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THE STRUCTURE OF BAKKENOLIDE-A

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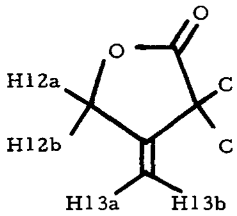
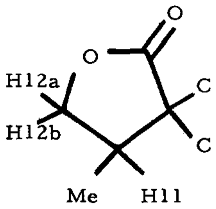
From the bud of Petasites japonicus subsp. giganteus Kitam., (local name : Bakke), a plant restricted to the northern part of Japan, two new bitter sesquiterpenoids, bakkenolide-A and bakkenolide-B, have been isolated. The structure of bakkenolide-A is discussed in this communication ; bakkenolide-B, $C_{22}H_{30}O_6$, mp 101.5-102.5° will be discussed elsewhere.

Bakkenolide-A (B-A), (I), mp 80-81° (from n-pentane), has molecular formula $C_{15}H_{22}O_2$ (M^+ 234 ; mol wt. 234.33), ν_{max}^{KBr} 3090, 1767, 1668 and 899 cm^{-1}, and only end absorption in the UV. The presence of a terminal methylene group and a γ-lactone grouping, indicated by the spectral data, is confirmed by the following observations which lead to part structure (Ia) and indicate that the molecule is tricyclic.

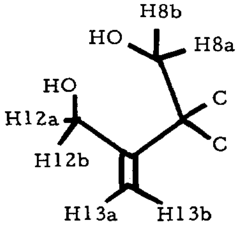
B-A is insoluble in cold alkali but readily dissolves in hot aqueous alkali to form a sodium salt which regenerates B-A on acidification.



Ia



II



III

The NMR spectrum [1] of B-A in C_6D_6 (Fig. 1) exhibits low-field absorption due to four protons[δ H_{12a} and H_{12b} near 4.21, with J(12a-12b) = 13; δ H_{13a} and H_{13b} at 4.78 and 4.50 with J(13a-12a) = J(13a-12b) = ca 2, J(13b-12a) = ca 2, and J(13a-13b) = ca 0.5] which belong to the grouping $-COO-CH_2-\underset{|}{C}=CH_2$.

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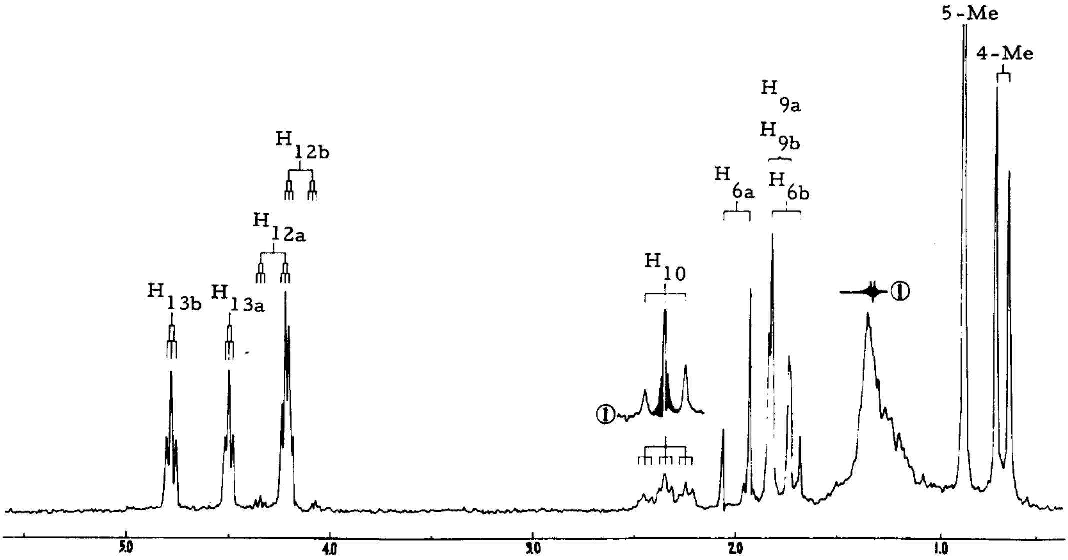


Fig. 1. 100 Mc NMR spectrum of Bakkenolide-A in C_6D_6

Catalytic hydrogenation of B-A in ethanol with Pd-C resulted in the consumption of one mole of hydrogen and the formation of a mixture of stereoisomeric dihydro-derivatives, $C_{15}H_{24}O_2$. The NMR spectrum of the predominant isomer in $CDCl_3$ showed the presence of two secondary methyl groups, doublets at 1.05 (J = 7) and 0.82 (J = 6), an $-OCH_2-$ grouping[δH_{12a} = 3.79 (dd), δH_{12b} = 4.26 (dd); J(12a-12b) = 8.8, J(12a-11) = 4.5, J(12b-11) = 6], and a multiplet (H_{11}) at 2.29 which became a 1 : 3 : 3 : 1 quartet when decoupled from both H_{12a} and H_{12b}. Since strong irradiation of H_{11} at 2.29 resulted in decoupling of the secondary methyl at 1.05 as well as both H_{12a} and H_{12b}, it is apparent that the dihydro-derivative has part-structure II.

Reduction of B-A with lithium aluminum hydride afforded a crystalline diol (III), $C_{15}H_{26}O_2$, mp 81-81.5°, the NMR spectrum of which in $CDCl_3$ exhibited signals in accord with part-structure III : δH_{8a} and H_{8b} at ca 3.37, an AB-quartet with J(8a-8b) = 10.5 ; δH_{13a} = 5.24 (d), δH_{13b} = 5.09 (ddd); J(13a-13b) = 1.3, J(13b-12a) = 0.9, J(13b-12b) = 0.9 ; δH_{12a} = δH_{12b} = 4.12.

The remainder of the structure of B-A was deduced as follows. Oxidation of B-A, or the diol (III), with potassium permanganate in aqueous alkali afforded, as the major degradation product, a crystalline dicarboxylic acid (IV), $C_{11}H_{18}O_4$, mp 141.5°, which can be readily converted to a six-membered anhydride (V), $C_{11}H_{16}O_3$, $\nu_{max}^{liq.}$ 1803, 1760 cm^{-1} .

The tertiary (hindered) nature of one of the carboxyl groups in IV was demonstrated by treatment of the dimethyl ester of IV with CD_3ONa in CD_3OD, first at room temperature for two days and then at the reflux temperature, which resulted in rapid conversion of one of the

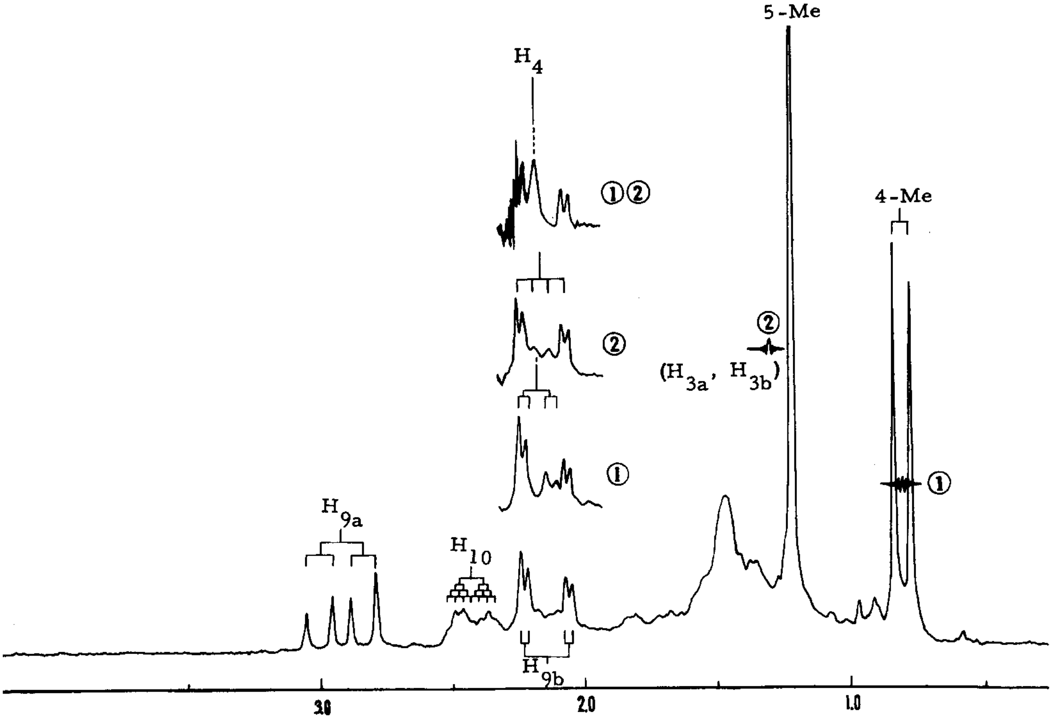
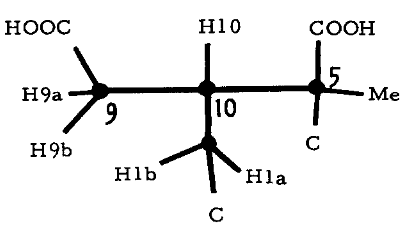


Fig. 2. NMR spectrum of C_{11}-dicarboxylic acid in $CDCl_3$

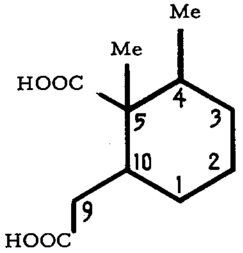
$COOCH_3$ groups to $COOCD_3$ but almost no effect on the second -COOMe group (NMR evidence).

The 100 Mc NMR spectrum of IV in $CDCl_3$ (Fig. 2), shows, in addition to a tertiary methyl group (singlet at 1.23) and a secondary methyl group (doublet, J = 6.5, at 0.82), a group of signals characteristic of an ABC-pattern where the C-proton is further coupled to two additional protons [cf. Fig. 2 and structure IVa : δ H_{9a} = 2.93, δ H_{9b} = 2.17, δ H_{10} = 2.45; J(9a-9b) = 16.5, J(9a-10) = 9.5, J(10-1a) = ca 3, J(10-1b) = ca 3]. The chemical shifts of the tertiary methyl, H_9, and H_{10}, and the magnitude of J(9a-9b), as well as the ease with which the dicarboxylic acid forms a six-membered ring anhydride, and the tertiary nature of one of the carboxyl groups, all point to the presence of part-structure IVa. Moreover, the presence of part-structure IVa and only one additional methyl group (the secondary methyl at 0.82), and the absence of any olefinic protons, means that the dicarboxylic acid IV must be a saturated cyclohexane derivative.

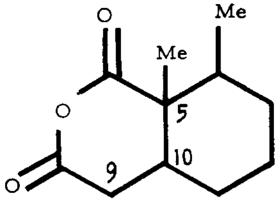
The position of the secondary methyl group, and hence structure IV, was decided from the following evidence. (i) Irradiation of the secondary methyl at 0.82 causes the broad multiplet (H_4) underlying the H_{9b} signal to show as a doublet of doublets centered at 2.17 ppm, whereas (ii) irradiation near 1.30 ppm changes this H_4 signal to a broad quartet again centered near 2.2 ppm, and (iii) simultaneous irradiation at both 0.80 and 1.33 ppm converts the signal at 2.17 to a broad singlet (the broadness of the quartet and singlet in the last two cases is attributed to incomplete decoupling of the apparently broad multiplet near 1.30 ppm due to the C_3 -protons). These



IVa



IV



V

decoupling results, particularly those of (i), are best explained in terms of a ■-CH(Me)-CH_2-grouping[*3] which immediately leads to proposal of structure IV for the dicarboxylic acid and of V for the anhydride.

The NMR spectra of B-A (I), dihydro B-A (II), the diol (III), and the norketone (VI) (see below), all exhibit an AB-quartet (H_{6a}, H_{6b}) centered near 1.5 ppm ($CDCl_3$ solutions) with J(A-B) = 13.8 and indicative of a ■-CH_2-■ grouping, as well as signals near 2.0 ppm due to three protons which form the ABC of an $ABCX_2$ system. Although an exact first-order analysis of this system is not possible, it seems clear that the three protons correspond to H_{9a}, H_{9b} and H_{10}.

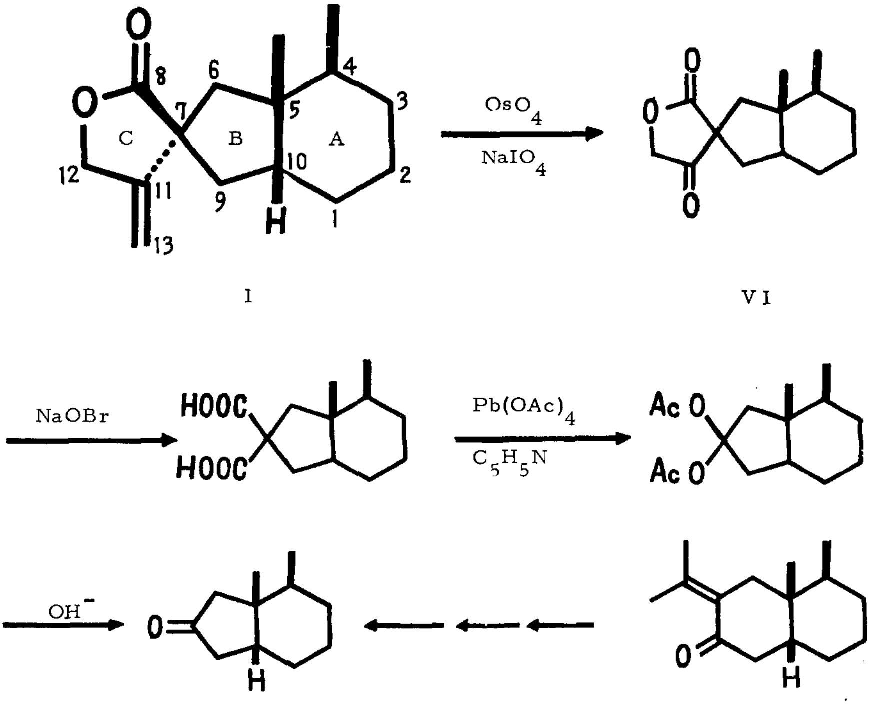
Consideration of all the evidence presented so far leads to postulation of structure I for B-A, with the exception of the stereochemistry which was established as follows.

Strong irradiation of the C_1-protons (near 1.32 ppm) in B-A converts the H_{10} signal (a triplet of triplets with splittings of 10 and 3.5 cps) into a triplet with 10 cps splittings (see Fig. 1), thus showing both J(10-1a) and J(10-1b) to be small (ca 3 cps). The magnitude of these couplings indicates that the C_{10}-H bond bisects the angle between the bonds of the methylene hydrogens at C_1, which is the case with a cis-A/B but not a trans-A/B ring junction.

The configuration at C_7 relative to the A/B ring junction was deduced from the effects of the ring C carbonyl and exocyclic double bond on the C_5-Me and H_{10}. Removal of the 11,13-double bond (by hydrogenation) has little effect on the chemical shifts (in $CDCl_3$) of the C_5-Me or H_{10} (δ C_5-Me = 0.98 in B-A and 0.96 in II ; H_{10} = ca 2.2 in B-A and ca 2.1 in II) compared to that of removal of the carbonyl group (δ C_5-Me = 0.87, H_{10} = ca 1.8 in the diol III), which results in significant up-field shifts in each case, and suggests that the carbonyl group and the tertiary methyl are on the same side of the molecule in B-A.

The absolute configuration and stereochemistry at all centers excepting C_7 were established by conversion of B-A to the cyclopentanone derivative (VII) of known[2] structure and stereochemistry. Oxidation of the norketone (VI) with sodium hypobromite, followed by treatment of the products with lead tetraacetate[3], and hydrolysis of the resulting diacetate with methanolic potassium hydroxide led to the ketone (VII) which is identical with that obtained from Fukinone by Naya et al.

[*3] The symbol ■ refers to a carbon atom bearing no hydrogen.



I VI

VII Fukinone

Bakkenolide-A which represents the first of a new class of sesquiterpenoid appears to be biogenetically related to the eremophilanes[4] which are widely distributed in the genus Petacites.

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3) J. J. Tufariello, W. J. Kissel, Tetrahedron Letters, No. 49, 6145 (1966).

4) for example, L. Novotný, V. Herout, F. Šorm, Tetrahedron Letters, No. 20, 697 (1961).