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THE STRUCTURES OF BAKKENOLIDES-B, -C AND -D AS DETERMINED BY THE USE OF A NUCLEAR OVERHAUSER EFFECT.

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In addition to the previously reported bakkenolide-A, structure I[1], and bakkenolide-B,[1,2,3] two new sesquiterpenoids, bakkenolides-C and -D, have been isolated from the bud of Petasites japonicus subsp. giganteus Kitam. The structures of the last three compounds are discussed in this communication[4].

Bakkenolide-B (II), [m.p. 101-102°, $C_{22}H_{30}O_6$, M^+ 390, $\nu_{max}^{CHCl_3}$ 3040, 1775, 1736, 1706, 1669, 1646, 902, 848 cm^{-1}], when hydrolysed under vigorous conditions (25% KOH in aqueous methanol) affords angelic acid (identified by comparison with an authentic sample) and the diol (III), [m.p. 181°, $C_{15}H_{22}O_4$, $\nu_{max}^{CHCl_3}$ 3490, 3090, 1764, 1669, 895 cm^{-1}]; milder conditions of hydrolysis (1% KOH or HCl in aqueous methanol) furnish the hydroxy-angelate (IV), [m.p. 167°, $C_{20}H_{28}O_5$, $\nu_{max}^{CHCl_3}$ 3590, 3020, 1768, 1714, 1670, 1647, 899, 848 cm^{-1}]. The latter compound (IV), which was found to be identical with bakkenolide-C (by mixed mp., and infrared spectrum), re-affords B-B (II) on acetylation. Oxidation of B-C (IV) with chromium trioxide in acetone gave the keto-angelate (V), [m.p. 96°, $C_{20}H_{26}O_5$, ν_{max}^{KBr} 3080, 1784, 1747, 1710, 1670, 1650, 900 cm^{-1}]. Oxidation of the diol (III), however, with chromium trioxide in pyridine afforded the hydroxy-ketone (VI), [m.p. 140-141°, $C_{15}H_{20}O_4$, $\nu_{max}^{CHCl_3}$ 3550~3300 (broad), 3020, 1766, 1694, 1675, 900 $^{-1}$].

Bakkenolide-D (VII), [m.p. 207°, $C_{21}H_{28}O_6S$, M^+ 408, ν_{max}^{KBr} 3050, 1780, 1745, 1695, 1670, 1650, 1568, 900 cm^{-1}], also gives the diol (III) on alkaline hydrolysis. Thus B-B (II), B-C (IV), and B-D (VII), are all derivatives of the diol (III).

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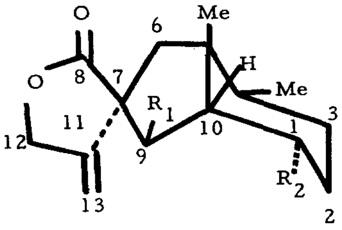
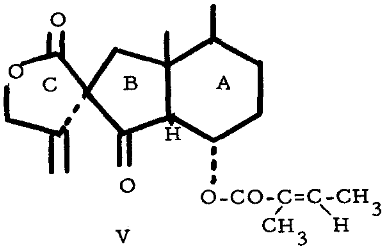
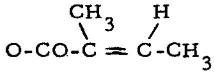




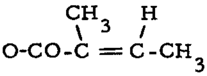
V

I (B-A) : $R_1 = R_2 = H$

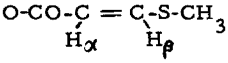


II (B-B) : R_1 = OAc, R_2 = $\text{O-CO-}\overset{CH_3}{C} = \overset{H}{C}\text{-CH}_3$

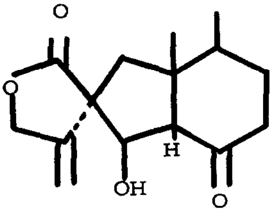
III : R_1 = R_2 = OH



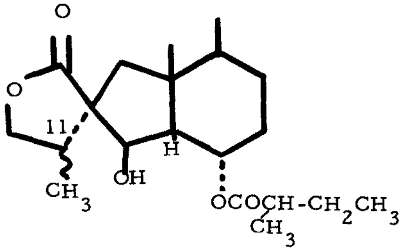
IV (B-C) : R_1 = OH, R_2 = $\text{O-CO-}\overset{CH_3}{C} = \overset{H}{C}\text{-CH}_3$



VII (B-D) : R_1 = OAc, R_2 = $\text{O-CO-}\underset{H_\alpha}{C} = \underset{H_\beta}{C}\text{-S-CH}_3$



VI



VIII

Table 1

	H_{6a}, H_{6b}	H_9	H_{10}	H_1	C_5-Me	C_4-Me
I	1.95$^+$	ca 2.0(m)	ca 2.2(m)	?	0.98(s)	0.84(d)
II	2.10$^+$	5.75(d)$^{++}$	2.82(dd)*	5.15(ddd)**	1.13(s)	0.91(d)
III	1.95$^+$	4.47(d)$^{++}$	2.51(dd)**	4.10(ddd)**	1.02(s)	0.85(d)
IV	2.02$^+$	4.56(d)$^{++}$	2.57(dd)*	5.30(ddd)**	1.10(s)	0.89(d)
V	2.28$^+$	——	3.02(d)*	5.07(ddd)**	1.22(s)	0.97(d)
VI	1.99$^+$	4.37(d)$^{++}$	2.91(dd)*	——	1.15(s)	0.98(d)
VII	2.07$^+$	5.74(d)$^{++}$	2.74(d)*	5.15(ddd)**	1.10(s)	0.89(d)

\+ Center of AB-quartet, J(6a-6b) = 14 cps.

++ $J(9_\alpha - 10_\beta)$ = 11 cps, [d = doublet, m = multiplets, s = singlet]

* $J(1_\beta - 10_\beta)$ = 5 cps; in VI, $J(10_\beta - 2_\beta)$ = 0.8 cps.

** first order splittings indicate $J(1_\beta - 2_\beta)$ = ca 5 and $J(1_\beta - 2_\alpha)$ = ca 11 cps.

The ring-C structure in compounds II-VII was deduced from their infrared absorption in CHCl$_3$ solution [γ-lactone band near 1770 cm^{-1}; C=CH$_2$ bands near 3040, 1670 and 900 cm^{-1}] and their 100 Mc NMR spectra[5] [δ13a, δ13b at ca 5.1 ppm; δ12a, δ12b near 4.8 ppm; J(12a-13a) = J(12a-13b) = J(12b-13a) = J(12b-13b) = ca 2; J(12a-12b) = 13 cps].

The ring-B structures in these compounds were derived from the 100 Mc data[5] shown in Table 1 and from the fact that the keto-angelate (V) has infrared absorption at 1747 cm^{-1} (in KBr), indicative of a cyclopentanone grouping.

The hydroxy-ketone (VI) exhibits an infrared band at 1694 cm^{-1} (CHCl$_3$) which can be attributed to a hydrogen-bonded carbonyl in a six-membered carbocyclic ring. This fact, together with decoupling experiments on the 100 Mc spectra of VI in CDCl$_3$ and C$_6$D$_6$ solutions (Fig 1), leads to the structure of ring-A in VI and thence to the full structures of compounds II-VII.

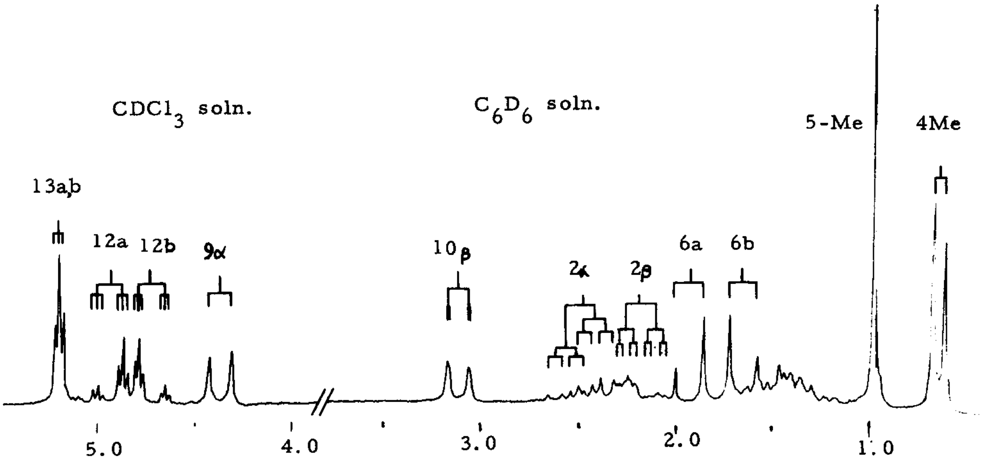


Fig. 1. 100 Mc Spectrum of the hydroxy ketone (VI).

The 100 Mc spectrum (cf Fig 1 and Table 1) of VI in C$_6$D$_6$ shows H$_{10β}$ as a doublet of doublets at 3.12 [J(10β-9α) = 11.2; J(10β-2β) = 0.8] and the C$_2$-methylene protons as a clear AB of an ABXY... system [H$_{2α}$ at 2.45 (ddd) and H$_{2β}$ at 2.20 (br. ddd) with splittings corresponding to J(2α-2β) = 16, J(2α-3β) = 12, J(2α-3α) = 7, J(2β-3β) = 3 or 6, J(2β-3α) = 6 or 3, J(2β-10β) = 0.8]. Irradiation of the H$_{10β}$ signal sharpens the H$_{2β}$ multiplet to a doublet of doublets of doublets. Although the signals (1.0-2.0 ppm) due to H$_{4α}$ and the C$_3$-protons are too complicated for a first-order analysis, the structural moiety giving rise to them can be deduced from the following double resonance experiments.

Strong irradiation of the secondary methyl at 0.64 ppm causes the complex pattern due to H$_{4α}$ (near 1.6 ppm) to become a doublet of doublets with splittings of ca 5 and 11 cps [J(4α-3α) and J(4α-3β), respectively]. Simultaneous irradiation (triple resonance) at 0.64 (secondary methyl) and 2.33 ppm (center of H$_{2α}$ and H$_{2β}$ signals) results in the same doublet of doublets for H$_{4α}$ at 1.6 ppm and, in addition, causes severe perturbation of the signals due to $H_{3\alpha}$ and $H_{3\beta}$ (multiplets near 1.4 ppm). These experiments show that $H_{4\alpha}$ is coupled to $H_{3\alpha}$ and $H_{3\beta}$ but not to $H_{2\alpha}$ or $H_{2\beta}$, and that the C_2-protons are coupled to the C_3-protons, thus indicating the presence of the sequence -$COCH_2CH_2CH(Me)$-■. Confirmation of this proton arrangement is provided by the fact that irradiation near 1.39 ppm perturbs the $H_{2\alpha}$ and $H_{2\beta}$ signals but does not affect the secondary methyl signal, whereas irradiation near 1.63 ppm ($H_{4\alpha}$) perturbs the secondary methyl signal without affecting the $H_{2\alpha}$ and $H_{2\beta}$ signals.

Although the splittings seen in the $H_{2\alpha}$, $H_{2\beta}$ and $H_{4\alpha}$ (secondary methyl decoupled) signals, in the spectrum of VI, are not necessarily equivalent to the coupling constants, it is apparent that both $H_{4\alpha}$ and $H_{2\alpha}$ are involved in a much stronger coupling with the C_3-protons than is $H_{2\beta}$; ie, the former two protons are axial and the latter one is equatorial. This, plus the fact that $H_{2\beta}$ shows a long-range coupling of 0.8 cps with $H_{10\beta}$ (in accord with these two protons being cis-equatorial)[6], means that ring-A is in the chair configuration and that the C_4-methyl is equatorial and on the same side of the ring as H_{10}.

Since H_1, in compounds II, III, IV and VII, shows apparent couplings of ca 5 and 11 cps (first-order splittings) with the C_2-protons, and J(1-10) = 5 cps (see Table 1), it is apparent that the oxygen function at C_1 is equatorial. From the fact that irradiation of the C_5-methyl in VI causes a 10% increase in the area of the H_{10} signal, without affecting its band-width (a nuclear Overhauser effect)[7], it follows that H_{10} and the C_5-methyl must be on the same side of the ring. The configuration at C_9 is deduced from the magnitude of J(9-10)[= 11 cps] and the chemical shifts of H_{10} in compounds I-IV and VII, which indicate that the C_9-oxygen function and H_{10} are cis.

Hydrogenation of B-C (IV) affords a mixture of tetrahydroderivatives (VIII ; epimeric at C_{11}), in which the C_5-methyl absorbs at 1.07 and H_{10} appears at 2.58 ppm. Since neither of these signals is appreciably shifted by hydrogenation of the exocyclic double bond, it can be assumed that C_{11} is on the opposite side of ring-B to H_{10} and the C_5-methyl, as in the case of B-A (I)[1].

B-D (VII) shows NMR absorption characteristic of a cis-β-methylthioacrylate group [δ S-Me = 2.37 (s), δH_α = 5.60 (d) ; H_β = 7.02 (d); J(H_α-H_β) = 10.0; J(H_β-SMe) = ca 0.2 cps].

From the evidence given above, it is clear that B-B, B-C, and B-D have the structures and stereochemistry shown in II, IV and VII, respectively, the absolute stereochemistry being assumed identical with that established for B-A (I)[1].

Naya and his co-workers[8] have independently arrived at the same structures for B-B (II) and B-D (VII), based on an X-ray crystallographic analysis of the bis-bromoacetate of the diol (III)[8].

The symbol ■ refers a carbon bearing no hydrogen.

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4) The structures of B-B (II), B-C (IV), and B-D (VII) were reported at the 11th Symposium on the Chemistry of Perfume, Terpenes and Essential Oils, at Matsuyama, in October 1967.

5) Unless otherwise stated, NMR data refer to $CDCl_3$ solutions, with chemical shifts (δ-values) given in ppm down-field from internal TMS. Assignments are based on first-order analyses and have been confirmed by double-resonance experiments.

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