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Hydroxylation of Cedrol by *m*-Chloroperbenzoic Acid. Synthesis of an Epimer of the Alleged "Senoxydene"

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Cedrol was hydroxylated by *m*-chloroperbenzoic acid to give four tertiary alcohols and two secondary alcohols, one of which was converted into an epimer of "senoxydene" in four steps.

The hydroxylation of natural products at unactivated positions has been effected by dry ozonization,[1] remote oxidation,[2] the Barton reaction,[3] microbial oxidation,[4] and mammalian metabolism.[5] In 1979, Deno and Meyer reported a method of hydroxylation of the 25-position of a steroidal side chain using hydrogen peroxide and trifluoroacetic acid.[6] Schneider described a practical method of hydroxylation of polycyclic hydrocarbons by *m*-chloroperbenzoic acid (*m*CPBA) yielding tertiary alcohols.[7] However, no examples of the use of *m*CPBA as a reagent for the hydroxylation of natural products have been reported.

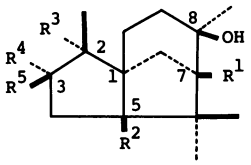
We have been studying the oxidation of natural products by not only biological but also chemical methods. The hydroxylation of terpenoids in rabbits has been investigated in these laboratories.[8] We have recently applied *m*CPBA to the hydroxylation of unactivated carbon atoms of triterpenes belonging to the dammarane,[9] lupane,[10] and friedelane[10] classes.

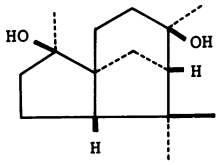
Cedrol(**1**) is a sesquiterpene found in cedar wood. Ourisson and co-workers[11] subjected **1** to dry ozonization which afforded cedrane-2α,8β-diol (**5**) in 79% yield (50% conversion). Moreover, it has been reported by Wang *et al.*[12] that microbial oxidation of **1** produced cedrane-3α,8β-diol (**6**), 8β-hydroxycedran-3-one, and cedrane-3β,8β-diol (**7**).

We became interested in the structure of **1** which is very similar to an epimer of "senoxydene." If we could hydroxylate the 7-position of cedrol (**1**), oxidative bond cleavage and intramolecular aldol condensation would lead to a triquinane skeleton.

In a continuation of our work, the hydroxylation of natural products using *m*CPBA, we have examined the reaction of cedrol (**1**) with this reagent. We now report the products of this reaction as well as the conversion of one of these to an epimer[13] of the alleged "senoxydene."[14]

Cedrol (**1**, 2.2 g) was treated with *m*CPBA (1.2 equiv) in chloroform (75 ml) under reflux for 6 h. The usual work-up and chromatographic separation (see Experimental) afforded three novel compounds (**2**, **3**, and **4**) in addition to the previously known cedrane-2α,8β-diol (**5**),[11] cedrane-3α,8β-diol (**6**),[12,15,16] and cedrane-3β,8β-diol (**7**).[12,15,16] The least polar compound, the diol **2** [IR($CHCl_3$) 3570 and 3450 cm^{-1}; *m/z* 238 (M^+)] had signals characteristic of three tertiary methyl groups [δ 1.35, 1.21, and 0.97 (each s)] and a secondary methyl group [δ 0.87 (d, J=7 Hz)] in its ^1H NMR spectrum. As no resonance due to an oxygenated methine group was observed, it followed that the compound was either cedrane-7β,8β-diol (**2**) or cedrane-5β,8β-diol (**3**). The correctness of the former structure was demonstrated by ^{13}C NMR spectroscopy and $Pb(OAc)_4$ cleavage to the diketone (**8**) [IR($CHCl_3$) 1730 and 1715 cm^{-1}; *m/z* 236 (M^+)].





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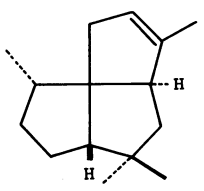
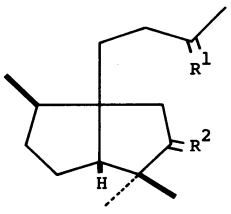
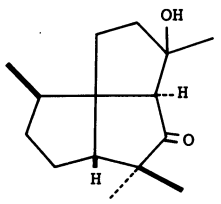
1 $R^1=R^2=R^3=R^4=R^5=H$
2 $R^1=OH$, $R^2=R^3=R^4=R^5=H$
3 $R^2=OH$, $R^1=R^3=R^4=R^5=H$
5 $R^3=OH$, $R^1=R^2=R^4=R^5=H$
6 $R^4=OH$, $R^1=R^2=R^3=R^5=H$
7 $R^5=OH$, $R^1=R^2=R^3=R^4=H$



"senoxydene"



8 $R^1=R^2=O$
13 $R^1=R^2=H$



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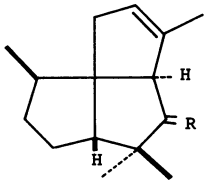
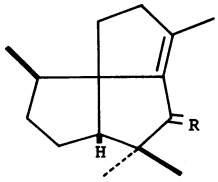


10 R=O
14 $R=H_2$



11 R=O
12 $R=H_2$

An analogous argument based on spectroscopic data led to the assignment of structure **3** [IR($CHCl_3$) 3600 and 3550 cm^{-1}; *m/z* 238 (M^+)] to a further product of cedrol oxidation. The ^1H NMR spectrum of the final product, a diol **4** [mp 114 °C; $[\alpha]_D$ +14.1 ° (*c*, 0.28 in $CHCl_3$); IR ($CHCl_3$) 3600 and 3400 cm^{-1}] indicated the presence of four tertiary methyl groups which led directly to structure **4**, cedrane-2β,8β-diol. Dehydration (HCOOH) of **4** gave cedra-2,8-diene,[11] which was obtained by a similar reaction of **5**.[11]

In order to demonstrate the synthetic utility of this method, the diol **2** was transformed into an epimer of the alleged "senoxydene." The glycol **2** was converted to the diketone (**8**) (*vide supra*) which, on treatment with methanolic sodium methoxide, underwent an intramolecular aldol condensation to afford the hydroxy ketone (**9**) [IR(CCl_4) 3600, 3400, and 1720 cm^{-1}; *m/z* 236 (M^+)] in 63% yield. Subsequent dehydration [$SOCl_2$/Py/0 °C] gave an equimolar mixture of enones **10** and **11**, separation of which was effected by column chromatography over silica-gel (EtOAc–hexane gradient as eluent). Upon Huang-Minlon reduction (KOH/NH_2NH_2/diethylene glycol) of **10**, a mixture of olefin **12** and bicyclic hydrocarbon **13** (presumably arising *via* a retro-aldol reaction) was obtained. However, when the preformed hydrazone (NH_2NH_2/diethylene glycol/180 °C/3 h) was subjected to base treatment (KOH/240 °C/9 h/Ar atmosphere) the desired olefin (**14**) ($[\alpha]_D$ −42.5° (*c*, 0.17 in $CHCl_3$)) was isolated in 27% yield after purification. The spectral data were in accord with those reported by Tsunoda *et al.*[13]

In conclusion, cedrol was hydroxylated by *m*CPBA to give cedrane-7β,8β-diol and the transformation of this diol into the optically active triquinane type hydrocarbon, which is the C-2 epimer of "senoxydene," was achieved in four steps.

Experimental

General Procedures. Melting points were determined on a Yanaco Micro Melting Point apparatus (Yanagimoto) and are uncorrected. IR spectra were taken on a Shimadzu IR-27G infrared spectrophotometer. ^1H and ^{13}C NMR spectra were determined on a JEOL JNM GX 400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer in $CDCl_3$ with TMS as internal standard. Low and high resolution mass spectra were obtained on a Shimadzu LKB-9000B and JEOL HX-100 spectrometer, respectively. Precoated silica gel 60 F_{254} (E. Merck) glass supported plates were used for the purposes of analytical (0.25 mm) and preparative (0.5 mm) thin-layer chromatography.

Oxidation of Cedrol (1) by mCPBA. *m*CPBA (2.7 g, 1.2 equiv) was added to a solution of cedrol (**1**, 2.2 g) in chloroform (75 ml) and the mixture was refluxed for 6 h. The cooled solution was washed succesively with 5% Na_2SO_3, 5% $NaHCO_3$, and brine, dried over $MgSO_4$ and the solvent removed to give a residue (2.5 g). Column chromatography over silica gel (155 g, EtOAc–PhH gradient as eluant) gave cedrane-7β,8β-diol (**2**, 36 mg), a mixture of cedrane-3α,8β-diol (**6**), cedrane-3β,8β-diol (**7**), and cedrane-5β,8β-diol (**3**), cedrane-2β,8β-diol (**4**, 49 mg), and cedrane-2α,8β-diol (**5**, 193 mg) as well as unchanged cedrol (**1**, 1.8 g). The mixture of **6**, **7**, and **3** was separated by HPLC (TSK gel; MeOH–H_2O 7:3, 1.2 ml/min) to give **6** (2.5 mg), **7** (1.5 mg), and **3** (33 mg). **2**: mp 95—97 °C (sublime); Found: *m/z* 238.1938. Calcd for $C_{15}H_{26}O_2$: M 238.1933; $[\alpha]_D$=+14.1 ° ($CHCl_3$); IR ($CHCl_3$) 3570—3450 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.35 (3H, s), 1.21 (3H, s), 0.97 (3H, s), and 0.87 (3H, d, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=85.3 (s), 77.9 (s), 57.3 (d), 49.3 (s), 45.6 (s), 45.5 (t), 42.3 (d), 36.4 (t), 34.8 (t), 31.3 (t), 26.5 (t), 26.1 (q), 25.4 (q), 24.7 (q), and 15.2 (q); MS *m/z* 238 (M^+), 220, 193 (base), 165, 121, 109, and 43. **3**: oil; Found: *m/z* 238.1945. Calcd for $C_{15}H_{26}O_2$: M 238.1933; $[\alpha]_D$=+10.6 ° ($CHCl_3$); IR ($CHCl_3$) 3600—3550 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28 (6H, s), 1.10 (3H, s), 0.92 (3H, d, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) 91.9 (s), 75.0 (s), 60.4 (d), 56.0 (s), 46.1 (s), 41.2 (t), 41.0 (d), 36.8 (t), 36.3 (t), 35.1 (t), 31.5 (q), 30.5 (q), 27.1 (t), 23.0 (q), and 16.6 (q); MS *m/z* 238 (M^+), 220, 205, 178 (base), 121, and 43. **4**: mp 114 °C; Found *m/z* 223.1722 ($M-CH_3$)$^+$. Calcd for $C_{14}H_{23}O_2$. M 223.1698; $[\alpha]_D$=+14.1 ° ($CHCl_3$); IR ($CHCl_3$) 3600—3400 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.31 (3H, s), 1.28 (3H, s), 1.17 (3H, s), and 1.01 (3H, s); ^{13}C NMR ($CDCl_3$) δ=80.9 (s), 75.0 (s), 59.4 (s), 59.1 (d), 53.3 (d), 45.0 (s), 40.3 (t), 39.1 (t), 35.7 (t), 30.5 (q), 30.3 (q), 29.3 (t), 28.6 (q), 23.0 (q), and 22.4 (t); MS *m/z* 223 ($M-CH_3$)$^+$, 220, 205, 151 (base), 93, 43.

Oxidation of Cedrane-7β,8β-diol (2). The diol (**2**, 10 mg) was treated with $Pb(OAc)_4$ (18 mg) in benzene (5 ml) at rt for 2 h and worked up as usual to give 4,4,8-trimethyl-1-(3-oxobutyl)bicyclo[3.3.0]octan-3-one (**8**, 9.3 mg) as an oil. Found: *m/z* 236.1799. Calcd for $C_{15}H_{24}O_2$: M 236.1776; IR ($CHCl_3$) 1730 and 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ=2.18 (3H, s), 1.09 (3H, s), 0.99 (3H, s), and 0.95 (3H, d, *J*=7 Hz); ^{13}C NMR ($CDCl_3$) δ=223.1 (s), 208.4 (s), 55.4 (d), 48.4 (s), 48.3 (s), 45.9 (t), 44.9 (d), 39.7 (t), 32.8 (t), 30.2 (q), 28.6 (q), 27.6 (t), 25.1 (t), 22.0 (q), and 14.0 (q); MS *m/z* 236 (M^+), 221, 193, 165, 81, and 43.

Intramolecular Aldol Condensation of the Diketone (8). The diketone (**8**, 25 mg) was treated with NaOMe in MeOH [prepared from Na (*ca.* 0.1 g) and MeOH (4.5 ml)] at rt for 3 h. The usual work up and chromatography over silica gel (elution with hexane–EtOAc) afforded 4-hydroxy-4,7,7,11β-tetramethyl-(5α,8β)-tricyclo[6.3.0.0^{1,5}]undecan-6-one (**9**, 16 mg) as an oil. Found: *m/z* 236.1751. Calcd for $C_{15}H_{24}O_2$: M 236.1776; IR ($CHCl_3$) 3600, 3400, and 1720 cm^{-1}; ^1H NMR δ=2.34 (1H, s), 2.22 (1H, dd, *J*=9.5 and 5.5 Hz), 1.45 (3H, s), 1.06 (3H, s), 0.98 (3H, d, *J*=6.5 Hz), and 0.95 (3H, s). ^{13}C NMR δ=226.0 (s), 80.2 (s), 66.2 (d), 59.3 (d), 58.8 (s), 50.8 (s), 43.6 (d), 42.1 (t), 34.3 (t), 32.9 (t), 29.1 (q), 26.0 (q), 23.8 (t), 23.1 (q), and 13.8 (q); MS *m/z* 236 (M^+), 221, 193 (base), 178, 165, and 43.

Dehydration of the Ketol (9). The ketol (**9**, 2.3 mg) was treated with $SOCl_2$ (3 drops) in pyridine (0.6 ml) at 0 °C for 30 min. The usual work up and prep. TLC gave 4,7,7,11β-tetramethyl-(5α,8β)-tricyclo[6.3.0.0^{1,5}]undec-3-en-6-one (**10**, 0.5 mg) [oil; Found: *m/z* 218.1655. Calcd for $C_{15}H_{22}O$:M 218.1671; IR ($CHCl_3$) 1720 cm^{-1}; ^1H NMR δ= 5.33 (1H, brs), 2.84 (1H, brs), 2.71 and 2.12 (each 1H, d, *J*=19.5 Hz), 2.22 (1H, dd, *J*=9 and 6 Hz), 1.75 (3H, s), 1.06 (3H, s), 0.98 (3H, s) and 0.97 (3H, d, *J*=7 Hz); MS *m/z* 218 (M^+), 190, 175, 147 (base), 120, 108, 91, and 55] and

4,7,7,11β-tetramethyl-(8β)-tricyclo[6.3.0.0^{1,5}]undec-4-en-6-one (**11**, 0.6 mg) [oil; IR ($CHCl_3$) 1725 cm^{-1}; ^{1}H NMR δ= 2.05 (3H, brs), 1.04 (6H, s), and 0.94 (3H, d, J=6.6 Hz); MS m/z 218 (M^+), 203, 193 (base), 175, 121, and 43].

Reduction of the Enone (10). The enone (**10**, 18 mg) was heated with hydrazine (0.3 ml) in diethylene glycol (2 ml) at 180 °C for 3h under Ar. After removal of water and excess of hydrazine, the mixture was heated with KOH (50 mg) at 220—240 °C for 9h. The usual work up and chromatography over silica gel afforded 4,7,7,11β-tetramethyl-(5α,8β)-tricyclo[6.3.0.0^{1,5}]undec-3-ene (**14**, 4.7 mg) as an oil. Found: m/z 204.1878. Calcd for $C_{15}H_{24}$: M 204.1878; $[\alpha]_D$=−42.5° ($CHCl_3$, c=0.17); IR ($CHCl_3$) 1460, 1380, 1365 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=5.09 (1H, brs), 2.59 (1H, brd, J=16.8 Hz), 2.45 (1H, m), 2.02 (1H, brd, J=16.8 Hz), 1.89 (1H, t, J=8.1 Hz), 1.72 (1H, dd, J=13 and 8.5 Hz), 1.65 (3H, brs), 1.43 (1H, dd, J=13 and 4.6 Hz), 0.96 (3H, s), 0.92 (3H, s), and 0.90 (3H, d, J=6.5 Hz); MS m/z 204 (M^+), 189, 161, 147, 133, 123 (base), 105, and 91.

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16) We found that the previous assignments[12,15] of these compounds are contrary to each other. Therefore, we have carried out difference NOE experiments for these compounds. When the 3β-proton of **6** was irradiated, an NOE upon the 2β-methyl group was observed. However, no NOE appeared in the case of the 2β-methyl group of **7**, when the 3α-proton was saturated. From these results, **6** was determined to be cedrane-3α,8β-diol and **7** to be cedrane-3β,8β-diol, which is in agreement with Ourisson's results.[15]