

ASYMMETRIC REDUCTION OF *p*-ALKYLACETOPHENONES*

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Asymmetric reduction of *p*-alkylacetophenones *Ia*–*VIIa* with lithium aluminium hydride in the presence of (–)-quinine affords optically active alcohols *Ib*–*VIIb* of the (*R*)-(+) configuration in optical yields of about 50%.

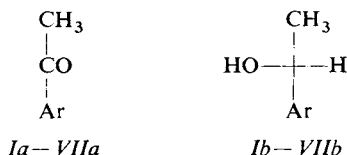
Within the framework of studies on asymmetric reduction of alkyl aryl ketones we reduced some *p*-alkylacetophenones with the chiral reducing agent, prepared *in situ* from equimolar amounts of lithium aluminium hydride and (–)-quinine in ether. According to our previous results^{1,2}, alkyl aryl ketones are reduced to secondary alcohols of the (*R*)-(+) configuration. It was of interest to check the validity of these results for the whole ketone series and to study the effect of *para*-substituents on the optical yield.

Reduction of ketones *Ia*–*VIIa* afforded dextrorotatory alcohols *Ib*–*VIIb* in optical yields of about 50%. As expected, substituents in the *para*-position did not affect the enantioselectivity of the reduction. The optical purity of the alcohols *Ib*–*VIIb* was determined by measurement of their ¹H NMR spectra in the presence of tris(heptafluorobutyrylcamphorato)europium(III) as chiral shift reagent. In all cases, the methine proton signal of the (*R*)-enantiomer was shifted upfield.

Both the absolute configuration and specific rotation of alcohol *Ib* are known³ ($(\alpha)_D^{20} + 43.5^\circ$ (neat)). The maximal rotation, calculated from the polarimetric measurements and from the enantiomeric excess determined from the ¹H NMR data (error $\pm 0.5\%$), amounts to $(\alpha)_D^{20} + 41.2^\circ$ (neat). The enantiomeric purity of alcohol *Ib* and the maximal rotation of the pure enantiomer in chloroform calculated from it agree well (error of 5%) with data obtained by resolution of the enriched mixture on a Pirkle HPLC column^{4,5}. On the other hand, our calculated maximal rotations of neat *Ib* and *IIIb* are lower than the values reported by Jacques and Vigneron^{6,7} who did not specify conditions of the measurement. The absolute configuration of *Ib* and *IIIb* is (*R*)-(+) , in accord with the literature and, according

* Part LXIII in the series Asymmetric Reactions; Part LXII: This Journal 51, 404 (1986).

to the obtained results, the alcohols *IV–VIIb* can be also assigned the (*R*)-(+) configuration.



Ar = *Ia,b* C₆H₅, *IIa,b* *p*-CH₃C₆H₄, *IIIa,b* *p*-C₂H₅C₆H₄, *IVa,b* *p*-C₃H₇C₆H₄,
Va,b *p*-*i*-C₃H₇C₆H₄, *VIa,b* *p*-C₄H₉C₆H₄, *VIIa,b* *p*-*t*-C₄H₉C₆H₄

EXPERIMENTAL

Boiling points are uncorrected. Optical rotation was measured on an objective polarimeter with an experimental error of 0.02°. Purity of the starting ketones and the obtained alcohols was checked by gas-liquid chromatography (Carbowax 20 M/5% at 154°C). Optical purity of the alcohols was determined from the ¹H NMR spectra measured in the presence of (+)-tris (heptafluorobutrylcamphorato)europium(III) with tetramethylsilane as internal standard. The starting ketones were prepared by Friedel-Crafts acylation of the corresponding alkyl aromates. The purity and identity of the obtained secondary alcohols follows from their gas-liquid analyses and ¹H NMR spectra.

Asymmetric Reductions of Ketones

Quinine (3.75 g; 11 mmol) was gradually added during 40 min to a suspension of lithium aluminium hydride (0.42 g; 11 mmol) in ether (20 ml). (To obtain reproducible results, (–)-quinine,

TABLE I

Asymmetric reduction of ketones *Ia–VIIa* with lithium aluminium hydride in the presence of (–)-quinine in ether

Alcohol	B.p. °C/kPa ^a	(α) _D (neat)	% E.p.
<i>Ib</i>	107/4	+19.68	47.8
<i>IIb</i>	112/2	+21.20 ^b	47.0
<i>IIIb</i>	120–121/1,7	+18.4	42.6
<i>IVb</i>	124–126/2	+16.69	41.4
<i>Vb</i>	117–119/2,2	+20.54	50.6
<i>VIb</i>	134/2	+17.09	45.0
<i>VIIb</i>	59–62 ^a	+17.81 ^c	51.4

^a M.p., °C; ^b [α]_D²⁰ + 25.1° (c 3, CHCl₃); ^c (c 3.94, ethanol).

liberated from its hydrochloride, was recrystallized from benzene. After drying, the base was finely ground and dried *in vacuo* (oil pump) at 120°C for 5 h. Prior to each reduction, the quinine was ground and dried again.)

The suspension was stirred for 45 min and a solution of the ketone (*Ia*–*VIIa*; 10 mmol) in ether (35 ml) was added in the course of 60 min with stirring. The mixture was refluxed for 4 h, cooled and decomposed by dropwise addition of water (15 ml), followed by 20% sulfuric acid (15 ml). The aqueous layer was extracted with ether (10 ml), the ethereal solution was shaken with 20% sulfuric acid (6 × 10 ml), dried over magnesium sulfate and the product was distilled. The alcohol *VIIb* was purified by chromatography on a column of silica gel in ether–light petroleum 2 : 8. The results are given in Table I.

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