

Reaction of Benzylidenecyclohexanone with Borane

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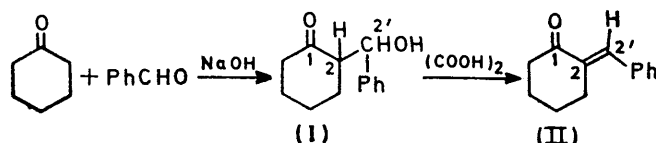
The reaction of 2-benzylidenecyclohexanone (II) with borane has been investigated. Three asymmetric centres were generated in a stereospecific manner in fair yield. The mechanism and stereochemistry of the reaction are discussed. The reduction of 2-hydroxy(phenyl)methylcyclohexanone (I) with borane has been also studied. The relative configurations of (I) and those of its reduction products have been determined.

WE have shown previously that the hydroboration of cyclohex-2-enones is a stereospecific process yielding diequatorial cyclohexane-1,2-diols.¹ Two asymmetric centres have been generated in a stereospecific way in relative high yield (40–70%). We were interested to see if this process could be applied to generate three asymmetric centres in a stereospecific manner by choosing an adequate system.

In order to test this possibility we decided to investigate the hydroboration of 2-benzylidenecyclohexanone (II). We assumed that the hydroboration of (II) would yield mainly 1,3-diols thus generating three asymmetric centres in one step, possibly in a stereospecific manner.

¹ (a) J. Klein and E. Dunkelblum, *Tetrahedron*, 1968, **24**, 5701; (b) E. Dunkelblum, R. Levene and J. Klein, *ibid.*, 1972, **28**, 1009.

Condensation of benzaldehyde with cyclohexanone gave 2-hydroxy(phenyl)methylcyclohexanone² (I) with unknown configuration, which was converted into (II) by

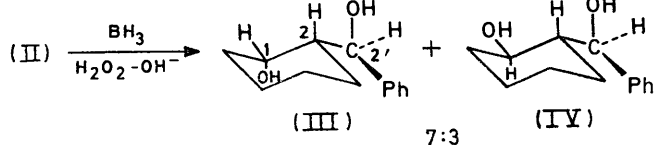


dehydration.² The geometry of the double bond in (II) is known to be *trans*.³ Hydroboration of (II) gave a mixture of diols in 72% yield. The n.m.r. spectrum of this mixture showed that it consisted mainly (80–90%) of the two 1,3-diols (III) and (IV) in the approximate

² J. D. Billimoria, *J. Chem. Soc.*, 1955, 1126.

³ J. H. Brewster and J. E. Privett, *J. Amer. Chem. Soc.*, 1966, **88**, 1419.

ratio 7:3. The remaining 10–20% of the product probably contained monoalcohols and 1,2-diols derived from boron attack on C-2; they were not analysed.



Both (III) and (IV) have the bulky hydroxy(phenyl)-methyl group in the equatorial position, thus simplifying the n.m.r. spectra and the structure determination. The relative configuration of C-2 and -2' in (III) and (IV) is the same, *threo*.^{*} This relation was derived from the *cis*-addition of borane to the *trans*-double bond of (II). The relative configuration of C-1 in (III) and (IV) is evident from the n.m.r. spectrum of the mixture. The proton at C-1 in the *cis*-isomer (III) is equatorial with δ 4.10 ($W_{\frac{1}{2}}$ 7 Hz). The proton at C-1 in the *trans*-isomer (IV) is axial with δ 3.45 ($W_{\frac{1}{2}}$ 16 Hz). The integrated area of this proton in (III) and (IV) was used to establish the ratio of the two isomers. The major isomer (III) was separated by fractional crystallization in 50% yield. The n.m.r. spectrum (100 MHz) of (III) confirmed the structure of both isomers. The signals for the equatorial proton at C-1 and the benzylic proton at C-3 [δ 4.71 (d, J 5 Hz)] are characteristic. Thus the relative configuration of C-1, -2, and -2' in (III) and (IV) is established and the structure of (III) is *cis-threo*-2-hydroxy(phenyl)methylcyclohexanol and that of (IV) is the *trans*-isomer. Attempts to isolate pure (IV) failed.

In order to establish the sequence of the two steps in the hydroboration, the reaction was run with excess of compound (II). One of the isolated products, was *trans*-2-benzylidenecyclohexanol (V) (by t.l.c.). It was identified by comparison with an authentic sample, obtained by LiAlH_4 reduction of (II)⁴ thus proving that the first step in the hydroboration of (II) is the reduction of the keto-group to yield the allylic borate (VI). This sequence is identical with that found for the hydroboration of cyclohex-2-enones¹ and is probably correct for the hydroboration of all $\alpha\beta$ -unsaturated ketones.

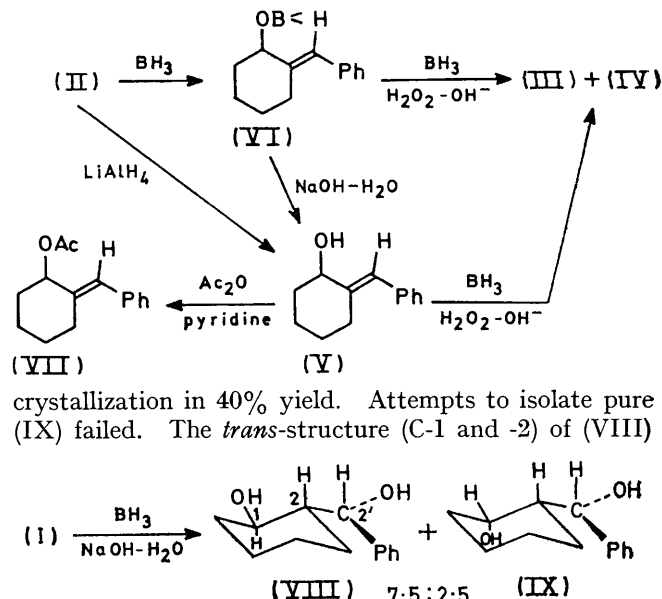
Hydroboration of (V) gave, as expected, (III) and (IV) in similar yield (74%) and ratio (7:3) to the direct hydroboration of (II).

trans-2-Benzylidenecyclohexyl acetate (VII) gave (III) and (IV) in the ratio 6.5:3.5 in 90% yield. The acetoxy-group has a similar directive effect on the addition of borane to the double bond of (VII) as the borate group in (VI).

In order to obtain a *trans*-isomer, we reduced (I) with

* The *erythro-threo* nomenclature is used for the steric relation between C-2 and -2' in order to simplify the notation of the relative configurations of C-1, -2, and -2'. As C-2 and -2' have only one common substituent, namely hydrogen, the OH group on C-2' was regarded as similar to the CHOH group [or C=O in (I)] on C-2. This notation is used in the text for (I) and for all 1,3-diols.

borane. The reaction was very clean and gave a mixture of the two 1,3-diols (VIII) and (IX) in 85% yield in the ratio 7.5:2.5, determined by n.m.r. spectroscopy as described earlier [δ 3.48 [$W_{\frac{1}{2}}$ 18 Hz, axial 1-H in (VIII)] and 3.9 [$W_{\frac{1}{2}}$ 6 Hz, equatorial 1-H in (IX)]]. The major isomer (VIII) was separated by fractional



crystallization in 40% yield. Attempts to isolate pure (IX) failed. The *trans*-structure (C-1 and -2) of (VIII)

was unambiguously demonstrated by n.m.r. spectroscopy (100 MHz) which confirmed the ratio and the *cis-trans* relation of (VIII) and (IX) in the mixture. However, the relative configuration of C-2' was not established as the relative configuration of C-2 and -2' in (I) was unknown. In the condensation of cyclohexanone with benzaldehyde two isomeric aldols are probably formed.⁵ Only one crystalline isomer was isolated² and submitted to borane reduction.

In order to establish the relative configuration of C-2' in (VIII) and (IX), we compared them with (III) and (IV) for which the relative configuration of all the asymmetric centres has been elaborated. The isolated isomers (III) and (VIII) and the two mixtures [(III) + (IV) and (VIII) + (IX)] were converted into the corresponding diacetates (IIIa), (IIIa) + (IVa), (VIIIa), and (VIIIa) + (IXa) which could be analysed by g.l.c. The separation was difficult but it could be shown unambiguously that the diacetate (VIIIa) was different from (IVa) and that the diacetate (IIIa) was different from (IXa). This experiment allowed us to determine the correct structure of (VIII) and (IX). The major isomer is *trans-erythro*-2-hydroxy(phenyl)methylcyclohexanol and (IX) is the *cis*-isomer. Compound (I) is therefore *erythro*-2-hydroxy(phenyl)methylcyclohexanone.

We have shown that the hydroborations of *trans*-2-benzylidenecyclohexanone (II), the corresponding alcohol (V), and the acetate (VII) are both regiospecific and

⁴ P. B. Russel, *J. Chem. Soc.*, 1954, 1771.

⁵ (a) A. T. Nielsen and W. J. Houlihan, *Org. Reactions*, 1968, 16, 11; (b) J. E. Dubois and M. Dubois, *Bull. Soc. chim. France*, 1969, 3120, 3126.

stereospecific. Most of the boron is attached to C-2' because this carbon is less substituted than C-2,⁶ and because of the phenyl group which directs the boron attack α to itself.⁶ The allylic borate group has, to some extent, an opposite effect. The relative high stereospecificity is due to a combination of the absolute *cis*-addition of borane to double bonds⁶ and to the steric and polar effect of the allylic borate group (or acetoxy) which directs the borane attack *trans* to itself. A similar *trans*-directing effect has been shown previously in the case of cyclohex-2-enones, cyclohex-2-enols, and derivatives.¹

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer Infracord 337 spectrometer for CCl_4 solutions. N.m.r. spectra were recorded with Varian T-60 or HA100 spectrometers with tetramethylsilane as internal standard. G.l.c. was performed on a F and M 810 apparatus. The column used was Carbowax 20M 20% on Chromosorb W, 2 m long, at 220° with helium as carrier gas.

2-Hydroxy(phenyl)methylcyclohexanone (I) and trans-Benzylidenecyclohexanone (II).—The condensation of cyclohexanone with benzaldehyde was performed according to a published procedure² and gave 82% of crude (I). Two crystallizations from light petroleum (b.p. 40–60°) gave pure compound (I) in 23% yield, m.p. 100–101°. Crude (I) was dehydrated² and gave compound (II) (56%), m.p. 55–56° (from acetone).

trans-Benzylidenecyclohexanol (V) and Acetate (VII).—Reduction of (II) with LiAlH_4 in ether⁴ gave compound (V) in 55% yield, m.p. 57–58° (from pentane), δ (CDCl_3 - D_2O) 7.0br (5H, s, Ph), 6.3 (1H, s, =CH), 4.05 (1H, m, CHOH), and 2.4–1.2 (8H, 4 \times CH_2). Acetylation of (V) with Ac_2O and pyridine gave (VII) (90%), b.p. 160–165° at 0.5 mmHg (ball oven), δ (CDCl_3) 7.10 (5H, m, Ph), 6.38 (1H, s, =CH), 5.22 (1H, m, CHOAc), 2.42 (2H, m, $\text{CH}_2\text{C}=\text{O}$), 2.06 (3H, s, OAc), and 1.90–1.10 (6H, 3 \times CH_2).

Hydroboration Reactions.⁶—All the hydroborations were carried out in tetrahydrofuran with stock solutions of borane in tetrahydrofuran under nitrogen. The borane was added dropwise to the substrate at 0° and then stirred for 3 h at room temperature. Excess of borane was decomposed carefully with ice and the mixture was oxidized with 10% sodium hydroxide and 30% hydrogen peroxide. Potassium carbonate was added to saturation, the layers separated, the aqueous layer was extracted several times with CH_2Cl_2 , and the combined extracts were dried and concentrated to dryness *in vacuo*.

Hydroboration of trans-benzylidenecyclohexanone (II). Compound (I) (5.5 g, 20 mmol) in tetrahydrofuran (10 ml) with borane (70 ml; 0.5M) gave the crude diol mixture (III) + (IV) (4.3 g, 72%), b.p. 150–162° at 0.5 mmHg, ratio 7:3 (n.m.r.). Slow crystallization from hexane (or carbon tetrachloride-pentane) gave (III) (3 g, 50%), m.p. 84–85°, δ (CDCl_3 - D_2O) 7.30br (5H, s, Ph), 4.71 (1H, d, J 5 Hz, 2'-H), 4.10 (1H, m, 1-H), and 2.0–1.0 (9H, cyclohexyl). This product contained *ca.* 5% of (IV) (n.m.r.), ν_{max} 3630sh and 3350br cm^{-1} OH (Found: C, 75.8; H, 8.4. Calc. for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.8; H, 8.7%).

Hydroboration of (II) with a deficiency of borane. Compound (II) (1.86 g, 10 mmol) in tetrahydrofuran (5 ml) with borane (5 ml; 1.6M) was stirred for 30 min at room temperature and then worked up as usual. Distillation gave

material (1.3 g), b.p. 180–190° at 0.7 mmHg (ball oven). Crystallization from hexane gave (III) (0.4 g, 20%), m.p. 78–80°. From the residue *trans*-benzylidenecyclohexanol (V), m.p. 57–59° (from pentane), was isolated (0.2 g, 10%) by t.l.c. (benzene). This material was identical by n.m.r. and i.r. spectroscopy with authentic (V) (Found: C, 83.1; H, 8.5. Calc. for $\text{C}_{13}\text{H}_{16}\text{O}$: C, 83.0; H, 8.5%).

Hydroboration of trans-benzylidenecyclohexanol (V). Compound (V) (1.13 g, 6 mmol) in tetrahydrofuran (5 ml) with borane (20 ml; 1.5M) gave (III) + (IV) (0.9 g, 74%), b.p. 160–165° at 0.5 mmHg, in the ratio 7:3 (n.m.r.). Crystallization from CCl_4 gave (III) (0.52 g, 42%), m.p. 84–85° (Found: C, 75.6; H, 8.8. Calc. for $\text{C}_{13}\text{H}_{18}\text{O}_2$: C, 75.8; H, 8.7%).

Hydroboration of trans-2-benzylidenecyclohexyl acetate (VII). Compound (VII) (0.8 g, 3.5 mmol) in tetrahydrofuran (2 ml) with borane (5 ml; 1.5M) gave (III) + (IV) (0.7, 90%), b.p. 170–175° at 0.2 mmHg (ball oven), in the ratio 6.5:3.5 (n.m.r.).

Reduction of 2-hydroxy(phenyl)methylcyclohexanone (I). Compound (I) (4.1 g, 20 mmol) in tetrahydrofuran (10 ml) with borane (35 ml; 1.6M) gave after hydrolysis with aqueous sodium hydroxide (VIII) + (IX) (3.5 g, 85%), b.p. 160–170° at 0.2 mmHg (ball-oven), in the ratio 7.5:2.5 (n.m.r.). Crystallization from carbon tetrachloride-pentane gave *trans*-erythro-2-hydroxy(phenyl)methylcyclohexanol (1.6 g, 40%), m.p. 100–101°, δ (CDCl_3 - D_2O) 7.29br (5H, s, Ph), 4.91 (1H, d, J 3 Hz, 2'-H), 3.48 (1H, td, J_1 10, J_2 4 Hz, 1-H), and 2.1–1.0 (9H, cyclohexyl), ν_{max} 3630sh and 3370br cm^{-1} (OH) (Found: C, 75.8; H, 8.6. $\text{C}_{13}\text{H}_{18}\text{O}_2$ requires C, 75.8; H, 8.7%).

Preparation of Diacetates.—The acetylation of the diols was performed with excess of acetic anhydride in pyridine. The mixtures were left overnight at room temperature and then decomposed with ice and hydrochloric acid. The diacetates were extracted with methylene chloride and washed with dilute hydrochloric acid, water, and aqueous sodium hydrogen carbonate. The extracts were dried and concentrated to dryness *in vacuo*. *cis*-threo-2-Acetoxy(phenyl)methylcyclohexyl acetate (IIIa) (85%) had m.p. 102–103° (from pentane), δ (CDCl_3) 7.1br (5H, s, Ph), 5.50 (1H, d, J 10 Hz, 2'-H), 5.39 (1H, m, 1-H), 2.08 (3H, s, OAc), 1.99 (3H, s, OAc), and 1.9–1.0 (9H, cyclohexyl), ν_{max} 1740s cm^{-1} (OAc) (Found: C, 70.2; H, 7.4. $\text{C}_{17}\text{H}_{22}\text{O}_4$ requires C, 70.0; H, 7.6%). *trans*-erythro-2-Acetoxy(phenyl)methylcyclohexyl acetate was obtained in 90% yield, m.p. 88–90° (from pentane), δ (CDCl_3) 7.25 (5H, m, Ph), 6.07 (1H, d, J 3 Hz, 2'-H), 4.75 (1H, td, J_1 10, J_2 4 Hz, 1-H), 2.10 (3H, s, OAc), 2.0 (3H, s, OAc), and 1.9–1.0 (9H, cyclohexyl), ν_{max} 1740s cm^{-1} (OAc) (Found: C, 70.2; H, 7.3%).

The diacetate mixture (IIIa) + (IVa) was obtained in 85% yield, ν_{max} 1740s cm^{-1} (OAc). The diacetate mixture (VIIIa) + (IXa) was obtained in 90% yield, ν_{max} 1740s cm^{-1} (OAc).

G.l.c. analysis. The pure diacetates and diacetate mixtures were injected separately and together. The separation was difficult especially that of (VIIIa) from (IXa). The retention times were long: (IIIa) 44.8; (IVa) 59.2; (VIIIa) 52; and (IXa) 56.8 min.

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⁶ G. Zweifel and H. C. Brown, *Org. Reactions*, 1963, **13**, 31.