A Cyclopropanol Derivative as an Intermediate for the Preparation of A-Homopimarane

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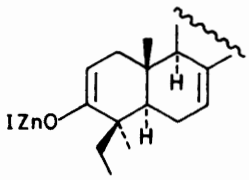
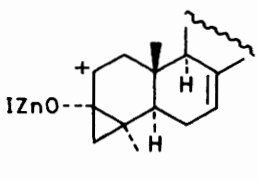
The hydroxycyclopropane (**4**) and the cyclobutanone (**3**) derivatives of isopimara-7,15-diene were prepared by the reduction of 3-oxo-19-tosyloxy isopimara-7,15-diene (**2**) with zinc and sodium iodide in hexamethylphosphoric triamide. On exposure to air compound (**4**) was oxidized to give the peroxide (**6**), in equilibrium with the corresponding hydroperoxide (**7**). The sequence (**2**) → (**4**) → (**6**) represents a new route to A-homopimaranes.

In connection with a study of the chemistry of virescenol C (**1**), the aglycone of the fungal virescenoside metabolite,[1] the reduction of the 19-tosyloxy derivative (**2**)[2] with metal in solution was investigated.

Treatment of compound (**2**) with zinc and sodium iodide in hexamethylphosphoric triamide at 90 °C gave two products that were easily separated by chromatography. The less polar one (10%) was shown to be the cyclobutanone (**3**) by its ^{1}H n.m.r. and chromatographic data, which were identical with those of a sample prepared by an alternative synthetic route.[2] The formation of the cyclobutanone (**3**) can be explained by assuming that the toluene-*p*-sulphonate (**2**) is initially enolized to give intermediate (**i**); this undergoes a homo-Favorskii reaction to give (**ii**), which then undergoes skeletal rearrangement.[3]



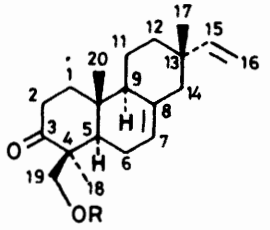
(**i**)



(**ii**)

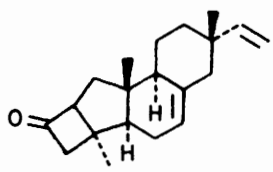
The major product (55%) was the hydroxycyclopropane derivative (**4**); its structure was established by treating it with acid[4] to give the ketone (**5**), identical in all respects with the 3-oxopimara-7,15-diene prepared by the oxidation of 3β-hydroxypimara-7,15-diene.[5]

The hydroxycyclopropane (**4**) proved very sensitive to air, being oxidized readily to give the peroxide (**6**), in equilibrium (*vide infra*) with the corresponding hydroperoxide (**7**). The mass spectrum of this mixture showed a molecular ion at *m/z* 318, $C_{20}H_{30}O_3$, which successively loses H_2O (*m/z* 300), H_2O + CH_3 (*m/z* 285), and OH + OH (*m/z* 284). The i.r. spectrum exhibited intense hydroxy and carbonyl absorptions, and the ^{1}H n.m.r. spectrum showed the product to be a mixture (60:40) of two compounds, and had a sharp singlet band at δ 9.1 which was exchangeable on D_2O addition, probably due to a hydroperoxide group.[6] In addition, (**6**) and (**7**) gave a positive peroxide iodide–iodide test and were quantitatively transformed into the oxoalcohol (**8**) by reduction with triphenylphosphine in methanol.[7] The final proof for the structural assignment was provided by acetylation of compound (**6**) with acetic anhydride in pyridine, leading to the acetate (**9**) as the only product; the i.r. spectrum of this compound showed absorption at 1 720 (C=O) and 1 790 (diagnostic for the hydroperoxy acetate),[8] and sodium boron hydride reduction of (**9**) led to the corresponding hydroxy derivative (**10**).†

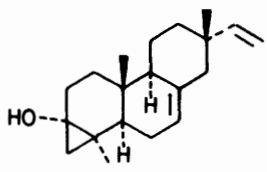


(**1**) R = H

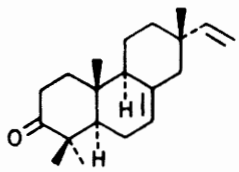
(**2**) R = $SO_2C_6H_4Me$-*p*



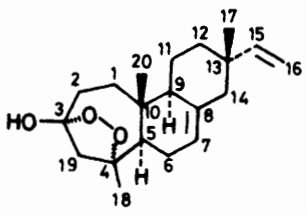
(**3**)



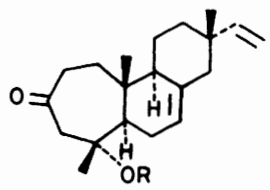
(**4**)



(**5**)



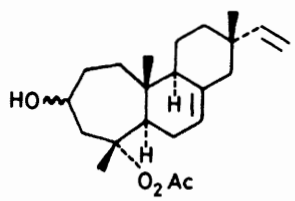
(**6**)



(**7**) R = OH

(**8**) R = H

(**9**) R = OAc



(**10**)

† The C-3 stereochemistry of the compound has been left unspecified since there is, at present, no basis for selecting one or other epimer.

Table. ^{13}C N.m.r. data for compounds (**5**)—(**7**) and (**9**) [a]

Carbon	δ_c (5)	(6)	(7)	(9)
C(1)	38.1 t	31.8 t	32.5 t	32.4 t
C(2)	34.6 t	34.8 t	37.9 t	38.0 t
C(3)	216.0 s	107.5 s	214.2 s	210.6 s
C(4)	37.4 s	89.0 s	85.0 s	87.6 s
C(5)	51.8 [b] d	51.7 [b] d	48.0 d	48.1 d
C(6)	23.8 t	27.9 t	23.5 t	23.5 t
C(7)	121.2 d	122.5 d	121.7 d	121.5 d
C(8)	135.6 s	136.9 s	135.3 s	135.8 s
C(9)	51.1 [b] d	51.4 [b] d	52.7 d	52.7 d
C(10)	35.2 s	36.1 s	36.5 s	37.0 s
C(11)	21.6 t	20.8 t	21.1 t	21.1 t
C(12)	36.1 t	36.9 t	36.9 t	36.5 t
C(13)	36.8 s	37.4 s	37.3 s	37.5 s
C(14)	45.9 t	46.5 t	46.5 t	46.4 t
C(15)	149.9 d	149.9 d	149.9 d	149.9 d
C(16)	109.4 t	109.4 t	109.4 t	109.6 t
C(17)	21.5 q	21.6 q	21.6 q	21.6 q
C(18)	23.8 q	26.2 q	20.0 q	17.8 q
C(19)	20.3 q	47.0 t	48.5 t	48.0 t
C(20)	14.8 q	15.1 q	16.9 q	16.5 q

[a] δ Values in p.p.m. downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ p.p.m. See structures for numbering scheme. [b] Assignments in any vertical column may be interchanged.

The stereochemistry at C-4 of the peroxide (**6**) and the hydroperoxide (**7**) was proposed on the basis of mechanistic reasoning: in the oxygen–cyclopropane interaction, the oxygen attacks the α-face of the diterpene skeleton probably because steric hindrance due to the methyl groups at C-4 and C-10 prevents attack on the β-face.

The structures of the ketone (**5**), the hydroxyperoxide (**6**) and the hydroperoxy tautomer (**7**), and the peroxyacetate (**9**) were confirmed by ^{13}C n.m.r. spectroscopy; the carbon shifts are based on those of isopimaradienes[9] and virescenol C[10] and are listed in the Table. The oxygen mediated opening of the hydroxycyclopropane, easily derived from 3-oxo-19-tosyloxy-pimarenes, represents a new route to A-homopimaranes. Although many one-carbon rearrangements have been reported in the pimaranic diterpene field, none of the aforementioned type has been observed previously.

Experimental

M.p.s were determined on a Reichert hot-stage and are uncorrected. I.r. spectra were of CCl_4 solutions and were obtained on a Perkin-Elmer 1320 spectrophotometer. Mass spectra were determined on a Varian MAT 311 A instrument at 70 eV using an all-glass inlet system. ^1H N.m.r. spectra were of $CDCl_3$ solutions (Me_4Si; $\delta = 0$) and were recorded on a Varian EM-390 spectrometer. ^{13}C N.m.r. spectra were produced on a Varian XL-100-15 spectrometer operating at 25.2 MHz in the Fourier transform mode. Column chromatography was performed with 0.063—0.0200 mm mesh Merck silica gel adsorbant.

*Treatment of Virescenol C Toluene-*p*-sulphonate* (**2**) *with Zinc and Sodium Iodide in Hexamethylphosphoric Triamide.*—To a solution of virescenol C toluene-*p*-sulphonate (**2**) (2 g) and sodium iodide (4 g) in hexamethylphosphoric triamide (60 ml) was added powdered zinc (3.6 g) and the mixture was stirred at 90 °C, under nitrogen, for 24 h. It was then diluted with water and extracted with ether. The organic phase was washed with water, dried ($MgSO_4$), and concentrated under reduced pressure. Chromatography of the residue (1.1 g) on silica gel and elution with benzene gave 2,4-cyclo-3(4→19)*abeo*-isopimara-7,15-dien-3-one (**3**) (0.125 g, 10%) (for analytical and spectroscopic data, see ref. 2). Further elution with benzene–ethyl acetate (24:1) gave 3,19-cycloisopimara-7,15-dien-3-ol as a semisolid (**4**) (0.7 g 55%); $\nu_{max.}$ 3 610 cm^{-1} (OH); δ_H 0.62, 0.88, and 1.18 (9 H, s, Me_3).

Treatment of the Hydroxycyclopropane (**4**) *with Hydrochloric Acid.*—To a solution of (**4**) (0.1 g) in chloroform (10 ml) was added 4 drops of conc. HCl and the mixture was stirred for 3 h at room temp. The solution was washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated under reduced pressure. Chromatography of the residue on silica gel and elution with benzene gave *isopimara-7,15-dien-3-one* (**5**) (85 mg), m.p. 74—75 °C (Found: C, 83.7; H, 10.6. $C_{20}H_{30}O$ requires C, 83.86; H, 10.56%); $\nu_{max.}$ 1 712 cm^{-1} (C=O); δ_H 0.89, 1.06, 1.07, and 1.12 (12 H, s, Me_4).

3,4-*Epidioxy*-3(4→19)-abeo-*isopimara*-7,15-*dien*-3-*ol* (**6**) *and* 4-*Hydroperoxy*-3(4→19)-abeo-*isopimara*-7,15-*dien*-3-*one* (**7**).—A solution of the hydroxycyclopropane (**4**) (0.5 g) in chloroform (20 ml) was kept at room temp. for 2 h, then the solvent was removed under reduced pressure and the residue chromatographed on silica gel. Elution with benzene–ethyl acetate (9:1) gave the hydroxyperoxide (**6**); and the hydroperoxy-ketone (**7**) (0.45 g); m.p. 121—123 °C (unsatisfactory analytical data); *m/z* 318 (M^+), 300 ($M^+ - 18$), 285 ($M^+ - 33$), and 284 ($M^+ - 34$); compound (**6**), $\nu_{max.}$ 3 600 (OH) cm^{-1}; δ_H 0.89, 1.01, 1.33 (9 H, s, Me_3), 2.18, 2.96 (2 H, dd, *J*, 13 Hz, 19-H). Compound (**7**): $\nu_{max.}$ 1 710 (C=O) cm^{-1}; δ_H 0.89, 0.91, 1.23 (9 H, s, Me_3), 2.83, 3.15 (2 H, dd, *J* 13 Hz, 19-H), and 9.1 (1 H, s, OOH).

Reduction of the Peroxide (**6**) *and the Ketone* (**7**) *with Triphenylphosphine.*—To a solution of (**6**) and (**7**) (0.1 g) in methanol (10 ml) was added a solution of triphenylphosphine (0.2 g) in methanol (5 ml), and the solution was stirred at room temperature for 15 min. The usual work-up, chromatography on silica gel, and elution with benzene gave 4-*hydroxy*-3(4→19)-abeo-*isopimara*-7,15-*dien*-3-*one* (**8**) (90 mg) m.p. 98—100 °C (Found: C 79.6; H, 9.8. $C_{20}H_{30}O_2$ requires C 79.42; H 10.00%); $\nu_{max.}$ 3 610 (OH) and 1 700 (C=O) cm^{-1}; δ_H 0.90, 0.90, 1.28 (9 H, s, Me_3), and 2.80, 2.90 (2 H, dd, *J* 12 Hz, 19-H); *m/z* 302 (M^+), 284 ($M^+ - 18$), and 269 ($M^+ - 33$).

Acetylation of the Peroxide (**6**) *and the Ketone* (**7**).—A solution of (**6**) and (**7**) (0.1 g) in pyridine (5 ml) and acetic anhydride (0.5 ml) was stirred at room temperature for 24 h. Work-up and chromatography on silica gel with benzene as eluant gave 3-*oxo*-3(4→19)-abeo-*isopimara*-7,15-*dien*-4-*yl peracetate* (**9**) as a semisolid (85 mg) (Found C, 73.1; H, 9.0. $C_{22}H_{32}O_4$ requires C, 73.30; H, 8.95%); $\nu_{max.}$ 1 720 (C=O) and 1 790 cm^{-1} ($OOCOCH_3$); δ_H 0.90, 0.91, 1.31 (9 H, s, Me_3), 2.03 (3 H, s, $OCOCH_3$), and 2.90, 3.10 (2 H, dd, *J* 13 Hz, 19-H).

Reduction of the Peracetate (**9**).—To a solution of (**9**) (50 mg) in methanol (3 ml) was added a solution of sodium borohydride (10 mg) in methanol (1 ml). The mixture was stirred at room temperature for 10 min, 0.25M sulphuric acid (0.5 ml) was added, and it was extracted with chloroform and the extract washed with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography of the residue on silica gel and elution with benzene–ethyl acetate (24:1) gave 3-hydroxy-3(4→19)-*abeo*-isopimara-7,15-dien-4-yl peracetate (**10**) as a semisolid (35 mg) (Found C, 73.4; H, 8.8 $C_{22}H_{34}O_4$ requires C, 73.30; H, 8.95%);

$\nu_{max.}$ 3 630 (OH), 1 790 cm^{-1} ($OOCOCH_3$); δ_H 0.88, 0.90, 1.33 (9 H, s, Me_3), 2.03 (3 H, s, $OOCOCH_3$), and 4.23 (1 H, m, 3-H).

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