Lithium Alkyl(hydro)dipinan-3a-ylborates. New Reagents for Asymmetric Reduction of Ketones ¹

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The preparation and characterisation of a new class of reducing agents, lithium alkyl(hydro)dipinan-3α-ylborates, is described. These reagents have been used to reduce a series of ketones (of the type RCOR') to optically active alcohols with optical yields in the range 5—45%. The stereochemistry of reduction of a series of substituted cyclohexanones is discussed.

THE reaction of dipinan-3a-ylborane (di-isopinocampheylborane) with unhindered *cis*-olefins and oxidation of the resultant borane with alkaline hydrogen peroxide is a well founded method for the preparation of optically active alcohols. The preferred configuration of the newly created chiral carbon atom can be related to a sterically preferred transition state in which the reagent is considered to be either the monomeric borane 2a-c or the dimeric tetrapinan- 3α -ylborane.³ The original suggestions of Brown and his co-workers ² have been modified and extended by Varma and Caspi^{4,5} to explain the mode of asymmetric induction during addition to cisolefins, terminal methylene groups, ketones, and aldehydes; there are conflicting views on the chirality of alcohols derived from ketones. A possible explanation of the discrepancies is that both di- and tri-pinan- 3α -ylboranes are responsible for reduction, the proportion varying with experimental conditions.

We were interested in preparing optically active alcohols of known chirality from ketones, and in view of the difficulties associated with the use of dipinan- 3α -ylborane we sought to convert optically active boranes into optically active hydroborates. Our ultimate aim was to synthesise a tetrahedral hydroborate of the type $R^1R^2R^3BH^-$ with a chiral boron atom. In ketone reductions the chiral boron atom would be in close proximity to the incipient chiral centre. As a first attempt the known susceptibility of trigonal boron atoms to attack by nucleophiles was exploited. Addition of n-butyl-lithium or methyl-lithium to a suspension of dipinan- 3α -ylborane in bis-(2-methoxyethyl) ether gave a clear solution of lithium alkyl(hydro)dipinan- 3α -ylborate. This reagent was used to reduce a series of

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$$R_{2}BH + R'Li \longrightarrow R_{2}BR'H^{-}Li^{+}$$
$$R = pinan-3\alpha-yl$$

unsymmetrical ketones. The resulting alcohols were purified by preparative g.l.c. (in particular from traces of pin-2-ene and pinan- 3α -ol, and their rotations were measured. As a further check on purity each alcohol was converted into a solid derivative whose rotation was again measured. The optical purities of the alcohols so obtained, together with their absolute configurations, are summarised in Table 1.

As in the reactions of dipinan- 3α -ylborane described by Brown and Bigley,^{2d} inversion of the induced configuration occurs in the series on going from methyl isopropyl to methyl t-butyl ketone, and any attempted correlation of the chirality of the reagents with the configuration induced at the new chiral centre must account for the anomalous behaviour of methyl t-butyl ketone.

³ D. R. Brown, S. F. A. Kettle, J. McKenna, and J. M. McKenna, *Chem. Comm.*, 1967, 667.

⁴ K. R. Varma and E. Caspi, Tetrahedron, 1968, 24, 6365.

⁵ K. R. Varma and E. Caspi, J. Org. Chem., 1969, **34**, 2489.

¹ Preliminary communication, D. R. Boyd, M. F. Grundon, and W. R. Jackson, *Tetrahedron Letters*, 1967, 2101.

² (a) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *J. Amer. Chem. Soc.*, 1964, **86**, 397; (b) H. C. Brown and G. Zweifel, *ibid.*, 1961, **83**, 2544; (c) H. C. Brown, N. R. Ayyangar, and G. Zweifel, *ibid.*, 1964, **86**, 1071; (d) H. C. Brown and D. B. Bigley, *ibid.*, 1961, **83**, 3166.

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Characterisation of Lithium Butyl(hydro)dipinan- 3α -ylborate.—When the solution obtained by adding n-butyllithium to a suspension of dipinan- 3α -ylborane in bis-(2-methoxyethyl) ether, was evacuated to dryness, a clear gum was obtained. On trituration with pentane nearly all of the gum dissolved, and only a few crystals were obtained on cooling. The crystals were removed and the pentane was evaporated off to give a gummy material whose mass spectrum showed a very small solution by samples of lithium butyl(hydro)pinan- 3α ylborate isolated as already described. The ratios of diastereoisomeric alcohols produced (Table 2) were determined by g.l.c. For ease of comparison the alkyl group is assumed to hold the equatorial conformation and the results are quoted as the ratio of axial to equatorial alcohols. The percentage of axial alcohol produced is high in comparison with that obtained with other nucleophilic hydrides.⁷ This result is consistent with the

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Reductions of ketones with t	the methyl(hydro)borate for	med from (-)-pin-2-ene *

	Alcohol			Hydrogen phthalate				
Ketone	$\begin{bmatrix} \alpha \end{bmatrix}_{D}^{20}$ (neat)	Lit. [a] _D	Optical purity (%)	Con- figuration	M.p.	$[\alpha]_{D}^{20}$ (in ethanol)	Lit. $[\alpha]_D$ (in ethanol)	Optical purity (%)
Ethvl methvl ketone	$+0.73^{\circ}$	14·0° ⊄	5	S	$45 - 46^{\circ}$	$+2.7^{\circ}$ (c 22.5)	39∙0° a	7
Isopropyl methyl ketone	+0.2	5.3 0	4	S	42 - 43	+1.8 (c 27.0)	41·4 ª	4
Methyl t-butyl ketone (pinacolone)	-0.61	8·1 °	8	R	84—86	-5.5 (c 22.7 in CHCl ₃)	64·0 ·	9
Pinacolone †	+0.71	8.1 °	9	S				
Ethyl isopropyl ketone	-4.4	9.6 d	46	S	72 - 73	-2.3 (c 23.9)	4.0 d	58
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* The (-)-pin-2-ene was 83% optically pure. \dagger By use of lithium butyl(hydro)dipinan- α -ylborate formed from (+)-pin-2-ene (74.5-75.5% optical purity).

^a R. H. Pickard and J. Kenyon, J. Chem. Soc., 1911, 45. ^b P. A. Levene and R. E. Marker, J. Biol. Chem., 1933, 101, 413. ^c P. Newman, P. Lutkin, and K. Mislow, J. Amer. Chem. Soc., 1958, 80, 465; J. Jacobus, Z. Majeiski, K. Mislow, and P. von R. Schleyer, *ibid.*, 1969, 91, 1988. ^d R. H. Pickard and J. Kenyon, J. Chem. Soc., 1912, 633. ^e R. H. Pickard and J. Kenyon, J. Chem. Soc., 1914, 1115.

parent peak at m/e 343 (C₂₄H₄₄B) and fragment ions at m/e 286, 206, and 149 corresponding to the loss of butyl and pinan-3 α -yl residues. The n.m.r. spectrum is also consistent with the structure R₂BBuH⁻Li⁺, but showed peaks due to bis-(2-methoxyethyl) ether as well as those due to the butyl and pinan-3 α -yl groups. A constant ratio of ether to borate (1 : 2.5) was obtained from several preparations, suggesting that the compound existed as a discrete ether complex. The hydride proton could not be detected, because of the expected strong coupling and quadrupole broadening by the adjacent boron atom.

The solid product was formulated as dibutylpinan- 3α -ylborane-bis-(2-methoxyethyl) ether on the basis of mass spectral and n.m.r. evidence, and thus is the product of a side reaction involving displacement of a pinan- 3α -yl residue by the butyl-lithium. Similar displacements of alkyl groups in boranes by carbanionic species, *e.g.* Grignard reagents, have been observed.⁶

TABLE 2

Stereochemistry of alkylcyclohexanone reductions with the butyl(hydro)borate in pentane solution

	Axial	Equatorial
Ketone	alcohol (%)	alcohol (%)
2-Methylcyclohexanone	65	35
3-Methylcyclohexanone	33	67
4-Methylcyclohexanone	31	69
3,3,5-Trimethylcyclohexanone	89	11
2,2,6-Trimethylcyclohexanone	66	34
4-t-Butylcyclohexanone	34	66

Stereochemistry of Cyclohexanone Reductions.—A series of substituted cyclohexanones was reduced in pentane

⁶ W. Gerrard, 'The Organic Chemistry of Boron,' Academic Press, London and New York, 1961, p. 104.

occurrence of attack on the carbonyl group by a bulky nucleophilic hydride species such as butyl(hydro)pinan- 3α -ylborate, where the product isomer ratios are dominated by steric approach control.⁷ A brief study of the effect of solvents on the stereochemistry of reduction (Table 3) showed that in solvents more polar than pentane the proportion of axial alcohol tended to decrease.

EXPERIMENTAL

All operations involving boranes were carried out under an inert atmosphere with dry, oxygen-free solvents.

(+)-Pin-2-ene (Fluka) was distilled over sodium under nitrogen. The fraction of b.p. $155-156^{\circ}$, $[\alpha]_{D}^{22} - 38-39^{\circ}$ (neat) was collected (lit.,⁸ $[\alpha]_{D}^{20} + 51^{\circ}$). (-)-Pin-2-ene, $[\alpha]_{D}^{22} - 42 \cdot 5^{\circ}$ (neat) was purified in a similar manner. Tetrahydrofuran, b.p. $66-67^{\circ}$ was distilled from lithium aluminium hydride. Bis-(2-methoxyethyl) ether (2 l) (I.C.I.) was stirred vigorously over calcium hydride (20 g) for 12 h and distilled at atmospheric pressure (b.p. 160-162°). The distillate was treated with lithium aluminium hydride (10 g) and distilled under reduced pressure under nitrogen. The ether, b.p. 78° at 37 mmHg, was collected over 4A molecular sieves and stored under nitrogen. Boron trifluoride-diethyl ether complex was distilled under reduced pressure under nitrogen; the fraction of b.p. 55-56° at 25 mmHg was collected.

Asymmetric Reductions of Ketones with Lithium Hydro-(methyl)dipinan- 3α -ylborate.—A suspension of dipinan- 3α ylborane (0.132 mol) was prepared from (--)-pin-2-ene in bis-(2-methoxyethyl) ether (75 ml) with external generation of diborane.^{2b} A cold solution of methyl-lithium (1.93M in ether; 68 ml, 0.132 mol) was added dropwise during

⁷ E. L. Eliel and Y. Senda, *Tetrahedron*, 1970, **26**, 2411, and references therein.

⁸ F. H. Thurber and R. C. Thielke, J. Amer. Chem. Soc., 1931, 53, 1030.

The mixture was stirred for 3 h at 0° after which all 0.5 h. of the white precipitate had dissolved. The ketone (0.05)mol) in bis-(2-methoxyethyl) ether (20 ml) was added dropwise during 0.5 h at 0° . The mixture was stirred for a further 3 h at 0° and then overnight at room temperature. Ice-water (150 ml) was carefully added and the mixture was heated for 0.5 h at 50°, saturated with sodium chloride, and extracted (\times 3) with ether. The extract was dried (MgSO₄) and the ether was removed through a short Fenske column. Fractional distillation gave in all cases a product alcohol contaminated with much pin-2-ene. The alcohols were purified by preparative g.l.c. with a Perkin-Elmer F21 Preparative Gas Chromatograph, firstly through a column (2.7 m) of Versamid 930 (20% w/w) on 40-60 mesh, acidwashed Chromosorb W, and secondly through 1,2,3-tris-(2-cyanoethoxy)propane (20% w/w) on the same support.

Each alcohol was heated with an equimolar quantity of phthalic anhydride for ca. 10 h at 115° on an oil-bath, except in the case of butan-3-ol which was heated on a boiling water-bath. The cooled mixture was poured into an excess of sodium carbonate solution, extracted with ether (\times 3), and made acid with hydrochloric acid. The oily precipitate was extracted into chloroform; the chloroform layer was washed with water, dried (MgSO₄), and evaporated under reduced pressure to give a white crystalline mass of hydrogen phthalate ester. The results are summarised in Table 1.

Reduction of Methyl t-Butyl Ketone (Pinacolone) with Lithium Butyl(hydro)dipinan- 3α -ylborate.—A solution of n-butyl-lithium (0·15 mol) in hexane was added dropwise to a suspension of dipinan- 3α -ylborane (0·15 mol) prepared from (+)-pin-2-ene in bis-(2-methoxyethyl) ether (75 ml) at 0°. Pinacolone (7·5 g, 0·075 mol) in bis-(2-methoxyethyl) ether (25 ml) was added during 0·5 h and the mixture was stirred for 12 h at 0° and for 8 h at room temperature. The product (7·7 g) was isolated in ether as before; the alcohol, purified as already described, had $[\alpha]_{\rm D}$ +0·58° (neat) (7% optical purity); 1-naphthylurethane, $[\alpha]_{\rm D}$ +1·2° (c 5·0 in CHCl₃).

A repeat experiment in which the mixture was stirred for 12 h at room temperature gave 3,3-dimethylbutan-2-ol, $[\alpha]_{\rm D} + 0.71$ (neat) (9% optical purity); 1-naphthylurethane, $[\alpha]_{\rm D} + 1.3^{\circ}$ (c 5.0 in CHCl₃).

Attempted Isolation and Characterisation of Lithium Butyl(hydro)dipinan- 3α -ylborate.—Dipinan- 3α -ylborane (0.2 mol)^{2b} was suspended in dry pentane (120 ml) cooled in ice. n-Butyl-lithium (22.1% in hexane; 65 ml, 0.2 mol) was added dropwise with stirring during 0.5 h. When a clear solution was obtained the solvent was removed under reduced pressure. A clear gum was obtained which could not be induced to crystallise. The hydride activity was measured by treatment with hydrochloric acid and estimation of the hydrogen evolved in a calibrated gas microburette. The hydride activity fell in the range 65—80%. Optical activity of the hydride showed similar variation; however a consistent (+) sign of rotation was obtained when (-)-pin-2-ene was used.

The gum was triturated with pentane and a small amount of a white crystalline solid was obtained. The spectral properties were consistent with the formulation dibutylpinan-3 α -ylborane-bis-(2-methoxyethyl) ether: C₁₈H₃₅B, m/e 262 (2%, M^+), 205 (6, $M - C_4H_9$), 148 (1, $M - Bu_2$), 125 (52, M — pinenyl), 68 (8, M — Bu — pinenyl), and 59 (100), τ (100 MHz) 7.8—9.2 (m), 6.4 (m), and 6.6 (s).

Evaporation of the pentane solution gave a clear gum which was soluble in bis-(2-methoxyethyl) ether, aliphatic hydrocarbons, dichloromethane, and chloroform. It could be stored unchanged under nitrogen for several weeks but decomposed rapidly in contact with moist air. Dropwise addition of water caused decomposition. Extraction of the resulting mixture with ether and purification by preparative g.l.c. gave pure samples of butanol, pinan- 3α -ol, and bis-(2-methoxyethyl) ether. The mass spectrum showed $C_{24}H_{44}B^-$, m/e 343 (0.2%, M^+), 286 (0.8, M - Bu), 206 (5.2, M - pinenyl), 149 (8.8, M - Bu - pinenyl), and 81 (100). The n.m.r. spectrum showed peaks due to bis-(2-methoxyethyl) ether at τ 6.4 (s) and 6.6 (m), with a complex multiplet for the hydrocarbon residue from τ 7 to 9.5. The ratio of ether to hydroborate was ca. 1:2. It was not possible to remove the ether even under vacuum for several hours.

Reductions of Substituted Cyclohexanones.-Lithium butyl-(hydro)dipinan- 3α -ylborate (ca. 0.2 mol; freshly analysed for hydride activity) was dissolved in pentane (25 ml) and cooled to 0°. A solution of the ketone (0.0125 mol) in pentane (10 ml) was added dropwise during 20 min. The mixture was stirred for 3 h at 0° and overnight at ambient temperature. Ice-water (30 ml) was added carefully to the mixture, which was then extracted with ether $(\times 3)$. The extract was dried $(MgSO_4)$ and analysed by g.l.c. with a Perkin-Elmer F11 gas chromatograph fitted with 50 m capillary columns coated with Carbowax (nitrogen flow rate was 10 ml min⁻¹; temperatures between 95 and 110° were used for the various alcohols). The compositions of the mixtures were estimated by measuring peak areas and comparing them with those from authentic mixtures of similar composition. In no case was any unchanged ketone detected. The product ratios are summarised in Table 2.

Solvent Effects in the Reduction of 3,3,5-Trimethylcyclohexanone with Lithium Butyl(hydro)dipinan- 3α -ylborate. The hydroborate (ca. 0.2 mol) was isolated as before and dissolved in the appropriate solvent (20 ml). 3,3,5-Trimethylcyclohexanone (1.75 g, 0.0125 mol) in the solvent (10 ml) was added and the reaction was carried out as already described. The diastereoisomeric alcohols were analysed with a Versamid column at 95°; the product ratios are summarised in Table 3.

TABLE 3

Solvent effects in the reduction of 3,3,5-trimethylcyclohexanone

Solvent	Axial alcohol (%)	Equatorial alcohol (%)
Pentane	89	11
Pentane $+ ca. 5\%$ bis-(2-meth-oxyethyl) ether	85	15
Ether	70	30
Dichloromethane	50	50

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