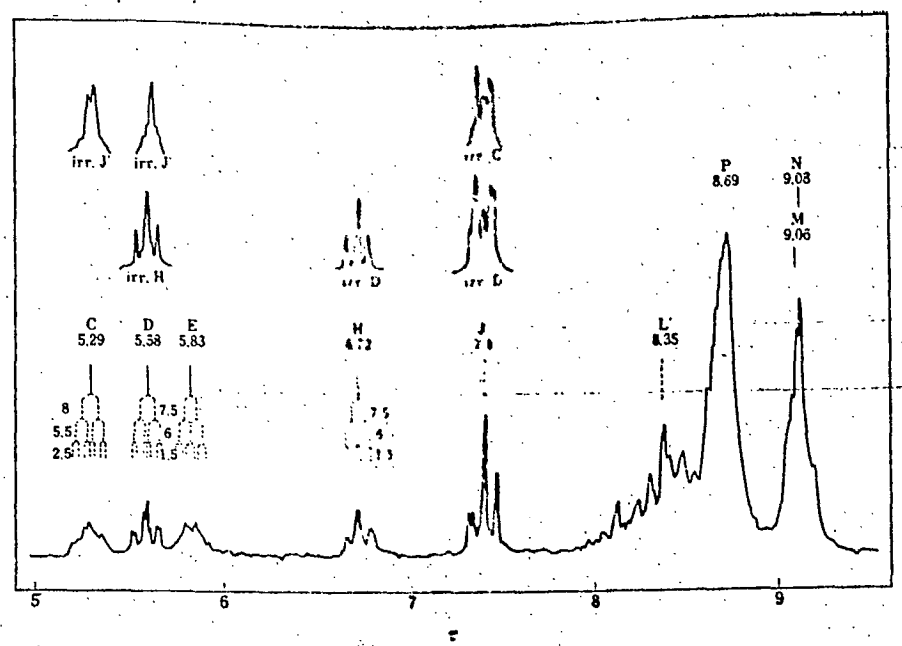
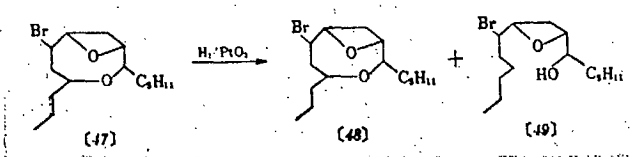


Figure 10: NMR spectrum of hexahydrobisdebromolaureatin [43] (100 Mc)

318, 316), which was then attempted to be hydrogenated in acetic acid over Pb-C catalyst, but ended in giving too many products without any satisfactory result. Then, the hydrogenation in acetic acid was done over platinum catalyst, so as to yield two products, hexahydromonodebromolaureatin [48], $C_{15}H_{27}O_2Br$ and hydroxybromoether [49], $C_{15}H_{29}O_2Br$ (ν3450, 1057, 972 cm^{-1}). The latter showed the signal due to the proton on the α -position of a 4-membered cyclic ether at τ 5.33 in its NMR spectrum and the presence of groups $C_6H_{12}Br$- and $C_6H_{13}O$- in its mass spectrum.



From these results, the formula [35-G] was given for hexahydrolaureatin and, therefore, the formula [19] for laureatin.

Next, as to isolaureatin [20], $C_{15}H_{20}O_2Br_2$, mp 83~84°C, $[\alpha]_D$+40°, its UV and IR spectra were very similar to those of laureatin [19], as mentioned earlier, and its mass spectrum also showed the fragmentation similar to that of laureatin as shown by many peaks due to common fragment ions (Figure 11). The NMR spectrum of isolaureatin (Figure 12) showed absorptions of an acetylenic proton at τ 6.94 (1H, d, J = 2 cps), two vinyl protons at τ 3.96 (1H, sex, J = 12, 7, 7 cps) and τ 4.45 (1H, finely splitted doublet, J = 12 cps), and methyl protons at τ 8.94 (3H, t, J = 7, 7 cps). These are very similar to the case of laureatin [20]. In addition, the signals appeared in the region of τ 5.7~6.6, which were corresponding to the protons at the root of bromine or ethereal oxygen, were also of 6H, but they were so overlapping one another except at τ 6.51 (1H, br, t, J = 6.5, 6.5 cps) and τ 6.23 (1H, dt) that they could not be analyzed. Nevertheless, from the foregoing results, isolaureatin [20] was supposed to have the groupings of $-CH_2-CH=CH-C\equiv CH$

/p.1194/

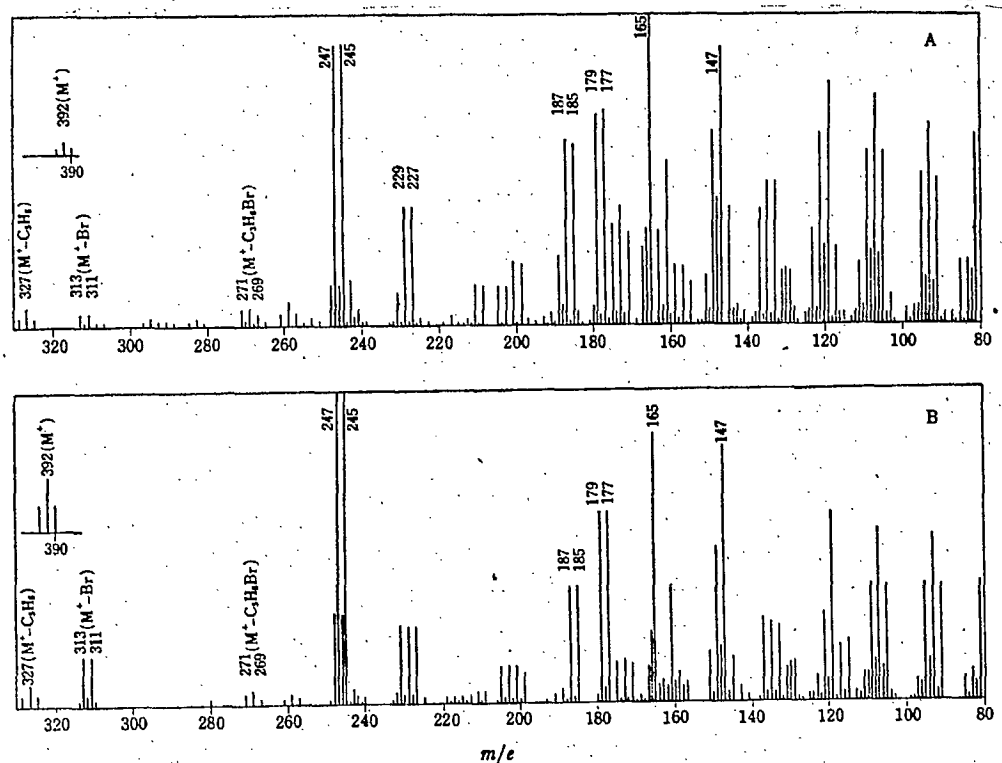


Figure 11: Mass spectra of (A) laureatin [19] and isolaureatin [20].

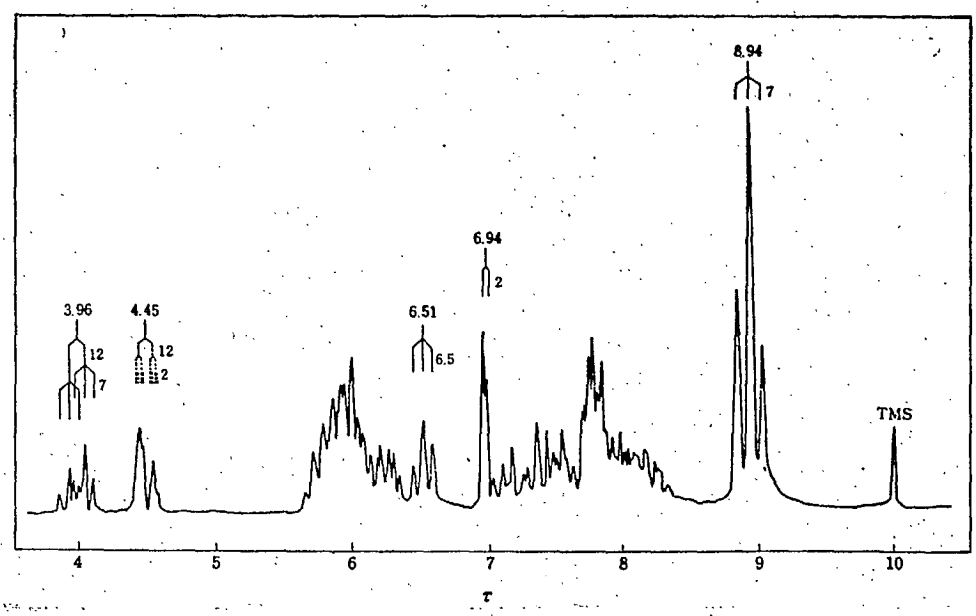


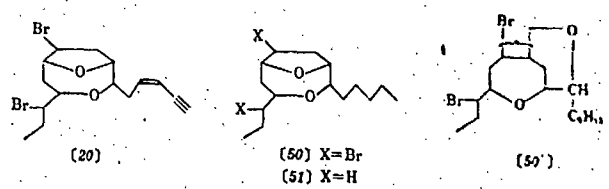
Figure 12: NMR spectrum of isolaureatin [20] (100 Mc, CCl_4)

and -CHBr-CH_2-CH_3 as in the case of laureatin [19] and also to have a structure closely related to the latter.

By contact catalytic reduction, isolaureatin [20] became hexahydroisolaureatin [50], $C_{15}H_{26}O_2Br_2$, which indicated the presence of oxyde groups (ν 1140, 1120, 1092, 1075 cm^{-1}) in its IR spectrum and showed in its NMR spectrum two methyl signals at τ 9.08 (3H, br, t) and 8.93 (3H, t, J = 7, 7 cps), a methylenio 6H signal at τ 8.65, and signals attributable to the protons at the root of bromine or ethereal oxygen at τ 6.69 (1H, t, J = 6.5, 6.5 cps), τ 6.2 (1H, m), and τ 5.7~6.1 (4H, m).

Treatment of [50] with zinc and acetic acid afforded an unsaturated glycol [36], which then gave the corresponding saturated glycol [38] on contact catalytic reduction. These glycols and the isopropylidene derivative of [38] were identical with those derived from hexahydrolaureatin in all respects. Therefore, the structure of hexahydroisolaureatin [50] must be represented by

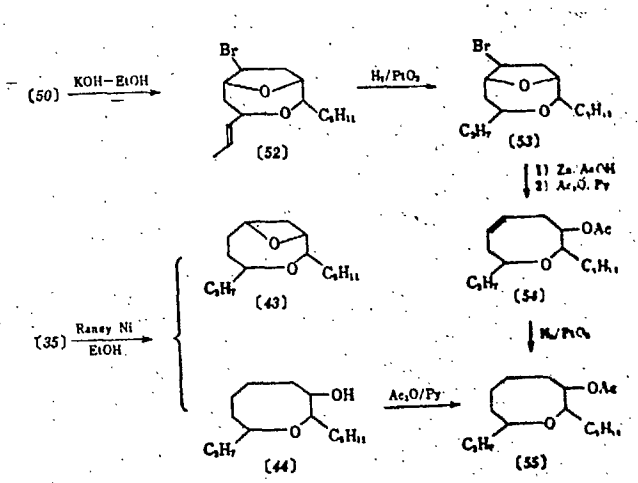
either [35-F] or [35-G]. Treatment of [50] with Raney nickel and alkali then /p.1195/ afforded hexahydrobisdebromoisolaureatin [51] in a good yield. This result is definately different from the case of [35]. The NMR spectrum of [51] showed only four 1H signals at τ 6.73 (br. t), 6.2 (br. m), 5.98 (br. t), and 5.77 (br. m) in the low magnetic field below τ 7.8; no signals were found in the region around 7.4. From these observations, it was concluded that hexahydroisoluareatin cannot be a stereo-isomer of hexahydrolaureatin [35], and also the possibility of the formula [50'] was excluded on the basis of the evidence that will be described below. Consequently, the following formula [50] was given for the structure of hexahydroisolaureatin.



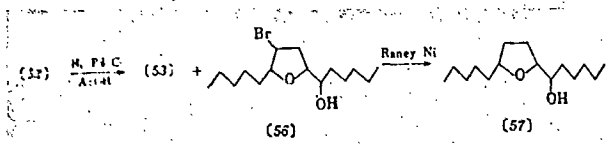
(20) (50) X=Br (51) X=H (50')

As for the evidence, treatment of [50] with an ethanolic potassium hydroxide solution effected its dehydrobromination and yielded dehydrobromohexahydroisolaureatin [52], $C_{15}H_{25}O_2Br$. After hydrogenation of [52], its product of a saturated bromic ether [53] was treated with zinc-acetic acid and then acetylated to afford an unsaturated acetoxy ether [54], which was further hydrogenared to a saturated acetoxy ether [55], $C_{17}H_{32}O_3(M^+ 284)$. This acetoxy ether was found to be identical in all respects with the specimen prepared by acetylation of the hydroxy ether [44] which was obtained from the above-mentioned hexahydrolaureatin [35] upon treatment with Raney nickel in ethanol. Accordingly, the formula [50] was given for hexahydroisolaureatin.

In order to substantiate the foregoing result, the following experiment was conducted. That is; dehydrobromohexahydroisolaureatin [52] was hydrogenated over 5% Pd-C catalyst to hexahydromonodebromoisolaureatin [53] and a type of



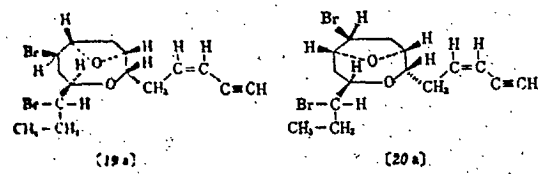
hydroxybromo ether [56], $C_{15}H_{29}O_2Br$. Then, the hydroxy ether [57], $C_{15}H_{30}O_2$ (M^+ 242), afforded on debromination of [56] with Raney nickel, exhibited in its mass spectrum the peaks due to ($M^+ - C_5H_{11}$) and ($M^+ - C_6H_{13}O$), supporting the formula of its structure.



From all these results, the formula [50] was determined for hexahydroisoluareatin, and, therefore, the formula [20] for isolaureatin.

As have been mentioned above, it became clear that the stereochemistry of the asymmetrical centers C-9 and C-10 in laureatin [19] and isolaureatin [20] takes a S-configuration. In the case of laureatin [19], however, the hydrogens at C-9 and C-7 were considered to be cis to each other, while the bromine at C-6 and the ethereal oxygen at C-7 were considered to be in the relation of near antiparallel to each other, so that both C-6 and C-7 could be supposed to have a R- configuration. Furthermore, from the fact that the C-4 protons (H-E) were shown to be shifted to extraordinary low magnetic fields in the NMR spectra of laureatin [19], hexahydrolaureatin [35], and hexahydromonodebromolaureatin [48], these hydrogens were located to be close

to the oxygen atoms of the oxycetane ring, so that the asymmetrical center of C-4 could be supposed to have a R-configuration. For these reasons, therefore, the formula [19a] was given for the stereo-structure of laureatin. Similarly, the formula [20a] was considered to be suitable for isolaureatin.



(19a) (20a)

Lastly, it was supposed that laureatin [19] and isolaureatin [20] may be biosynthesized through decarbonization and epoxidation of double bonds from a common precursor, hexadeca-4,7,10,13-tetraene acid, as was also supposed for laurencin. Thus, it might be expected that such a precursor will be discovered in marine algae.

Acknowledgement

This study has been carried out as a common study among many people whose names appeared in the references. The author is indebted especially to Professor Tadashi Masamune, Assistant Professors Nobukatsu Katsui and Etsuo Kurosawa, Research Associates Minoru Suzuki and Teruaki Suzuki, Dr. Mikio Izawa, and Mr. Akio Fukuzawa (M.A.). The author also wish to express his heartfelt thanks to Professor Emeritus Yukio Yamada, Professor Yoshiteru Nakamura of the Department of botany of the Faculty of Science (at the Muroran Marine Algae Research Laboratory), Dr. Iemasa Yamada, and Assistant Professor Hikaru Yabu of the Department of Fisheries, of Hokkaidō University for their assistance for collecting the algal specimens.