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Baccharis Oxide, a new Triterpenoid from *Baccharis halimifolia* L.

THORLEIF ANTHONSEN, TORGER BRUUN, ELLEN HEMMER, DAGNY HOLME, AUD LAMVIK, ERLING SUNDE and NILS ANDREAS SØRENSEN

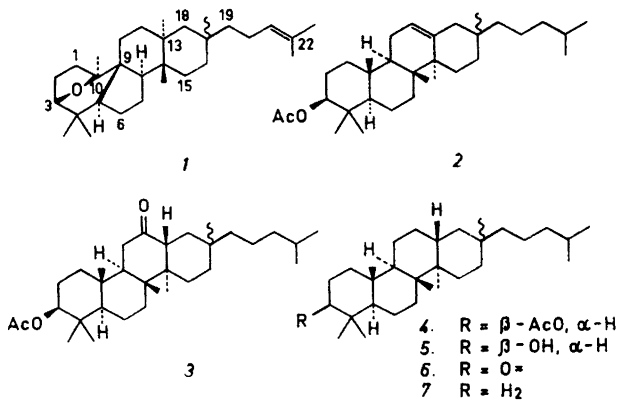
Institutt for organisk kjemi, Universitetet i Trondheim, Norges tekniske høgskole, N-7034 Trondheim-NTH, Norway

From *Baccharis halimifolia* L. a triterpenoid oxide (*1*) has been isolated with a skeleton originating from the same precursor as shionone (*8*). This precursor consists of four six-membered rings, but during its rearrangement the C-5,C-10 bond is changed to a C-5,C-9 bond and an oxide bridge is formed between C-3 and C-10.

During a search for acetylenic compounds in *Baccharis halimifolia* L. a colourless, crystalline, optically active substance, m.p. 148–149°, was obtained from the roots. The infrared spectrum contained no bands corresponding to hydroxyl or carbonyl functions. M^+ was found as 426.386, corresponding to $C_{30}H_{50}O$ (calc. 426.386). This in conjunction with the NMR spectrum, to be discussed below, suggested that the substance would be an oxide for which the name baccharis oxide is suggested.

The presence of a double bond was indicated by the NMR absorption (*vide infra*) and confirmed by catalytic hydrogenation and by treatment with *p*-nitroperoxybenzoic acid according to Ourisson and Mathis.[1] More specifically the double bond was shown to be contained in the grouping $-CH_2-CH=C(CH_3)_2$ by a study of the NMR and mass spectra, which are discussed below.

Various attempts at opening the oxide ring by hydrogenolysis failed. Particularly, baccharis oxide was recovered unchanged after treatment with lithium in boiling cyclohexylamine (not described in Experimental). Finally, the ether bridge of dihydrobaccharis oxide was cleaved by means of boron trifluoride in benzene.[2] The reaction mixture was complex, but a thin-layer chromatogram indicated the presence of two major components. One component, obtained in small amount by direct crystallisation, was an alcohol, $C_{30}H_{52}O$. It furnished an acetate, m.p. 181–182°, the mass spectrum of which had its base peak at *m/e* 220. This peak was very dominating (25 % of $\sum_{40}$) and suggested a close relationship to the triterpenes with a double bond at



C-12, *cf.* Refs. 3, 4. In the common triterpenoids this double bond is not hydrogenated in the presence of palladium or platinum, and so was found to be the case also with the rearranged baccharis oxide. It was removed, however, by epoxidation with peracid, rearrangement to the ketone (*3*), and treatment of the ketone with ethane dithiol and Raney nickel to give a saturated acetate (*4*), m.p. 169–170°; for details, see Experimental. Saponification of this acetate and oxidation of the derived alcohol afforded a ketone, m.p. 115–116°, which gave a circular dichroism curve "in perfect agreement (position, intensity and shape) with a dammarane-type-5α-3-ketone".[5] These data, together with the information from the NMR and mass spectra (*vide infra*) suggest formula (*1*) and Fig. 1 for baccharis oxide and (*2*) for the acetate, m.p. 181–182°, formed by opening of the oxide ring of the dihydro-oxide (above). There is no

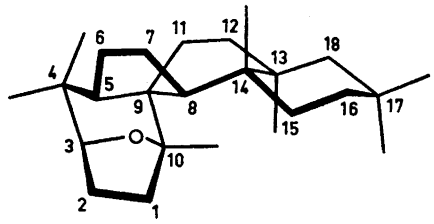
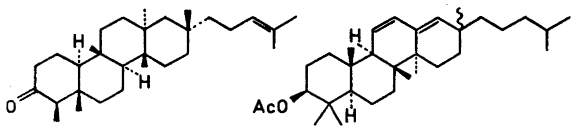


Fig. 1. Perspective drawing of the ring system of baccharis oxide.

evidence as to the stereochemistry of the side-chain. The remaining stereochemical points will be discussed below in the appropriate places. The formation of (*2*) from (*1*) is another example of the back-bone rearrangement, with the important difference that a 5,9-bond has moved to the 5,10-position instead of a methyl from C-9 to C-10.

The complex reaction mixture from which the keto-acetate (*3*) was isolated (above), also contained another major component, m.p. 152–153°. Its ultraviolet spectrum indicated a heteroannular diene system, and on hydrogenation a substance was produced, the mass spectrum of which was identical with that of the acetate (*2*). For this reason and on evidence presented below the diene acetate is given formula (*9*).

The rearrangement together with the NMR evidence (*vide infra*) suggest that one end of the ether bridge is located at C-10. Since triterpenoids almost without exception carry an oxygen function at C-3, this position suggests itself as the other end of the bridge. This was confirmed by the mass spectrum of the ethylene ketal of the ketone (*6*) derived from the acetate (*4*), which was completely dominated by the *m/e* 99 fragment; *cf.* Ref. 6.



8 *9*

Reduction of the ketone (*6*) as above furnished the corresponding hydrocarbon. Since it represents a new type of skeleton, the name baccharane is proposed for it. We regard the carbon skeleton of baccharane as being closer to squalene in the reaction sequence than that of baccharis oxide, which is thought to have arisen from the baccharane skeleton by proper rearrangements. For the hydrocarbon corresponding to baccharis oxide, so far unknown, the designation halimane is suggested.

THE NMR SPECTRA

The 100 MHz NMR spectrum of baccharis oxide contains signals corresponding to two vinylic methyl groups at τ 8.34 and 8.42, slightly broadened due to allylic coupling to an olefinic proton at 4.97. This proton, which appears as a broadened triplet ($J = 6$ Hz) by vicinal coupling to the neighbouring methylene group, collapsed to a broadened singlet by irradiation at 8.2.

Both the deuterochloroform and benzene spectra revealed the presence of six quaternary methyl groups at 8.80, 8.98, 8.99, 9.02, 9.12, and 9.12, of which the first is connected to a carbon atom (C-10) which carries an oxygen atom. The methine proton at the other end of the ether linkage (C-3) turns up as a doublet ($J = 5$ Hz) at 6.33, a value well below the normal one for an oxide proton. It suggests that the oxide is not a 1,2-oxide, in agreement with the chemical findings (above). The magnitude of the coupling constant suggests that the dihedral angle it forms with the two protons at C-2, be one small and one close to 90°. This, however, does not allow any conclusions as to the stereochemistry of the ether linkage, since model studies show that both α- and β-linkages will give dihedral angles of satisfactory magnitude. The signal collapsed to a singlet on irradiation at 8.2.

In the dihydro-oxide the positions of neither the methine proton nor any of the quaternary methyl groups are changed, in agreement with the notion that the double bond is part of the side-chain and far away from the oxide. The doublet ($J = 6$ Hz) due to the secondary methyl groups in the side-chain was found at 9.12.

The 100 MHz spectrum of the diene (*9*) (above) contained absorptions due to six quaternary methyl groups, at 9.05 (three groups), 9.08, 9.11, and 9.19,

and two secondary ones at 9.13 ($J = 6$ Hz), corresponding to the two identical methyl groups in the side-chain. The doublet collapsed to a singlet on irradiation of the methine proton at 8.24. The acetate methyl group resonated as a sharp singlet at 7.96, and the carbinyl proton at C-3 appeared as the X-part of an ABX-system at 5.52, with coupling constants $J_{AX} = 9.5$ Hz and $J_{BX} = 6$ Hz. This is indicative of an equatorial acetate group with the axial carbinyl proton coupled with one axial-axial and one axial-equatorial coupling to its vicinal protons at C-2.[7] Consequently, since the stereochemistry at C-5 is α-H (*vide supra*), the oxide ring must be positioned across the β-face of baccharis oxide.

The heteroannular diene system of the acetate (*9*) gave rise to three signals, at 4.18 (H-11), 4.60 (H-12), and 4.84 (H-18). Two of these (H-11 and H − 12) form the AB-part of an ABX-system ($J_{AB} = 10.5$, $J_{AX} = 3$, $J_{BX} = 1$ Hz). All couplings were demonstrated by double resonance experiments (Fig. 2); for example, the minor couplings in the AB-part were removed by irradia-

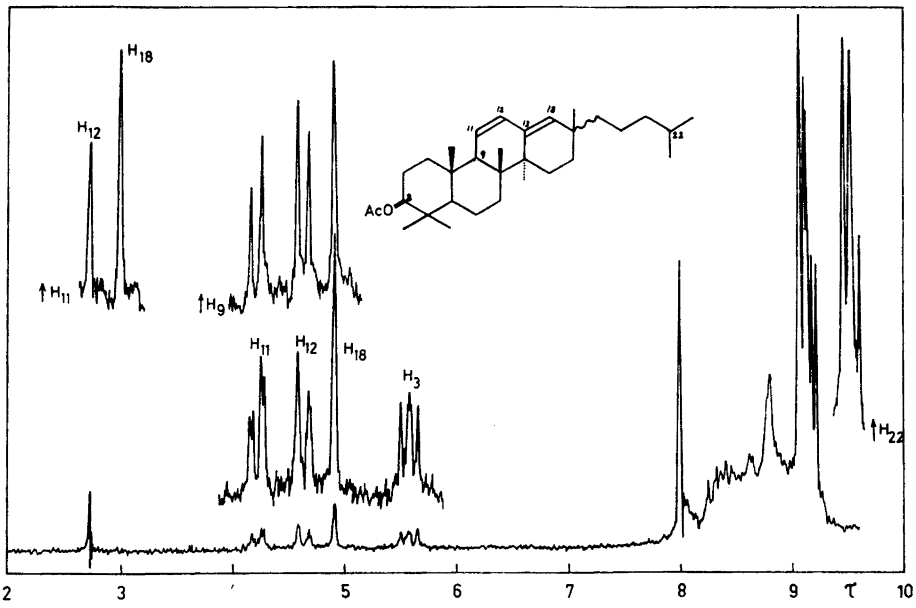


Fig. 2. NMR single and double resonance spectra at 100 Mc/s of the acetate *9*.

tion at 8.02, which is the resonance position of the X-proton (H-9). Irradiation at 4.18 (H-11) also seemed to sharpen the narrow signal at 4.84 (H-18), and thus suggested a small long-range coupling over five bonds along a "zig-zag" path.[8]

The NMR signals of the diene system together with the size of the side-chain as determined by mass spectrometry (below) indicate that ring D is six-membered. From this follows the close relationship between baccharis oxide (*1*) and shionone (*8*).[9]

THE MASS SPECTRA

The four oxides, baccharis oxide (*1*, Fig. 3), dihydrobaccharis oxide (*1*, saturated side-chain), the glycol (*10*) and the trisnoracid (*11*) show fragmentation patterns markedly different from those of the compounds with the normal baccharane type skeleton. Characteristic features are the very strong M^+ and

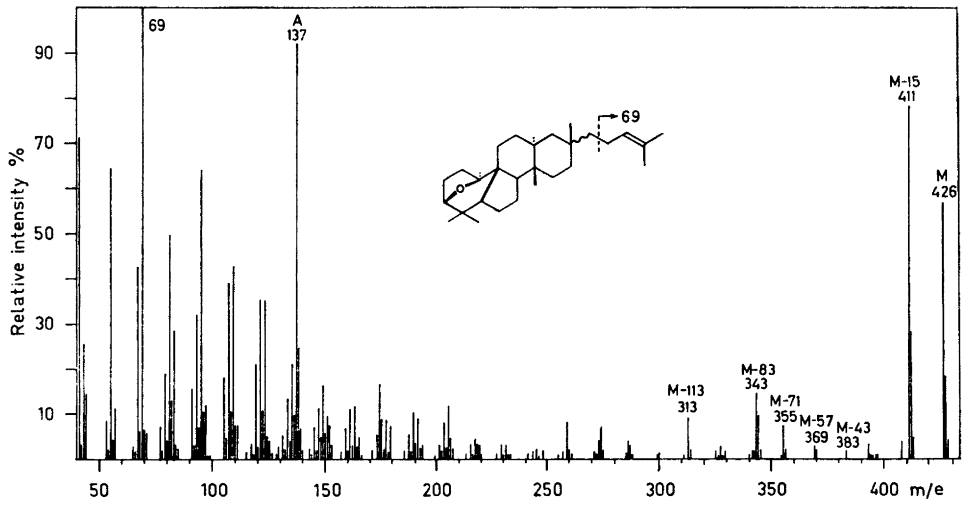
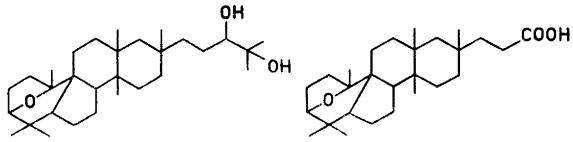


Fig. 3. Mass spectrum of baccharis oxide.

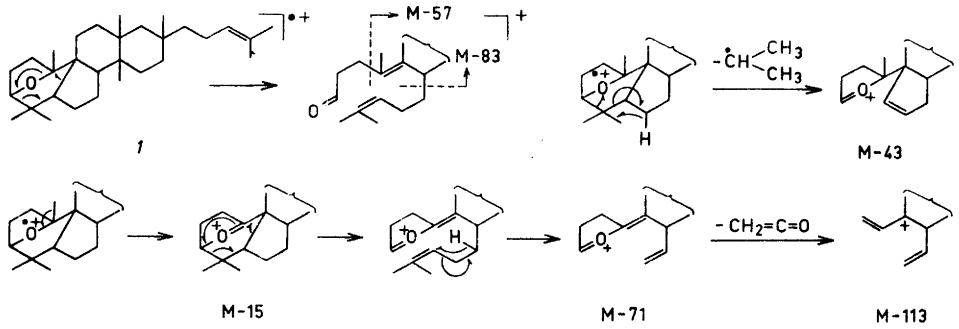


10 *11*

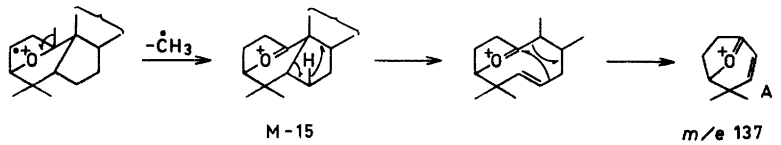
$[M-15]^+$ peaks together with a series of peaks in the upper part of the spectrum. These are due to M − 43 (C_3H_7), M − 71 (C_5H_{11}), M − 83 (C_6H_{11}), M − 113 ($C_7H_{13}O$) and M − 167 ($C_{11}H_{19}O$) and must have their origin in extrusion of parts of the rings A and B (Scheme 1).

A prominent peak at *m/e* 137 ($C_9H_{13}O^+$) is explained as an ion A (Scheme 2). Its formation from the M − 15 ion is confirmed by metastable peaks in all four spectra.

Opposed to those of the oxides, the spectra of the compounds with the baccharane type skeleton do not show this series of peaks in the upper part of the spectrum (*cf.* Fig. 4). This is in accordance with earlier observations in the mass spectra of oleanes, ursanes, and lupanes.[10] These spectra have the one feature in common that all types show pronounced cleavage through ring C to furnish an ion B (Scheme 3). This ion represents the base peak in the



Scheme 1.



Scheme 2.

spectra of the alcohol (*5*) and the hydrocarbon (*7*) while in the acetate (*4*) the base peak is formed after loss of acetic acid. The formation of ion B from the molecular ion is confirmed by a metastable peak in the mass spectrum of the alcohol (*5*) (m* 99.5; $430^+ \rightarrow 207^+ + 223$).

The double bond in the Δ^{12}-acetate (*2*) opens the possibility of a *retro* Diels-Alder cleavage diagnostic of this structure [3,4] to give ion C (Scheme 4)

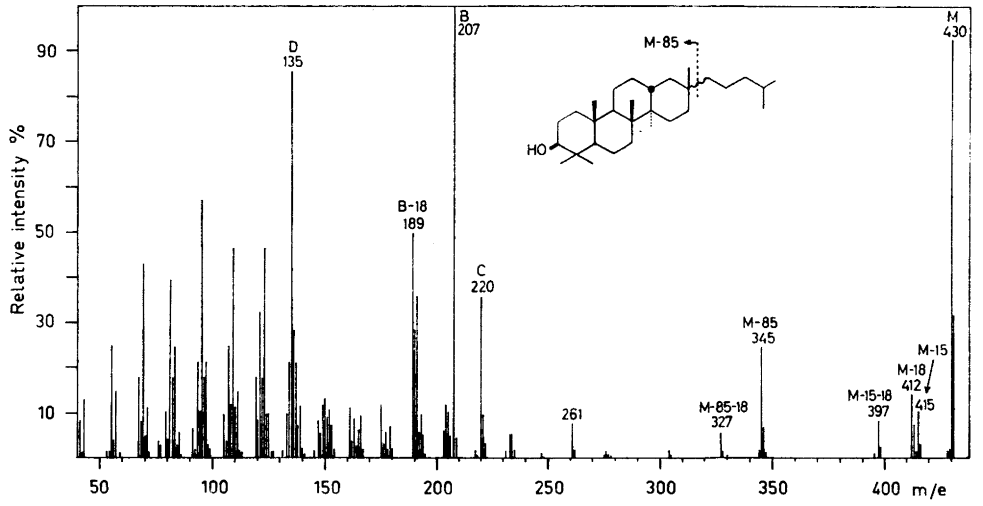
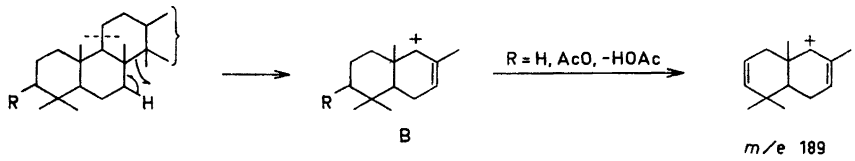
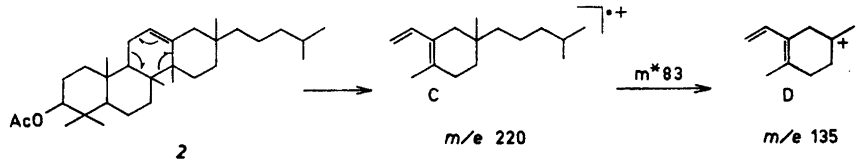


Fig. 4. Mass spectrum of baccharan-3β-ol (*5*).



4. R = β-AcO, α-H m/e 249 (30 %)
5. R = β-OH, α-H m/e 207 (100 %)
6. R = O= m/e 205 (60 %)
7. R = H_2 m/e 191 (100 %)

Scheme 3.



Scheme 4.

with charge retention on the diene fragment. This in turn looses the side-chain to furnish ion D (m* 83, $220^+ \rightarrow 135^+ + 85$). Ion C is present also in the spectra of some of the compounds without the Δ^{12}-double bond, but now of less abundance. In the spectrum of the acetate (*4*), however, its relative intensity is 70 %. In this case it is formed after a double hydrogen rearrangement.

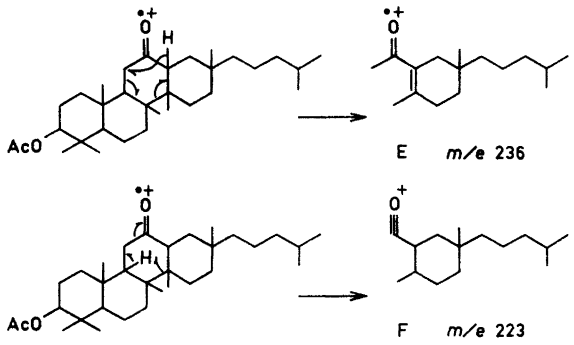
The introduction of a 12-keto function, as in the ketoacetate (*3*) leads to a radical ion of type E (Scheme 5) with charge retention on the oxygen carrying fragment.

Although ions B and B − 60 are still present in the spectrum, ions F and F − 28 (m* 170.5, $223^+ \rightarrow 195^+ + 28$) are of greater importance.

The mass spectrum of the diene acetate (*9*) does not show any pronounced cleavage through ring C. The spectrum is completely dominated by loss of the side-chain (100 %) and the subsequent loss of acetic acid. Loss of the side-chain is not a very favoured cleavage in the oxide series; however, in the spectra of some of the compounds with the baccharane skeleton it leads to peaks of considerable intensity. The easy loss of the side-chain suggests that it is in an allylic position to the diene system, and thus indicates that ring D is six-membered (also, compare above).

The large genus *Baccharis* L. from a botanical point of view is quite unusually well defined: all members are dioescious and the flowering heads mostly with very few flowers (1 − 3). For this reason we found it interesting to look for the occurrence of baccharis oxide in other members of the genus.

The roots of *B. glutinosa* Pers. and *B. salicina* Shinner were investigated. The former appeared to contain some baccharis oxide although insufficient for isolation in a crystalline form. From the latter, friedelan-3β-ol, one of the most common triterpenoids in members of the *Compositae*, was isolated in fair yield, whereas apparently baccharis oxide was absent.



Scheme 5.

EXPERIMENTAL

Infrared spectra were recorded on a Perkin-Elmer Model 21 or Model 257 spectrometer. Ultraviolet spectra were measured with a Hitachi Coleman 124 Double Beam spectrophotometer fitted with a Hitachi Perkin-Elmer 165 recorder. NMR spectra were obtained in deuterochloroform, the 60 MHz ones on Varian A-60A, the 100 MHz one on Varian HA 100 instruments. Mass spectra were obtained with AEI MS 902 or with MS 12 instruments. For thin-layer chromatograms Kieselgel G nach Stahl was used, and for column chromatography Kieselgel 0.05–0.2 mm, both from E. Merck. Rotations were measured in chloroform solution in a 1 dm tube.

Baccharis oxide. Dried roots (200 g) of *Baccharis halimifolia* grown locally in a greenhouse were extracted with acetone to give 1.22 g of an oily extract. During concentration of the acetone solution a sparingly soluble, crystalline material deposited. It was removed by filtration before concentration was continued. The oily residue was redissolved in petroleum (25 ml), when gradually colourless crystals were obtained on standing, m.p. 148°. When the mother liquor was chromatographed on alumina, more of these crystals were obtained by elution with petroleum:benzene 1:3. Recrystallised from petroleum *baccharis oxide* (*1*) melted at 148–149°, $[\alpha]_D$+42° (*c*, 2.16).

Hydrogenation with palladium-on-alumina in ethyl acetate furnished *dihydrobaccharis oxide* colourless needles from ethyl acetate, m.p. 127–128° $[\alpha]_D$+44° (*c*, 2.30). M^+ 428.403; calc. 428.402 for $C_{30}H_{52}O$.

Treatment of dihydrobaccharis oxide with boron trifluoride. Dihydrobaccharis oxide (145 mg) in dry benzene (15 ml) was treated with boron trifluoride/ether complex.[2] After 3 min the reaction was interrupted by addition of aqueous sodium hydrogen carbonate solution. The reaction product, isolated with ether, afforded a small amount of colourless crystals from ether-methanol. On further crystallisations pure *bacchar-12-en-3β-ol* was obtained, m.p. 147–148°, $[\alpha]_D$+39° (*c*, 1.82). M^+ 428.403; calc. 428.402 for $C_{30}H_{52}O$. The corresponding *acetate* (*2*), colourless blades from acetone-methanol, melted at 181–182°, $[\alpha]_D$+21° (*c*, 1.58). M^+ 470.411; calc. 470.412 for $C_{32}H_{54}O_2$.

Keto-acetate (3) from dihydrobaccharis oxide. Without isolation of the intermediates dihydrobaccharis oxide (500 mg) was treated as above with boron trifluoride/ether (0.5 ml) in benzene (20 ml). The crude reaction product was acetylated, and the acetate mixture was reacted with an ethereal solution of *p*-nitroperoxybenzoic acid[11] in excess. Acids were removed by filtration of the ethereal reaction mixture through a column of alumina. The oxidation products were treated on the steam-bath for 48 h with 90 % acetic acid. On thin layer chromatograms this final reaction mixture showed two major spots. When chromatographed on a column of silica gel (50 g), 130 mg were eluted with benzene, and 125 mg with benzene-ether 49:1.

The former material crystallised as colourless needles from acetone to give *3β-acetoxybacchara-11,13-diene (9)*, m.p. 152–153°, $[\alpha]_D$+7° (*c*, 2.65). M^+ 468.397; calc. 468.397 for $C_{32}H_{52}O_2$. Hydrogenation of 2 mg afforded a substance, the mass spectrum of which was identical with that of the acetate (*2*). M^+ 470.414; calc. 470.412 for $C_{32}H_{54}O_2$.

The latter material afforded *12-keto-3β-acetoxybaccharane* (*3*) as colourless needles from chloroform-petroleum, m.p. 271–272°, $[\alpha]_D$ +24° (*c*, 1.94). M^+ 486.409; calc. 486.407 for $C_{32}H_{54}O_3$.

3β-Acetoxybaccharane (4). Keto-acetate (*3*), m.p. 271–272°, (20 mg) was mixed with ethane dithiol (0.5 ml) and boron trifluoride/ether complex (0.5 ml) and left standing for 1 h. The reaction was interrupted by addition of methanol, and the reaction product was isolated with ether. The crude thioketal was refluxed for 2 h with Raney nickel in methanol. The reaction product, isolated with ether, crystallised from methanol to give *3β-acetoxybaccharane* (*4*) as colourless crystals, m.p. 169–170°, $[\alpha]_D$ +19° (*c*, 0.96). M^+ 472.428; calc. 472.428 for $C_{32}H_{56}O_2$. Saponification of the acetate with refluxing potassium hydroxide in methanol furnished *3β-hydroxybaccharane*, m.p. 162–163°, $[\alpha]_D$ +12° (*c*, 0.98), from chloroform-methanol. M^+ 430.417; calc. 430.417 for $C_{30}H_{54}O$.

The alcohol was oxidised with an equivalent amount of sodium dichromate in acetic acid with standing overnight at room temperature. *Baccharan-3-one* (*6*), isolated with ether, crystallised as needles from chloroform-methanol, m.p. 115–116°, $[\alpha]_D$ +40° (*c*, 0.77). M^+ 428.402; calc. 428.402 for $C_{30}H_{52}O$.

Baccharan-3-one (5 mg) was converted to the ethylene ketal by refluxing with ethylene glycol and a trace of *p*-toluenesulphonic acid in benzene and provided with a water estimator. The ketal was purified by thin-layer chromatography and crystallised from chloroform-methanol, m.p. 114–115°. M^+ 472.427; calc. 472.428 for $C_{32}H_{56}O_2$; *m/e* 99, found 99.043; calc. 99.045 for $C_5H_7O_2$.

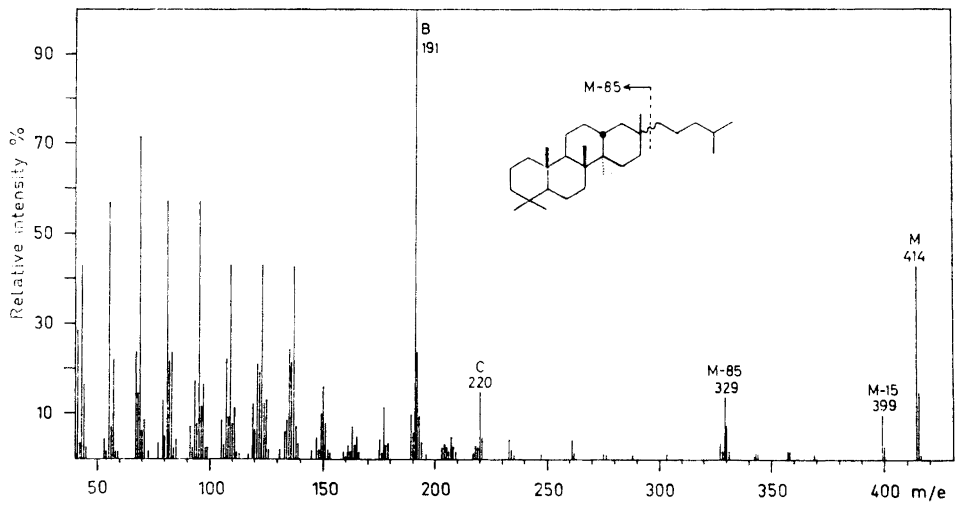


Fig. 5. Mass spectrum of baccharane (*7*).

Oxidation of baccharis oxide with osmium tetra-oxide. Baccharis oxide (1.7 g) in dry ether (55 ml) was treated with osmium tetra-oxide (1 g) in dry ether (25 ml). Pyridine (5 ml) was added, and the mixture was left at room temperature for 24 h. The complex was decomposed by reduction with lithium aluminium hydride. Several crystallisations from benzene and finally from chloroform afforded the *glycol* (*10*) as needles, m.p. 210–211°, $[\alpha]_D$ +30° (*c*, 2.08). M^+ 460.392; calc. 460.392 for $C_{30}H_{52}O_3$.

The glycol (44 mg) and sodium dichromate (20 mg) in acetic acid were left at room temperature overnight. The *trisnoracid* (*11*) was isolated with ether and crystallised from acetone as colourless needles, m.p. 205–210°. M^+ 416.328; calc. 416.329 for $C_{27}H_{44}O_3$.

Baccharane. Baccharan-3-one (19 mg) was reduced with ethylene dithiol and Raney nickel as above. M^+ 414.422; calc. 414.423 for $C_{30}H_{54}$, mass spectrum, see Fig. 5.

Baccharis glutinosa *Pers. roots.* Dried and ground roots (120 g) were extracted at room temperature with three portions of fresh acetone. The combined extracts were

evaporated, and the extracted material was isolated with ether. It was chromatographed crudely on silica gel to give 110 mg eluted with petroleum and 200 mg eluted with ether. The final eluate with methanol contained traces of material.

The petroleum eluate on silica gel thin-layer plates gave a spot which ran as baccharis oxide before and after treatment with *p*-nitroperoxybenzoic acid.

Baccharis salicina *Shinner roots*. Dried and ground roots (1.15 kg) were extracted with acetone as above. On concentration of the combined extracts colourless crystals precipitated. They were removed by filtration and crystallised twice from benzene, m.p. 278–280°, no depression on admixture with friedelan-3β-ol. However, the material probably is a mixture, since the infrared spectrum in KBr contained a low absorption at 1710 cm^{-1}. Otherwise the spectra of the two substances appeared identical.

The filtered acetone extract was evaporated to dryness in a vacuum, and the residue was extracted with boiling benzene. The benzene extract was chromatographed on silica gel, but no indication was found of the presence of baccharis oxide.

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