# STEREOCHEMICAL STUDIES

# VIII. SYNTHESIS OF cis-1-OXA-10-METHYLDECAL-2-ONE

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#### ABSTRACT

9-Methylhydrindan-1-one was obtained as a mixture (80% trans, 20% cis) in four steps from 10-methyl- $\Delta^{1,9}$ -octal-2-one. In the presence of alkali it epimerized to cis-9-methylhydrindan-1-one containing less than 1% of the trans isomer. Oxidation of this cis ketone with peroxytrifluoroacetic acid gave cis-1-oxa-10-methyldecal-2-one.

House and Schellenbaum (1) reduced 3-(1'-methyl-2'-oxocyclohexyl)propionic acid (I) with sodium borohydride and obtained, after acidification of the product, a neutral material. From the nuclear magnetic resonance (n.m.r.) spectrum of this material they concluded that it was made up of *trans*- (II) and *cis*-1-oxa-10-methyldecal-2-one (III) in the ratio 35:65. A broad multiplet (one proton) centered at about 4.0  $\tau$  was attributed to



the C-9 hydrogens of II and III. Sharp, unsplit peaks at 9.05  $\tau$  and 8.95  $\tau$  (total area three protons; relative areas 35:65) were attributed to the angular methyl groups of the *trans* (II) and *cis* (III) isomers, respectively, by analogy with the positions of the peaks of angular methyl groups in the spectra of *trans* and *cis* decalols (2). The isomers could not be separated completely by vapor phase chromatography.

We have repeated this work and confirmed most of House and Schellenbaum's observations. The n.m.r. spectrum of our product had peaks at 8.94  $\tau$  and 9.03  $\tau$ ; however, the peak at lowest field was a triplet at 5.93  $\tau$  (4.07  $\delta$ ), and not at 4.0  $\tau$ . A peak at 5–6  $\tau$  for the C-9 hydrogens of II and III is to be expected from previous studies of  $\delta$ -lactones (3).

Hydrogenation of the keto acid I over Adams' catalyst in acetic acid gave a lactone mixture, indicated by its n.m.r. spectrum to be made up of II and III in the proportions 2:1. This ratio was not affected by addition of hydrochloric acid to the acetic acid solvent (cf. ref. 3).

For stereochemical studies the pure isomers II and III were required, and consequently a stereospecific synthesis of  $(\pm)$ -III was carried out by the route outlined in Reaction Scheme 1. The stereochemistry of the various intermediates (all  $(\pm)$  mixtures) is not shown in this scheme, but is discussed below, separately for each compound.

## 1,9-Dihydroxy-10-methyldecal-2-one (V)

Osmium tetroxide hydroxylates a double bond cis (4), and consequently oxidation of the unsaturated ketone IV would be expected to yield a mixture of the diastereoisomeric diols Va and Vb. This expectation was realized. Although the solid product of the reaction had a sharp melting point after one recrystallization, its n.m.r. spectrum showed it to be a

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REACTION SCHEME 1.

mixture of Va and Vb in the proportions 70:30. Two peaks at lowest field, at  $5.55 \tau$  and  $5.96 \tau$ , had a total area equivalent to one proton, and could be assigned to the protons at the 1 position of Va and Vb. The two peaks at highest field, at  $8.92 \tau$  and  $8.74 \tau$ , with a total area equivalent to three protons, could be assigned to the angular methyl groups. In both cases the relative areas of the peaks were 70:30. The assignment of these peaks to the individual isomers Va and Vb as shown in the formulae comes from a comparison with the n.m.r. spectra of the known compounds,  $4\alpha, 5\alpha$ -dihydroxycholestan-3-one (XI) and



 $4\beta,5\beta$ -dihydroxycholestan-3-one (XII) (5, 6). The various peaks of these spectra may be assigned on the basis of the known n.m.r. spectra of steroids (7), and the chemical shifts of the relevant peaks are shown in the formulae XI and XII. It is apparent that the *cis* decalone is either in the non-steroid conformation of Vb (cf. refs. 2 and 8), or in a conformation in which one of the rings has become a twist-boat (9).

These results indicate the trans isomer Va to be the chief product from the oxidation of

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Can. J. Chem. Downloaded from www.nrcresearchpress.com by UNIV GUELPH on 11/13/14 For personal use only. Can. J. Chem. Downloaded from www.nrcresearchpress.com by UNIV GUELPH on 11/13/14 For personal use only. IV by osmium tetroxide, probably because the  $\beta$ -methyl group shields the  $\beta$  face of the molecule. Similarly, the oxidation of testosterone under the same conditions has been found to yield 70% of the  $4\alpha,5\alpha$ -diol (10). However, when a mixture of osmium tetroxide and hydrogen peroxide was used to oxidize IV, the proportion of Va in the product decreased to 40%, again paralleling the behavior of steroidal compounds (6).

# 1,9-Epoxy-10-methyldecal-2-one (VI)

Oxidation of the unsaturated ketone IV with alkaline hydrogen peroxide according to published procedures (11, 12) gave a liquid product, indicated by its n.m.r. spectrum to contain two compounds. Two sharp peaks at highest field (8.89  $\tau$  and 8.81  $\tau$ ; relative areas 1:2), having a total area equivalent to three protons, may be assigned with reasonable certainty (cf. ref. 8) to the angular methyl groups of the *trans* (VIa) and *cis* (VIb) isomers, respectively. The peaks at lowest field (7.15  $\tau$  and 7.22  $\tau$ ; relative areas 1:2), corresponding to one proton, are then assigned to the protons on the 1 position, as shown below. This



ratio of 2:1 for the *cis* and *trans* isomers in the product agrees with the ratio of 70:30 obtained by Shaw and Stevenson (12) from the oxidation of cholest-4-ene-3-one.

Treatment of the epoxide mixture with sulfuric acid in acetic acid (cf. ref. 13) or of the diolones (V) with lithium methoxide in methanol (cf. ref. 6) yielded the diosphenol (VII), which gave a characteristic blue color with ferric chloride.

## 1-Hydroxy-9-methylhydrindan-1-carboxylic Acid (VIII)

Diosphenols undergo a benzilic acid type rearrangement in alkali (14, 15), presumably because of a small amount of diketone in equilibrium with diosphenol. In the present instance, the diketone can have either a *trans* (XIII*a*) or *cis* (XIII*b*) fusion of the rings (Reaction Scheme 2). It seems to be likely (cf. ref. 16) that both diones have about the



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same stability, and so are present in roughly equal amounts, but that the *trans* compound XIII*a* reacts more rapidly with hydroxide ion, because of the better solvation possible for the highly charged intermediate (17) leading from XIII*a* to VIII*a*. In fact, it proved to be impossible to determine the proportions of *trans* (VIII*a*) and *cis* (VIII*b*) products from the n.m.r. spectrum of the hydroxy acid, which showed only a single peak for the carboxyl (2.30  $\tau$ ) and methyl (8.96  $\tau$ ) protons; however, the products from the next stage of the synthesis showed the ratio of *trans* (VIII*a*) to *cis* (VIII*b*) to be about 80:20.

## 9-Methylhydrindan-1-one (X)

Lead tetraacetate oxidation of the hydroxy acid VIII gave 9-methylhydrindan-1-one (X). The n.m.r. spectrum of this compound showed two peaks at 8.81  $\tau$  and 9.21  $\tau$ , with a total area equivalent to three protons and with relative areas of 20:80. As shown below, these are due to the angular methyl groups of the *cis* and *trans* forms of X.

Because it was feared that some epimerization could have taken place under the acidic conditions of lead tetraacetate oxidation, the preparation of 9-methylhydrindan-1-one was carried out by an alternative route which avoided acidic conditions. The mixture of hydroxy acids (VIII) was reduced with lithium aluminium hydride to a mixture of diols (IX), which was then oxidized with sodium metaperiodate in neutral solution (14). Again, the ratio of *trans* to *cis* was shown by n.m.r. to be 80:20.

Treatment of this *cis-trans* mixture with sodium hydroxide in methanol gave a product showing a peak at 8.81  $\tau$  (three protons) and no peak at 9.21  $\tau$ . Evidently, under these conditions conversion of the *trans* into the *cis* compound was almost complete, because the n.m.r. spectrum would have revealed the *trans* compound if it had been present to the extent of more than about 1%. This isomerization took place very readily: after 2 days in a Pyrex container, the proportion of *cis* isomer had risen to 70%, and after 2 months to 90%.

These results are in accord with expectation. Although the proportion of *cis*- to *trans*-hydrindan-1-one at equilibrium is 75:25 (18), the addition of an angular methyl group would be expected to increase this ratio considerably (16, 19).

# cis-1-Oxa-10-methyldecal-2-one (III)

The Baeyer-Villiger oxidation of *cis*-9-methylhydrindan-1-one (X) gave *cis*-1-oxa-10methyldecal-2-one (III). This reaction proceeds with retention of configuration of the migrating groups (20) and almost always, as in the present case, involves migration of the more alkylated of the two carbons flanking the carbonyl group (21). The n.m.r. spectrum of the lactone III showed a sharp methyl peak (three protons) at 8.93  $\tau$  and a triplet ( $J \sim 3.5$  c.p.s.) at 5.93  $\tau$  (one proton) caused by the proton at the 9 position. This confirms House's assignment of the methyl peak at lower field to III (1).

## EXPERIMENTAL

## Hydrogenation of 3-(1'-Methyl-2'-oxocyclohexyl)propionic Acid (I)

3-(1'-Methyl-2'-oxocyclohexyl)propionic acid (I) (2.014 g) in glacial acetic acid (2 ml) was hydrogenated over platinum oxide (0.794 g) at room temperature and atmospheric pressure. After  $1\frac{1}{2}$  h, uptake of hydrogen ceased. The solution was diluted with ether, filtered, and washed with 2% sodium hydroxide solution and with water. Distillation gave 1-oxa-10-methyldecal-2-one, b.p. 95–96° at 0.3 mm,  $n_{D^{24}}$  1.4909 (lit. (1) b.p. 102–104° at 0.8 mm,  $n_{D^{24}}$  1.4916).

Anal. Calcd. for C<sub>10</sub>H<sub>16</sub>O<sub>2</sub>: C, 71.39; H, 9.59. Found: C, 71.26; H, 9.56.

#### 1,9-Dihydroxy-10-methyldecal-2-one (V)

(a) With Osmium Tetroxide

A solution of 10-methyl- $\Delta^{1,9}$ -octal-2-one (IV) (1.1 g) in pyridine (150 ml) was stirred at room temperature for  $2\frac{1}{2}$  h with osmium tetroxide (1.79 g). The black mixture was then stirred for 10 min with a solution of sodium bisulfite (2.8 g) in water (40 ml) and pyridine (30 ml). This mixture was extracted with ether, and

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the ether solution dried ( $K_2CO_3$ ). Removal of the ether at reduced pressure left a black oil which was filtered through silica gel (20 g). Washing the silica gel with chloroform and concentration of the chloroform gave a brown solid (1.05 g), m.p. 85-89°, which, after several recrystallizations from hexane, was obtained as colorless needles, m.p. 90-92°;  $\nu_{max}^{CO14}$  3 580, 3 460, and 1 738 cm<sup>-1</sup>.

Anal. Calcd. for C11H18O2: C, 66.64; H, 9.15. Found: C, 66.52; H, 8.99.

# (b) With Osmium Tetroxide - Hydrogen Peroxide

Osmium tetroxide (2 g) was added to a solution of 10-methyl- $\Delta^{1,9}$ -octal-2-one (15 g) in ether (200 ml), and the mixture allowed to stand in the dark for 5 h. Hydrogen peroxide (30%, 30 ml) was then added slowly and the mixture was stirred at room temperature for 4 days. Portions of hydrogen peroxide (10 ml) were added when the solution darkened. The excess of hydrogen peroxide was removed, and the ether solution was washed with water and then treated with a slow stream of hydrogen sulfide for 30 min. The solution was filtered, washed with 2% sodium bicarbonate and with water, and dried. The oily residue obtained on evaporation was chromatographed on silica gel. Benzene-ether (75:25 v/v) eluted an oily, crystalline material (8.2 g) which crystallized from hexane as a colorless solid, m.p. 90–92°. The compound was identical (mixed melting point and infrared spectrum) with the material prepared above, but its n.m.r. spectrum showed different proportions of the isomers Va and Vb.

## 1,9-Epoxy-10-methyldecal-2-one (VI)

10-Methyl-Δ<sup>1,9</sup>-octal-2-one (29.7 g) in methanol (500 ml) was treated at 0° with ice-cold 30% hydrogen peroxide (308 ml) and then with ice-cold 10% sodium hydroxide solution (103 ml). The solution was kept at 0° for 48 h, and then diluted with water and extracted with ether. The ether solution was washed with water, dried, and evaporated, and the residue distilled to give 1,9-epoxy-10-methyldecal-2-one as an oil (22.5 g), b.p. 96–98° at 0.75 mm,  $n_D^{20}$  1.4992;  $\nu_{\max}^{CCl_4}$  1 720, 922, and 858 cm<sup>-1</sup>.

Anal. Calcd. for C11H16O2: C, 73.30; H, 8.95. Found: C, 73.27; H, 8.71.

# 1-Hydroxy-10-methyl- $\Delta^{1,9}$ -octal-2-one (VII)

## (a) From 1,9-Dihydroxy-10-methyldecal-2-one (V)

A solution of 4 M lithium methoxide in methanol (85 ml) was added to 1,9-dihydroxy-10-methyldecal-2-one (3.38 g) in methanol (200 ml), and the mixture was boiled under reflux for 2 h. The cooled solution was acidified to pH 3 with concentrated hydrochloric acid, diluted with a large excess of water, and extracted with ether. The ether was evaporated and the residue distilled to give an oil (2.3 g), b.p. 86–90° at 1.5 mm, which slowly crystallized. After recrystallization from hexane the diosphenol was obtained as a colorless solid, m.p. 84–85°,  $\lambda_{\text{max}}^{\text{EOH}}$  276 m $\mu$  ( $\epsilon_{\text{max}}$  20 000);  $\nu_{\text{max}}^{\text{ECH}}$  3 485, 1 720, 1 685, and 1 665 cm<sup>-1</sup>. Anal. Calcd. for C<sub>11</sub>H<sub>16</sub>O<sub>2</sub>: C, 73.30; H, 8.95. Found: C, 73.38; H, 8.97.

### (b) From 1,9-Epoxy-10-methyldecal-2-one (VI)

The epoxide (20 g) in glacial acetic acid (375 ml) containing concentrated sulfuric acid (37.5 ml) was left at room temperature for 24 h. The black solution was diluted with ice water (3 l) and neutralized with sodium bicarbonate. A solid separated and was distilled to give an oil, b.p. 90-100° at 2.8 mm, which slowly crystallized. After recrystallization from hexane the solid melted at 84-85°, and was shown by mixed melting point and ultraviolet and infrared spectra to be identical with the compound described in the preceding section.

## 1-Hydroxy-9-methylhydrindan-1-carboxylic Acid (VIII)

A solution of 1-hydroxy-10-methyl- $\Delta^{1,9}$ -octal-2-one (3.9 g) in methanol (50 ml) and 5% aqueous sodium hydroxide (500 ml) was kept at 100° for 16 h under nitrogen. The cooled solution was acidified to pH 3 and extracted with ether, and the ether in turn extracted with 5% aqueous sodium bicarbonate. The latter solution was acidified and extracted with ether. Evaporation of the ether gave an oil which slowly crystallized. Recrystallization from hexane gave plates of the hydroxy acid (VIII) (2.11 g), m.p. 108–111°. Two more crystallizations from hexane raised the melting point to 112–113°;  $\nu_{max}^{\rm CC14}$  3 575, 1 724, 1 448, and 1 272 cm<sup>-1</sup>. Anal. Calcd. for C<sub>11</sub>H<sub>18</sub>O<sub>3</sub>: C, 66.69; H, 9.15. Found: C, 66.67; H, 8.91.

### 1-Hydroxymethyl-9-methylhydrindan-1-ol (IX)

Under dry nitrogen, a solution of 1-hydroxy-9-methylhydrindan-1-carboxylic acid (1.2 g) in ether (25 ml) was added, with stirring, over 15 min to a suspension of lithium aluminium hydride (1.5 g) in ether (100 ml). The mixture was refluxed for 2 h, and then water (5 ml) and 10% aqueous sodium hydroxide (4 ml) were added dropwise, with continued stirring. The inorganic precipitate was removed by filtration and washed with ether. The filtrate and washings, on concentration, gave the diol as an oil (1.1 g) which could not be crystallized.

### 9-Methylhydrindan-1-one (X)

### (a) From 1-Hydroxy-9-methylhydrindan-1-carboxylic Acid (VIII)

A solution of the hydroxy acid (6.1 g) and lead tetraacetate (40 g) in methanol (200 ml) was left at room temperature overnight. The solution was concentrated, diluted with water, and extracted with ether. The ether solution was washed with 5% sodium bicarbonate and water, dried, and concentrated. Distillation of the residue (3.6 g) gave an oil (2.6 g), b.p. 60–68° at 1.3 mm,  $n_D^{20}$  1.4804,  $\nu_{max}^{CC1_4}$  1 760 cm<sup>-1</sup>. The n.m.r. spectrum showed this material to be a mixture of the cis and trans isomers.

Anal. Calcd. for C10H16O: C, 78.89; H, 10.59. Found: C, 78.62; H, 11.06.

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#### (b) From 1-Hydroxymethyl-9-methylhydrindan-1-ol (IX)

The diol (1.0 g) in methanol (50 ml) was treated with sodium metaperiodate (2 g) in water (40 ml), followed by sufficient 5% aqueous sodium bicarbonate to adjust the pH of the mixture to about 6. The suspension was stirred overnight at room temperature. The methanol was removed at reduced pressure, and the residual mixture extracted with ether. The residue, after removal of the ether, was distilled to give an oil, b.p.  $62-68^{\circ}$  at 1.4 mm,  $n_{D}^{21}$  1.4800, having an infrared spectrum identical with that of the ketone mentioned above.

### cis-9-Methylhydrindan-1-one

The mixture of trans- and cis-9-methylhydrindan-1-one obtained above (3.0 g) was dissolved in 2.7% methanolic sodium hydroxide (220 ml) and left overnight. The solution was then acidified, diluted with water, concentrated at reduced pressure, and extracted with other. Distillation of the residue from the ether gave cis-9-methylhydrindan-1-one as an oil (2.7 g), b.p. 70° at 1.25 mm,  $n_D^{20}$  1.4812,  $\nu_{max}^{CC14}$  1 760 cm<sup>-1</sup>.

Anal. Calcd. for C10H16O: C, 78.89; H, 10.59. Found: C, 78.81; H, 10.59.

#### cis-1-Oxa-10-methyldecal-2-one (III)

A solution of trifluoroperoxyacetic acid, prepared from trifluoroacetic anhydride (13 ml) and 90% hydrogen peroxide (2.6 ml) in methylene chloride (100 ml) (22), was added over a period of 1 h to a stirred solution of cis-9-methylhydrindan-1-one (2.6 g) in methylene chloride (160 ml) containing a suspension of disodiohydrogen phosphate (9 g). Stirring was continued for 2 h at room temperature. After dilution with ether and filtration, the solution was washed with 5% aqueous sodium bicarbonate and water, and dried. Slow distillation of the residue from evaporation of the ether gave starting material (0.23 g), b.p. 78-80° at 2.5 mm, followed by the lactone (III) (1.36 g), b.p. 130–134° at 2.5 mm,  $n_D^{20}$  1.4892,  $\nu_{max}^{CC14}$  1 737 and 1 210 cm<sup>-1</sup>. Anal. Calcd. for C10H16O2: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.46.

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