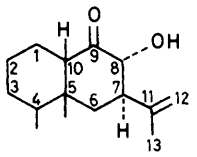
Synthesis of Hydroxydihydroeremophilone

By **A. Reginald Pinder** * and **W. Daniel Saunders**, Department of Chemistry, Clemson University, Clemson, S. Carolina 29631, U.S.A.

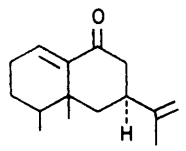
Hydroxydihydroeremophilone (HDE) has been synthesized from eremophilone by two procedures. In one the kinetic enolate of 1,10-dihydroeremophilone was oxidised with molybdenum peroxide to the 8β-epimeride of HDE, which was then epimerised by acid to HDE. Alternatively the trimethylsilyl ether of the kinetic enolate could be oxidised by peracid to an α-trimethylsilyloxyketone, which was then hydrolysed by acid to HDE.

HYDROXYDIHYDROEREMOPHILONE (HDE; 1) is one of a trio of non-isoprenoid bicyclic sesquiterpenes isolated over 40 years ago from the Australian shrub *Eremophila mitchelli*.[1,2] Its structure, established by degradation,[1,2] has been confirmed by *X*-ray diffraction analysis,[3] which also revealed its relative stereochemistry. The absolute stereochemistry was settled by molecular rotation difference comparisons [4] and by chemical correlations.[5] The other two members of the group, eremophilone (2) [6] and hydroxyeremophilone (3) [7] have both yielded to synthetic endeavours; we describe here the synthesis of HDE from natural eremophilone.

1,10-Dihydroeremophilone (4), available [1] from eremophilone (2) and known to have the desired *cis* and steroidal ring junction,[8] on treatment with ethyl formate afforded the 8-hydroxymethyleneketone (5), which crystallised in part. The product is presumably



(1)



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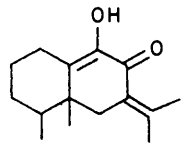

(3)

an equilibrium mixture of tautomers (5) and (6). The mixture, with ethanolic bromine in the presence of barium hydroxide,[9] yielded 8α-bromodihydroeremophilone (7) (see below) along with dihydroeremophilone (4). Seeking to improve the yield of the former we

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[2] For reviews of eremophilane sesquiterpenes see D. H. R. Barton, in ' Chemistry of Carbon Compounds', ed. E. H. Rodd, Elsevier, Amsterdam, 1953, vol. 11B, p. 689 ff; J. L. Simonsen, ' The Terpenes ', Cambridge University Press, 1952, vol. 111, pp. 212—224; A. R. Pinder, *Perfumery Essent. Oil Record*, 1968, 59, 280, 645; A. R. Pinder, *Fortschr. Chem. org. Naturstoffe*, 1977, **34**, 81.

[3] D. F. Grant and D. Rogers, *Chem. and Ind.*, 1956, 278; D. F. Grant, *Acta Cryst.*, 1957, **10**, 498.

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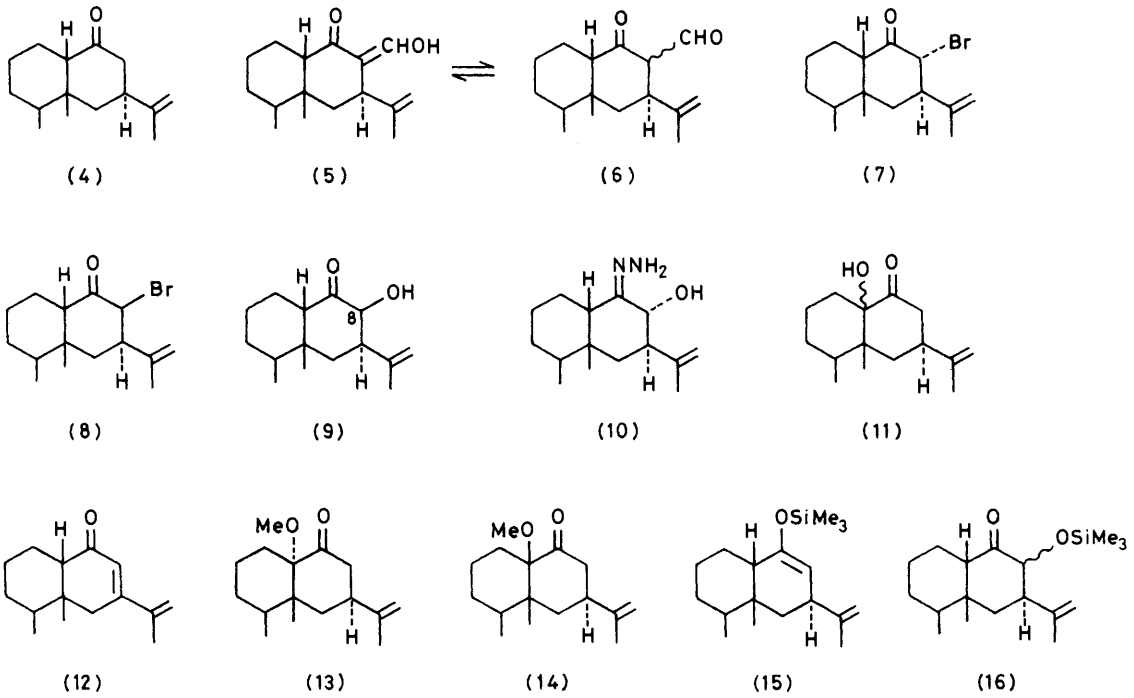
[8] C. Djerassi, R. Mauli, and L. H. Zalkow, *J. Amer. Chem. Soc.*, 1959, **81**, 3424.

[9] *Cf.* M. Sergent, M. Mongrain, and P. Deslongchamps, *Canad. J. Chem.*, 1972, **50**, 336.

formed the enolate anion of (4) under kinetically controlled conditions.[10] Reaction with bromine afforded in good yield a mixture of 8-bromoketones, separable into the equatorial (7) and axial (8) epimerides, both crystalline, in ratio 3 : 2, their configurations being settled by i.r. and n.m.r. spectroscopy. Efforts were made to hydrolyse these bromoketones to HDE (1) or its 8-epimeride (9). For example the equatorial epimeride (7) was treated with hydrazine in methanol with the hydroxyhydrazone (10) as objective,[11] hydrolysable to HDE.[11] However, only a Favorskii reaction resulted, acid [13] to give a mixture of products, including some dihydroeremophilone and some hydroxylic material. Intense i.r. absorption in the 1 250—1 260 and 755—840 regions (Si–C bonds), and a C=O band at 1 704 cm^{-1}, indicated the major product to be the trimethylsilyloxyketone (16),[13] which proved to be stable to cold alkali and acid possibly because of steric hindrance to hydrolysis. However hot mineral acid in diglyme effected hydrolysis to yield a mixture from which HDE (1) was separated by chromatography on silica gel. The same kinetic enolate was next treated with molybdenum



evidenced by the presence of an ester CO band in the i.r. spectrum. The same treatment was not applied to the axial epimeride (8) because of the anticipated ease of dehydrobromination in this case.

Exposure of (7) to potassium formate in the absence or presence of a crown ether regenerated dihydroeremophilone (4) by hydrogenolysis. Potassium carbonate treatment afforded a bromine-free hydroxyketone formulated as (11) (no C*H*OH signal in n.m.r. spectrum). The axial bromoketone (8) with potassium formate in methanol gave dienone (12) as principal product, $\lambda_{max.}$ 273 nm (ε 11 500), accompanied by what seemed to be the methoxyketones (13) and (14) (OCH_3 signal, and absence of C*H*OMe and C*H*OH signals in the n.m.r. spectrum).[12]

The kinetic enolate with trimethylsilyl chloride furnished the enol ether (15), which reacted with peroxide,[14] as its pyridine–hexamethylphosphoric triamide (HMPA) complex, MoO_5·py·HMPA.[15] The product, obtained in good yield, proved to be 8β-hydroxy-1,10-dihydroeremophilone (9), acid treatment of which caused epimerisation at position 8 to give crystalline HDE (1), identical in all respects with authentic material. Since HDE has been converted into hydroxyeremophilone (3) by bismuth oxide oxidation [8] the work constitutes a new synthesis of (3).

EXPERIMENTAL

M.p.s and b.p.s are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 137 spectrophotometer, n.m.r. spectra on Perkin-Elmer R-24 and Bruker HX-90

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[11] *Cf.* P. Catsoulacos and A. Hassner, *J. Org. Chem.*, 1967, **32**, 3723.

[12] *Cf.* W. B. Smith and C. Gonzalez, *Tetrahedron Letters*, 1966, 5751; H. O. House and H. W. Thompson, *J. Org. Chem.*, 1963, **28**, 164; C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez, and K. Smith, *Tetrahedron Letters*, 1974, 2417.

[13] *Cf.* A. Hassner, R. H. Russ, and H. W. Pinnick, *J. Org. Chem.*, 1975, **40**, 3427; A. G. Brook and D. M. Macrae, *J. Organometallic Chem.*, 1974, **77**, C19; G. M. Rubottom, M. A. Vasquez, and D. R. Pelegrina, *Tetrahedron Letters*, 1974, 4319.

[14] E. Vedejs, *J. Amer. Chem. Soc.*, 1974, **96**, 5944.

[15] H. Mimoun, L. S. de Roch, and L. Sajus, *Bull. Soc. chim. France*, 1969, 1481.

instruments, and g.l.c. analyses were performed on a F. and M. 810 research chromatograph.

8-Hydroxymethylene-1,10-dihydroeremophilone (5).—Freshly prepared sodium methoxide (734 mg, 13.6 mmol) was powdered under dry benzene (50 ml). Ethyl formate (670 mg, 9.1 mmol) was added and the mixture stirred and cooled in ice during the gradual addition of 1,10-dihydroeremophilone [1] (1.0 g, 4.5 mmol) in dry benzene (50 ml). After 24 h at room temperature ice–water was added and unchanged ketone removed by ether extraction. The aqueous layer was acidified and the product isolated therefrom by extraction with ether. It distilled at 125—135 °C (bath) (0.025 mmHg) (306 mg) (Found: C, 77.5; H, 9.7. $C_{16}H_{24}O_2$ requires C, 77.4; H, 9.7%) as a yellow oil which crystallised partially when kept and gave an intense deep red colour with ferric chloride; $\nu_{max.}$ (film) 1 639, 1 613, 1 575, and 887 cm^{-1}; $\delta(CDCl_3)$ 0.85 (3 H, d, *J* 6 Hz, $CHCH_3$), 0.96 (3 H, s, angular CH_3), 1.64 (3 H, s, allylic CH_3), 3.27 (1 H, dd, J_{cis} 6 Hz, J_{trans} 12 Hz, 7-H), 4.88 (2 H, s, $C{=}CH_2$), and 8.48 (1 H, s, CHOH). Bromination of the product in ethanol in the presence of barium hydroxide was incomplete, a low yield of the equatorial bromide (7) (see below) being obtained.

8α- and 8β-Bromo-1,10-dihydroeremophilone (7 and 8).—Triphenylmethane (5 mg) was added at −5 °C, in a helium atmosphere, to n-butyl-lithium (0.9 ml of a 2.1M-solution in hexane, 1.9 mmol) followed by dry, freshly distilled di-isopropylamine (193 mg, 1.9 mmol) in dry tetrahydrofuran (4 ml). The deep red solution was stirred at −5 °C for 30 min. Then 1,10-dihydroeremophilone [1] (379 mg, 1.7 mmol) in dry tetrahydrofuran (4 ml) was added during 10 min. After several minutes of additional stirring the mixture was cooled to −78 °C and bromine in methylene chloride (1.7 ml of 1.0M) was added all at once and the mixture stirred for 1 min. Aqueous sodium hydrogen carbonate was added, and the system allowed to reach room temperature. The products were isolated by ether extraction, the residue from solvent evaporation being taken up in hexane and chromatographed on neutral Woelm alumina (10 g, activity III) with hexane elution (25 ml portions). The first eluates yielded the 8β (axial) *bromoketone* (8) (164 mg, 32%), which separated from aqueous ethanol as needles, m.p. 118—124 °C, $\nu_{max.}$ (CCl_4) 1 715 (axial α-bromoketone), 1 650 (C=C), and 894 cm^{-1}; $\delta(CDCl_3)$ 0.76 (3 H, poorly resolved d, *J* 5.5 Hz, $CHCH_3$), 1.09 (3 H, s, angular CH_3), 1.76 (3 H, s, allylic CH_3), 3.10 (1 H, broad s, tertiary allylic H), 4.36 (1 H, d, *J* 5 Hz, CHBr), 4.84 (1 H, s, vinyl H), and 4.97 (1 H, s, vinyl H) (Found: C, 60.1; H, 7.8; Br, 26.9. $C_{15}H_{23}BrO$ requires C, 60.2; H, 7.7; Br, 26.7%). Later eluates provided the 8α (equatorial) *bromoketone* (7) (233 mg, 45%), which separated from aqueous ethanol as prisms, m.p. 110—112 °C, $\nu_{max.}$ (CCl_4) 1 721 (equatorial α-bromoketone), 1 645 (C=C), 892 ($=CH_2$), and 692 cm^{-1} (C–Br); $\delta(CDCl_3)$ 0.77 (3 H, d, *J* 5.5 Hz, $CHCH_3$), 1.02 (3 H, s, angular CH_3), 1.77 (3 H, s, allylic CH_3), 2.82 (1 H, td, J_{trans} 12 Hz, J_{cis} 4 Hz, allylic H), 4.53 (1 H, dd, J_{trans} 12 Hz, J_{cis} 1.2 Hz, CHBr), and 4.83—4.90 (2 H, broad s, $=CH_2$) (Found: C, 60.2; H, 7.8; Br, 26.8. $C_{15}H_{23}BrO$ requires C, 60.2; H, 7.7; Br, 26.7%). Attempts to replace Br by OH in these bromoketones using a variety of reagents were unsuccessful (see main section).

8β-Hydroxydihydroeremophilone (9).—Lithium di-isopropylamide [from n-butyl-lithium (0.65 ml of 2.1M in hexane; 1.36 mmol) and di-isopropylamine (146 mg, 1.36 mmol) in tetrahydrofuran (3.0 ml, freshly distilled from $LiAlH_4$)] was cooled to −78 °C and stirred during the gradual (30 min) addition of 1,10-dihydroeremophilone (200 mg, 0.91 mmol) in tetrahydrofuran (3.0 ml), under helium. After a further 10 min molybdenum peroxide–pyridine–hexamethylphosphoric triamide (MoO_5·py·HMPA) [14,15] complex (620 mg, 1.42 mmol) was added all at once, and stirring was continued at −78 °C for 1 h. The temperature was allowed to rise to 0 °C, water was added, and the product isolated with ether. The combined extracts were washed with sodium hydrogen carbonate, dilute HCl, and water, and then dried and concentrated. The residue (189 mg) was chromatographed on silica (4.0 g); elution with 40—50% benzene in light petroleum (b.p. 30—60 °C) gave, after evaporation, *8β-hydroxy-1,10-dihydroeremophilone* (9), which crystallised from light petroleum (b.p. 30—60 °C) as needles (56 mg), m.p. 98—99.5 °C. On admixture of this product with authentic HDE (m.p. 100—101 °C) the m.p. was depressed to 66—80 °C; $\nu_{max.}$ (CCl_4) 3 650 (OH), 1 715 (C=O), 1 629 (C=C), and 903 cm^{-1} ($=CH_2$); $\delta(CDCl_3)$ 0.75 (3 H, d, *J* 7 Hz, $CHCH_3$), 1.08 (3 H, s, angular CH_3), 1.80 (3 H, s, allylic CH_3), 3.92 (1 H, unresolved d, CHOH), 4.94 (1 H, s, vinyl H), and 5.06 (1 H, s, vinyl H) (Found: C, 76.3; H, 10.4. $C_{15}H_{27}O_2$ requires C, 76.2; H, 10.2%).

8α-Hydroxydihydroeremophilone (HDE; 1).—(*a*) The preceding crude keto-alcohol (185 mg, 0.78 mmol) in diglyme (10 ml) was heated on a water-bath with 2N-HCl (1 ml) for 30 min. Ice was then added and the mixture extracted with ether. The washed and dried extract was concentrated, and the residue chromatographed on silica (4.0 g) with 40% benzene–light petroleum (b.p. 30—60 °C) elution. This gave crystalline HDE (36 mg), which separated from methanol as needles, m.p. 98—100 °C, undepressed by admixture with an authentic sample (m.p. 100—101 °C; lit.,[1] m.p. 102—103 °C); $\nu_{max.}$ (CCl_4) 3 559 (OH), 1 701 (C=O), 1 634 (C=C), and 887 cm^{-1} ($=CH_2$); $\delta(CDCl_3)$ 0.78 (3 H, d, *J* 6 Hz, $CHCH_3$), 1.05 (3 H, s, angular CH_3), 1.83 (3 H, s, allylic CH_3), 3.99 (1 H, d, *J* 11 Hz, CHOH), and 4.90 (2 H, broad s, $=CH_2$). The behaviour of synthetic and natural products on g.l.c. and t.l.c. were identical, and spectral comparisons confirmed the identity.

(*b*) The kinetic enolate of 1,10-dihydroeremophilone (0.226 g) was prepared from n-butyl-lithium and di-isopropylamine as described above. The enolate, in dry tetrahydrofuran (2 ml), was stirred at −5 °C for 10 min, then treated with a solution of trimethylsilyl chloride (0.190 g) and triethylamine (0.041 g) in the same solvent (2 ml). After 15 min cold aqueous sodium hydrogen carbonate was added and the enol silyl ether (15) (0.297 g) isolated with ether; $\nu_{max.}$ (film) 1 647, 839, and 882 cm^{-1}, no C=O band; $\delta(CDCl_3)$ 0.20 (9 H, s, $SiCH_3$), and 4.70 (3 H, br, =CH and $=CH_2$). G.l.c. showed the product to be >95% pure; it was dissolved in methylene chloride (2 ml) and cooled to 0 °C. A little solid sodium hydrogen carbonate was added, followed by *m*-chloroperbenzoic acid (1 mol) in methylene chloride (2 ml) during several min. After 1 h aqueous sodium sulphite was added and the product isolated by hexane extraction. The i.r. absorption of the residual oil [$\nu_{max.}$ (film) 1 704, 1 250—1 260, and 755—840 cm^{-1}] indicated it was mainly the α-trimethylsilyloxyketone (16); it was heated on a water-bath with diglyme (10 ml) and 2N-HCl (3 ml) for 45 min then cooled and the mixture extracted with hexane. The dried extract was chromatographed on silica gel; benzene elution gave, after evaporation, an oil (20 mg) which solidified and crystallised from methanol as

needles, m.p. 98—100 °C alone or mixed with an authentic sample of HDE.

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