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OZONOLYSIS AND PERPHTHALIC ACID OXIDATION OF THE C(7):C(8) DOUBLE BOND IN SOME ISOPIMARANE DERIVATIVES[*]

C.R. Enzell[**] and B.R. Thomas
Chemistry Division, D.S.I.R., Petone, New Zealand.

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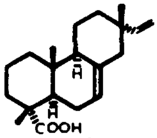
The trisubstituted double bond in isopimaric acid (1) was for a number of years taken to be at C(8):C(14) because isopimaric acid and pimaric acid (2) on ozonolysis gave the same oxotricarboxylic acid (3) and because dihydroisopimaric acid on ozonolysis gave the keto-aldehyde 4 which was converted to a hydrocarbon (5) identical with the corresponding hydrocarbon obtained from pimaric acid[1]. Recent synthetic work by Ireland and coworkers[2] showed that this assignment was incorrect and it has now been firmly established[3,4] that the double bond is at C(7):C(8).



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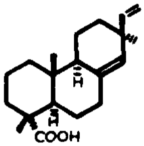

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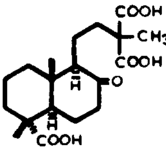

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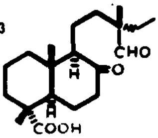

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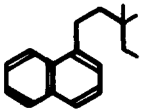
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During work on the structure of the isopimarane derivative araucarolone[5,6] a similar anomalous ozonolysis was

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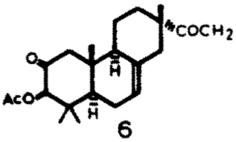
[**] New Zealand Senior Research Fellow. Present address: Org.Chem.Div., Royal Inst.of Technology, Stockholm 70, Sweden.

observed. The present paper describes some further studies of this reaction.

Araucarolone diacetate (6) on ozonolysis followed by reduction with zinc and acetic acid gives as main product an epoxide (65%) together with a small yield of the keto-aldehyde 7 (20%). The structure of the keto-aldehyde follows from the structure of araucarolone and from the nmr spectrum which shows an unsplit aldehyde band (595 cps).



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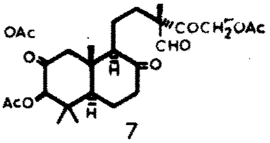

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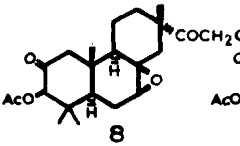
To demonstrate the structure of the epoxide, araucarolone diacetate was treated with monoperphthalic acid in ether. Unexpectedly the product was a mixture of the four epoxides listed in Table 1. Analyses, infrared spectra and nmr results show that two of these are the normal epoxides 8 and 9 expected from this reaction and that epoxide 9 is identical with the ozonolysis epoxide. The other two compounds (10 and 11) contain an extra oxygen atom.

TABLE 1 Epoxides from araucarolone diacetate

(nmr values in cps from TMS at 60 MC)

	m.p.	AcOC$\underline{H}$	AcOC$\underline{H}_2$	$\overset{O}{\frown}$CH	methyl protons					yield %
8	168-170°	297	294	183		83	66	55	53	9
9	liquid	294	301	187		77	62	53	50	40
10	140-141°	293	268	184	100		68	54	54	27
11	195-196°	297	274	186	97		65	55	52	19

The configuration of the epoxide group can be assigned from the splitting of the epoxide proton band. Inspection of Dreiding models indicates that the largest splitting should be that due to the 6α proton in the β-epoxide and thus epoxide 8 which shows a 4 cps splitting should have the β configuration and epoxide 9 which has a narrower unsplit band should have the α configuration. This assignment is confirmed by comparison with the simpler analogues described below.



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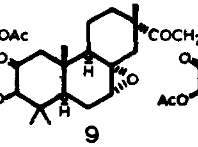

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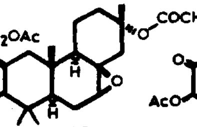

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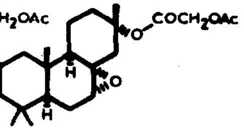

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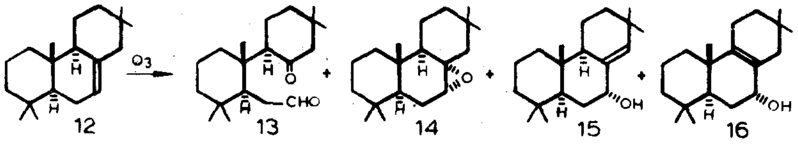
Epoxides 10 and 11 both contain an additional oxygen atom and give nmr spectra very similar to those of epoxides 8 and 9 but with one of the methyl bands displaced to low field and the C$\underline{H}_2$OAc band displaced to high field. The large displacement of the methyl band indicates that these compounds have been formed by insertion of an oxygen atom between C(13) and C(15) in a Baeyer-Villiger oxidation of the original epoxides. This was confirmed by further treatment of epoxides 8 and 9 with monoperphthalic acid giving epoxides 10 and 11 respectively.

In the light of these results it seemed of interest to study the action of ozone and monoperphthalic acid on the simpler analogue, 16-norpimar-7-ene (12), in which the oxygenated side chain is replaced by a methyl group and the oxygen functions in ring A are removed. In this case ozonolysis (ethyl acetate, -70°) followed by treatment with zinc and acetic acid gives a complex mixture but the primary product is the α-epoxide (14) together with a small amount of the normal keto-aldehyde (13). Monoperphthalic acid oxidation gives as primary products the two epoxides 14, m.p. 98-99°, and 17, m.p. 61-62°. However, under the conditions used in working up the ozonolysis product and even under much milder conditions, the α-epoxide is largely converted to a mixture of the allyl alcohols 15, m.p. 98-99°, and 16, m.p. 123-124°.



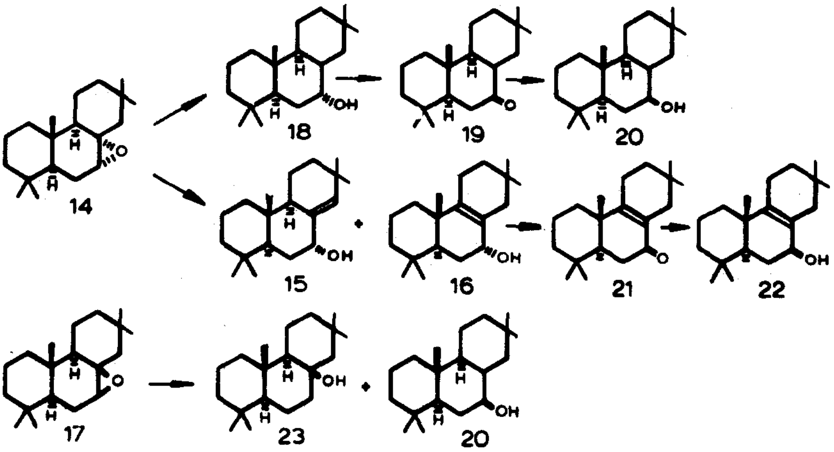
The keto-aldehyde (13) was obtained in insufficient amount (5%) for complete purification or for characterisation except by its nmr spectrum, but its structure is clear from the aldehyde band (595 cps, triplet, J 1.7 cps). The structures of the two allyl alcohols follow from analyses and from infrared and nmr spectra. Both allyl alcohols show broad $\mathrm{C\underline{H}OH}$ singlets indicating equatorial protons at C(7); an axial C(7) proton should show a peak with a splitting of about 10 cps and a $\mathrm{C\underline{H}OH}$ proton at C(14) should give a relatively sharp band. The double bond position in the $\Delta^{8:9}$-7α-ol (16) is shown by the presence of a strong allyl proton band (123 cps) and the absence of any vinyl proton band and in the $\Delta^{8:14}$-7α-ol (15) it is shown by the narrow vinyl proton band. The structure of the $\Delta^{8:9}$-7α-ol was confirmed by oxidation with manganese dioxide to an αβ-unsaturated ketone (21), m.p. 102-103°, (λ_{max}247 mμ, ε 10,000) and reduction of this ketone with lithium hydrido-aluminate to the $\Delta^{8:9}$-7β-ol (22), m.p. 106-108°.

The epoxide moving more slowly on silica gel should be the less hindered α-epoxide (14) and this is confirmed by its narrow epoxy proton band and by the formation of 7α-hydroxy-norpimarane (18), m.p. 107-108°, in 95% yield on reduction with lithium in ethylamine. The faster moving epoxide must therefore be the β-epoxide as indicated also by the split epoxy proton band (J 6 cps) and by the formation of 8β-hydroxy-norpimarane (23), m.p. 56-57°, in good yield (90%) on reduction with lithium in ethylamine. A small amount of 7β-hydroxy-norpimarane (20) was also isolated. In both cases this reduction thus gave diaxial opening almost exclusively.

The configuration of the 8β-hydroxy-norpimarane was shown by the displacement of two of the methyl bands to lower field. The configuration of the 7α-hydroxy-norpimarane indicated by the broad C$\underline{\text{H}}$OH singlet (228 cps) was confirmed by preparation of the equatorial epimer (20), m.p. 80-81°, (C$\underline{\text{H}}$OH proton at 193 cps, sextet, J 5,11,11 cps) by oxidation to the 7-oxo compound (19), m.p. 147-148°, and reduction with lithium hydrido-aluminate.

The norpimarane epoxides are reasonably stable under neutral conditions but are very sensitive to traces of acid. Thus the α-epoxide when left adsorbed on silica gel for several hours was converted to the $\Delta^{8:9}$-7α-ol and in deutero-chloroform in which traces of acid had probably formed it immediately gave the $\Delta^{8:14}$-7α-ol. The products obtained on treatment of the β-epoxide under a variety of conditions usually gave a hydrocarbon spot on thin layer chromatograms.

Both epoxides when spotted on a silica gel thin layer plate in a solution containing excess perphthalic acid were completely converted to a mixture of other products, the α-epoxide giving largely the $\Delta^{8:14}$-7α-ol. These conversions could be avoided by spotting the solutions on top of bicarbonate spots. Similarly the perphthalic acid reaction mixture could be worked up to give a mixture of the two epoxides without isomerisation by shaking with bicarbonate solution but gave a mixture of epoxides and allyl alcohols when shaken with water or treated with silica gel. The sensitivity of these epoxides and the ease of conversion to allyl alcohols parallels the behaviour of steroid 7:8 epoxides (cf ref 7).



Ozonolysis of isopimar-7-ene derivatives can apparently take place <u>via</u> three different routes leading to 7α, 8α-epoxide formation and to anomalous, C(8)-C(14), and normal, C(7)-C(8), cleavage. Normal cleavage occurs only to a very small extent or not at all. Of the two remaining routes, epoxide formation, which may be regarded as the result of stabilisation of an initial ozone-double bond complex by elimination of molecular oxygen due to steric hindrance, is not uncommon[8]; cholest-7-en-3β-ol acetate also gives the α-epoxide[9]. The anomalous cleavage may represent an alternative way for an ozone-double bond complex to stabilise, e.g. by a route reminiscent of that outlined for Feist's acid[10], or may be due to direct allylic attack at C(14) giving an intermediate, which could undergo a rearrangement similar to that involved in the conversion of cyclohexene hydroperoxide to hexanedial[11]. The three compounds discussed here that give anomalous cleavage differ from 16-norpimar-7-ene in having an oxygenated substituent on the α-side and in the bulk of the substituents at C(13), but these differences seem rather small.

All new compounds gave satisfactory analyses or mass spectrometric molecular weights.

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