Tetrahedron Letters No.16, pp. 1091-1099, 1965. Pergamon Press Ltd.
Printed in Great Britain.

LAURENCIN, A CONSTITUENT FROM LAURENCIA SPECIES[1]

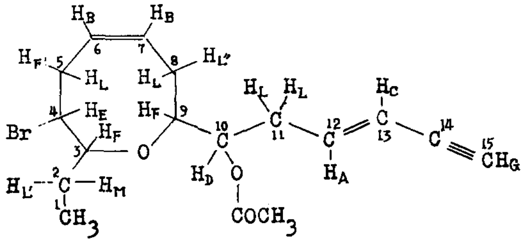
Toshi Irie, Minoru Suzuki and Tadashi Masamune

Department of Chemistry, Faculty of Science, Hokkaido University,
Sapporo, Japan

(Received 27 January 1965; in revised form 1 March 1965)

An investigation of constituents from Laurencia glandulifera, Kützing,[2] led to the isolation of a compound containing bromine, which was designated laurencin. In the present paper we wish to report that formula (I) is the most favorable structure for the compound.

Laurencin (I), m.p. 73-74° (methanol) and $[\alpha]_D^{23}$ +70.2° (in chloroform), was obtained in 0.035% yield by chromatographic purification of the neutral fraction from methanol extracts, and was analyzed for $C_{17}H_{23}O_3Br$ (Found: C, 57.42, 57.31; H, 6.54, 6.40; Br, 22.15; mol. wt. 354 and 356, from the mass spectrum). The infrared spectrum suggested the presence of a terminal methine (ν_{max}^{Nujol} 3285 and 2100 cm^{-1}), an acetoxyl (1735 and 1230 cm^{-1}) and an ether group (1168 and 1080 cm^{-1}), and trans and cis double bonds (3040, 950 and 750 cm^{-1}); and the ultraviolet spectrum (in ethanol), λ_{max} 224 mμ (ε 16,400) and $\lambda_{infl.}$ 232 mμ (ε 11,000), showed the presence of a conjugated diene or enyne. The N.M.R. spectrum[3] (FIG. 1) indicated the presence of four olefinic protons (the absorptions A, B and C; abbr. H-A, H-B and H-C) and an acetoxyl group (K), and also suggested the existence of an ethyl group (N, triplet). The latter was confirmed by isolation of propionaldehyde on ozonization[4] of I. However, only one proton is involved in the absorption M and, therefore, two protons of the methylene adjacent to the methyl group are not magnetically equivalent.[5] Another proton was found as a multiplet (L') in L, which was confirmed by



I

the decoupling study (TABLE runs 6c and 6d, FIG. 2C).

Laurencin consumed 4 moles of hydrogen over platinum in ethyl acetate to yield octahydrolaurencin (II) $C_{17}H_{31}O_3Br$ (Found: C, 56.38; H, 8.67), oil[6]; U.V. only end absorption, ε 710 at 220 mμ; I.R. ν_{max}^{film} 1735, 1189 and 1075 cm^{-1}. While the N.M.R. spectrum shows absorptions at τ 5.21, 6.13 and 8.02 which are comparable with D, E and K, the signals due to olefinic protons and the absorption G disappear, confirming that G is due to acetylenic proton. Furthermore, a complex multiplet centered at τ 6.5 comparable with F accounts for only two protons, which will be discussed later. On mild hydrolysis with methanolic potassium hydroxide, I gave deacetyllaurencin (III) $C_{15}H_{21}O_2Br$ (Found: C, 57.38; H, 6.75), oil, I.R. ν_{max}^{film} 3530 and 3420 cm^{-1}, which was reconverted to the original ester (I) in good yield by treatment with acetic anhydride and pyridine. The N.M.R. spectrum indicates almost the same as that of I, but the absorptions D and K are replaced by a sextet (1H) centered at τ 6.17 and a sharp singlet (1H) at τ 7.77 (hydroxyl proton), respectively. Thus D is assigned as signal due to proton on the carbon (C-OAc) to which the acetoxyl group is attached.

Reduction of II with lithium aluminum hydride afforded a debromo

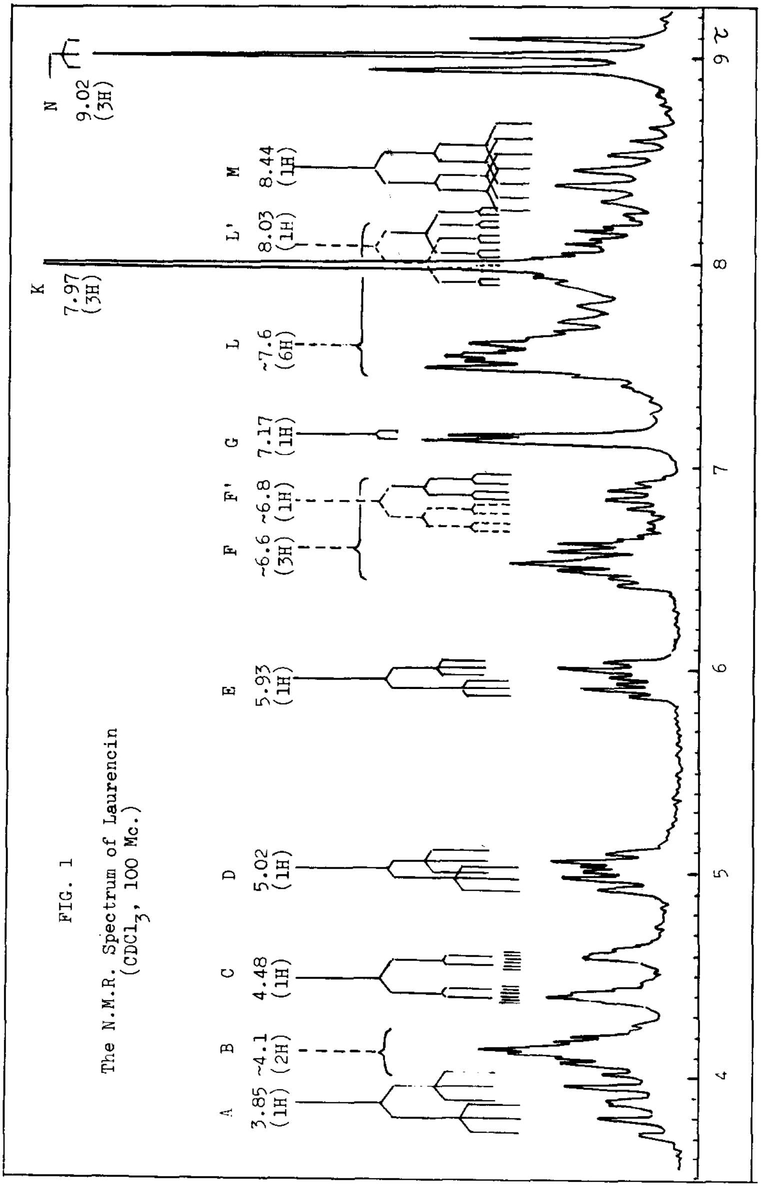
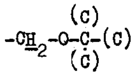


FIG. 1

The N.M.R. Spectrum of Laurencin ($CDCl_3$, 100 Mc.)

alcohol $C_{15}H_{30}O_2$ (Found: C, 74.18; H, 12.70), oil, which was converted to the corresponding acetate (IV) $C_{17}H_{32}O_3$ (Found: C, 71.58; H, 11.42), oil, I.R. ν_{max}^{film} 1740 cm^{-1}. The N.M.R. spectrum of IV exhibits almost the same as that of II except the absence of the signal corresponding to that at τ 6.13 of II. Hence, the absorption E is attributed to the proton on the carbon (C-Br) to which the bromine atom is attached. In addition, a broad multiplet centered at τ 6.6 comparable with F involves only two protons as in the case of II. These facts indicate that one of three protons in F has to be a proton (allylic proton) on the carbon adjacent to double bond, which appears as a multiplet (F') at τ ~6.8 in F, and the other two protons to be those on carbons (C-O) adjacent to the ether oxygen. On the other hand, the absorption L contains six protons and one of them is the proton (H-L') of the methylene in the ethyl group as mentioned already. The remaining five protons must be allylic protons from the chemical shifts. On the basis of these facts, laurencin should consist of the following units (V).

$C_{17}H_{23}O_3Br$ =
three allylic methylenes, 3 $-C\underline{H}_2-(C=C)$
$-C\equiv C\underline{H}$
trans and cis double bonds, 2 $-C\underline{H}=C\underline{H}-$
$>C\underline{H}-O-COC\underline{H}_3$
$>C\underline{H}-Br$
$>C\underline{H}-O-C\underline{H}<$ or 
$-C\underline{H}_2-\overset{(C)}{\underset{(C)}{O-C}}-(C)$
$-C\underline{H}_2-C\underline{H}_3$
V V

The spin decoupling experiments (TABLE) have now deduced the whole structure. The presence of partial structure (VI) is confirmed by the examination of runs (1,2a), (2b,3a), 11 and (3b,8a); the double bond conjugated with the triple bond was determined to be trans-oriented by

TABLE

Spin Decoupling Results in Deuterochloroform (100 Mc.)

Run	Proton^a (τ) Irradiated		Observed			Multiplicity change^b	Splitting decoupled^c (c.p.s.)
1	H-G, C-15, 7.17	$-C\equiv C\underline{H}$	4.48	(H-C)	C-13	de--se	2
2a	H-C, C-13, 4.48	$-CH=C\underline{H}-$ (*trans*)	7.17	(H-G)	C-15	do--si	2
b			3.85	(H-A)	C-12	se--tr	15
c			~7.6	(H-L)		ch	v.s.
3a	H-A, C-12, 3.85	$-C\underline{H}=CH-$ (*trans*)	4.48	(H-C)	C-13	de--si(b)	15
b			~7.6	(H-L)		ch	
4a	H-D, C-10, 5.02	$-C\underline{H}(OAc)-$	~6.6	(H-F)		ch(?)	
b			~7.6	(H-L)		ch	
5a	H-E, C-4, 5.93	$-C\underline{H}(Br)-$	~6.6	(H-F)		ch	
b			~6.8	(H-F')	C-5	ch	
c			~7.6	(H-L)		ch	
6a	H-F, C-3 ~6.6 and C-9	$>C\underline{H}-O-C\underline{H}<$	5.02	(H-D)	C-10	se--qu	5
b			5.93	(H-E)	C-4	se--tr(b)	9
c			8.03	(H-L')	C-2	de(?)--se(?)	3
d			8.44	(H-M)	C-2	sp--se	7
e			~7.6	(H-L)		ch	
f			~7.8	(H-L")	C-8	ch	
7a	H-F', C-5, ~6.8	allylic proton	5.93	(H-E)	C-4	se--qu(?)	3
b			~4.1	(H-B)		ch	
c			~7.6	(H-L)		ch	
8a	H-L, C-5, ~7.6 C-8 and C-11,	allylic proton	3.85	(H-A)	C-12	se--do	7,7
b			4.48	(H-C)	C-13	de--qu	1.5,1.5
c			5.93	(H-E)	C-4	se--qu	3
d			5.02	(H-D)	C-10	se--do(?)	5,8
e			~4.1	(H-B)		ch	
f			~6.6	(H-F)		ch	
g			~6.8	(H-F')	C-5	ch	
9a	H-B, C-6 ~4.1 and C-7,	$-C\underline{H}=C\underline{H}-$ (*cis*)	~6.8	(H-F')	C-5	oc(?)--qu	7
b			~7.6	(H-L)		ch	
c			~7.8	(H-L")		ch	
10a	H-N, C-1, 9.02	$-CH_2-C\underline{H}_3$	8.44	(H-M)	C-2	sp--qu	7,7,7
b			8.03	(H-L')	C-2	de(?)--qu	7,7,7
11	H-G, 7.17 and H-L, ~7.6		4.48	(H-C)	C-13	de--do	2,1.5,1.5
12	H-F, ~6.6 and H-L, ~7.6		5.02	(H-D)	C-10	se--si(b)	5,5,8
13	H-M, 8.44 and H-L', 8.03		9.02	(H-N)	C-1	tr--si(b)	7,7

Spin Decoupling Results in Benzene (100 Mc.)

Run	Proton[a](τ)						Multiplicity[b] change	Splitting[c] decoupled (c.p.s.)
	Irradiated				Observed			
14	H-F,	C-9,	~6.95	$-O-\overset{\prime}{C}\underline{H}-CH(OAc)-$	5.05 (H-D)	C-10	se--qu(?)	5
15	H-L,	C-11,	~7.8	allylic proton	5.05 (H-D)	C-10	se--do	5,8
16	H-F,	C-3,	6.62	$-O-\overset{\prime}{C}\underline{H}-CH(Br)-$	6.15 (H-E)	C-4	se--tr(b)	9
17	H-L,	C-5,	~7.6	allylic proton	6.15 (H-E)	C-4	se--qu(?)	3
18	H-F',	C-5,	~7.1	allylic proton	6.15 (H-E)	C-4	se--qu	3
19	H-E,	C-4,	6.15	$-C\underline{H}(Br)-$	~7.1 (H-F')	C-5	ch	
20	H-L',	C-2,	8.12	$CH_3-C\underline{H}(H)-$	6.62 (H-F)	C-3	sp--qu	3
21	H-M,	C-2,	8.43	$CH_3-C\underline{H}(H)-$	6.62 (H-F)	C-3	sp--qu	7

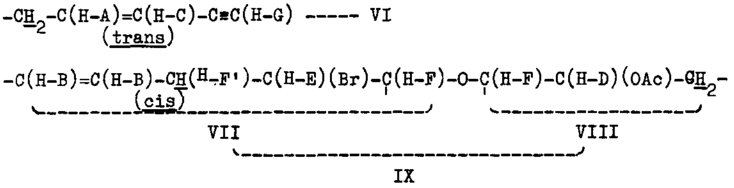
(a) "H-G" is referred to the proton in the absorption G and "C-15" to number of the carbon to which the proton is attached.

(b) Abbr.: "de" means decade; "se" sextet; "do" doublet; "si" singlet; "tr" triplet; "ch" change; "b" broad; "qu" quartet; "sp" septet; "oc" octet; "?" means that the multiplicity is not clear.

(c) Abbr.: "v.s." means "very small coupling constants". The error limits of J is 0.5 c.p.s.

---

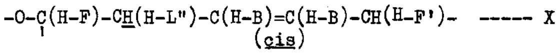
the coupling constant ($J_{H-C,H-A}$ = 15 c.p.s.).[7] Furthermore, laurencin should contain moieties (VII) and (VIII) from consideration of runs (4a,6a), (4b,8d) and 12, and of runs (5a,6b), (5b,7a), (5c,8c), (7b,9a) and (7c,8g), respectively. It should be noted that the allylic proton (H-F') appearing at the abnormally low field (τ 6.8) is located on the carbon between C-Br and the cis double bond. The studies in benzene (run 18, FIG. 3D and run 19) also supported the disposition of this proton. On irradiation of resonance pattern around τ 6.6 (H-F), both the protons H-D and H-E were decoupled (runs 6a and 6b), eliminating the possibility of the partial structure (V'). This was well confirmed by the experiments in benzene (runs 14 and 16). Hence, VII and VIII should be connected through the ether oxygen to give the following sequental order (IX).



$$-C\underline{H}_2-C(H\text{-}A)\underset{(\underline{trans})}{=}C(H\text{-}C)-C{\equiv}C(H\text{-}G) \text{ ----- VI}$$

$$\underbrace{\underbrace{-C(H\text{-}B)\underset{(\underline{cis})}{=}C(H\text{-}B)-C\underline{H}(H\text{-}F')-C(H\text{-}E)(Br)-C(H\text{-}F)}_{VII}-O-\underbrace{C(H\text{-}F)-C(H\text{-}D)(OAc)-C\underline{H}_2-}_{VIII}}_{IX}$$

Irradiation of resonance peak centered at τ 4.1 (H-B) not only led to change of the signals centered at τ 7.6 (run 9b) but also around τ 7.8 (run 9c, FIG. 2D), and the same was observed when the peak around τ 6.6 (H-F) was irradiated (run 6f, FIG. 2C). The proton in question whose signal appears around τ 7.8, which is named H-L", is <u>not</u> coupled to the protons H-D (FIG. 2B), H-E and H-C. Thus, a moiety (X) should be present in laurencin and, therefore, the methylene group adjacent to the <u>trans</u>



$$-O-C(H\text{-}F)-C\underline{H}(H\text{-}L'')-C(H\text{-}B)\underset{(\underline{cis})}{=}C(H\text{-}B)-CH(H\text{-}F')- \text{ ----- X}$$

double bond must be the same as that adjacent to C-OAc ($C\underline{H}_2$ in VI and VIII).[8]

Examination of runs 10a, 10b and 13 indicates that the ethyl group is combined with one of the carbons adjacent to the ether oxygen. The decoupling studies in benzene (FIG. 3) have revealed that the carbon in question is that adjacent to C-Br; the absorption due to two protons (H-F) on C-O, which appeared as a confused multiplet around τ 6.6 in chloroform, was divided into the two parts in the spectrum in benzene. The proton, which appeared as a clearly resolved septet centered at τ 6.62, was coupled not only to the proton H-E on C-Br (run 16, FIG. 3B), but also to the two protons H-L' and H-M adjacent to the methyl group (runs

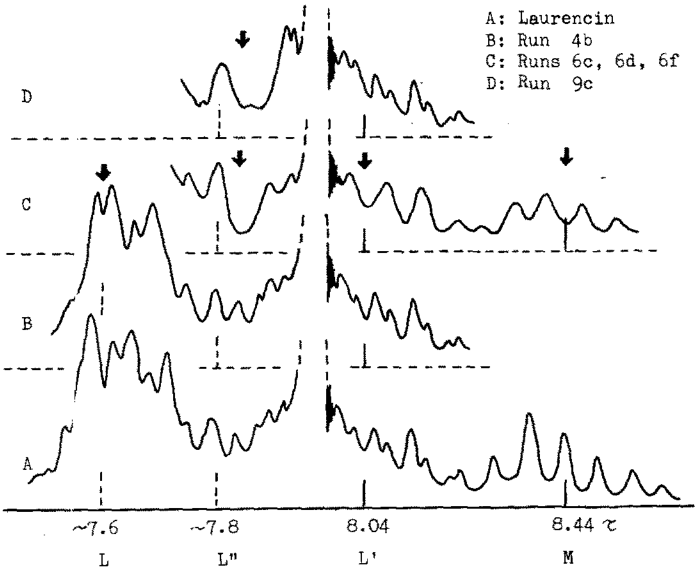


FIG. 2

The Decoupled Spectra of Laurencin ($CDCl_3$, 100 Mc.)

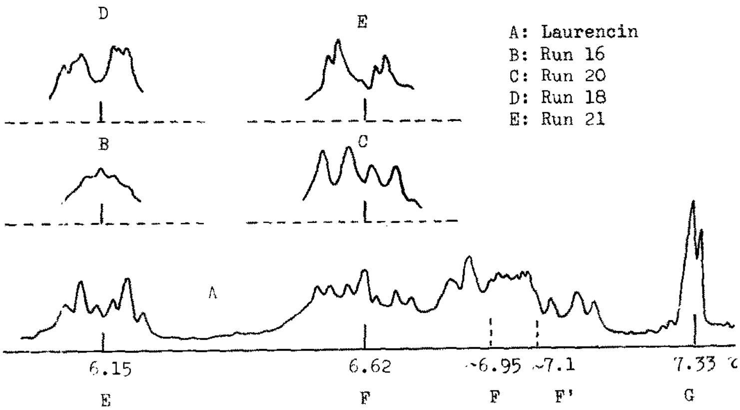
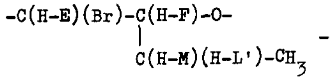


FIG. 3

The Decoupled Spectra of Laurencin (C_6H_6, 100 Mc.)

20 and 21, FIG. 3C and 3E), confirming the presence of unit (XI). Combi-



$$\begin{array}{l} \text{-C(H-E)(Br)-C(H-F)-O-} \\ \qquad\qquad\qquad\quad | \\ \qquad\qquad\qquad\quad \text{C(H-M)(H-L')-CH}_3 \end{array}$$

----- XI

nation of the partial structures (VI), (IX), (X) and (XI) has now established the whole structure (I).[9] Studies on the stereochemistry are in progress.

Acknowledgment. The authors wish to express their thanks to Dr. N.S. Bhacca, Varian Associates, Mr. S. Ohnishi, Toyo-rayon Co. Ltd., and also Mr. S. Shimokawa for the measurement of the N.M.R. spectra. They are also indebted to Dr. I. Yamada, Hokkaido University, for collecting the plants.

---

(1) Part II of "Constituents from Marine Plants"; Part I, T. Irie, K. Yamamoto and T. Masamune, *Bull. Chem. Soc. Japan*, **37**, 1053 (1964).

(2) The plant was collected in August at Oshoro Bay, Hokkaido, Japan.

(3) The spectra were determined at both 100 and 60 Mc. with tetramethylsilane as an internal reference. Deuterochloroform was used as a solvent, unless otherwise stated; on double resonance experiments, benzene was also used.

(4) The oxidation was carried out by M. Takasugi in glacial acetic acid at room temperature, and the aldehyde was isolated as 2,4-dinitrophenylhydrazone, m.p. 148-149°.

(5) *Cf*., N. S. Bhacca, L. F. Johnson and J. N. Shoolery, "NMR Spectra Catalogue", Varian Associates, Palo Alto, Calif., 1963, Spectrum No. 558; G. M. Whitesides, D. Holtz and J. D. Roberts, *J. Amer. Chem. Soc*., **86**, 2628 (1964).

(6) Homogenity of each compound was always checked by gas chromatography and by thin-layer chromatography.

(7) L. M. Jackman, "Application of NMR Spectroscopy in Organic Chemistry", Pergamon Press, New York, 1959, p. 85.

(8) The possibility of the structure containing a nine-membered ring instead of I would not be completely eliminated. The synthetic proof of IV is now in progress.

(9) The mass spectrum explains the structure (I) well, and will be discussed in the detailed paper.