Tetrahedron. Vol. 29, pp. 913 to 916. Pergamon Press 1973. Printed in Great Britain

STEREOCHEMISTRY OF MANNICH BASES—VII

ASYMMETRIC REDUCTION OF β-AMINOKETONES WITH OPTICALLY ACTIVE ALKOXY-LAH[a]

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(*Received in the UK* 23 *October* 1972; *Accepted for publication* 8 *November* 1972)

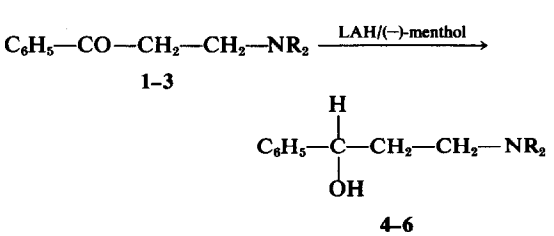
Abstract—The asymmetric reduction of achiral β-dialkyl-aminopropiophenones with LAH partly decomposed with (−)-menthol has been studied. The effects of the LAH/(−)-menthol ratio, the temperature, and the dialkylamino residue on the optical yield were investigated, and the absolute configurations of the predominant antipodes of the γ-dialkylaminoalcohols obtained were determined.

In the course of the investigations on the reactivity and stereochemistry of Mannich bases,[1] we have studied the reduction of some β-dialkylamino-propiophenones with LAH partly decomposed with (−)-menthol.

The reduction of achiral ketones with various asymmetric reducing agents has been the subject of numerous studies both from the synthetic and the mechanistic aspect.

In particular, attempts to obtain optically active alcohols from ketones with LAH in the presence of (+)-camphor have been reported[2] and was proved to be unsuccessful. On the other hand, very interesting results were obtained by Cervinka[3] in the reduction of a wide range of ketones with LAH and the aid of amino alcohols, and by Landor[4] with complex cyclic alkoxides of LAH.

The present article describes the initial results obtained in the following reactions:



$NR_2 = NMe_2$ (**1** and **4**); piperidino (**2** and **5**); morpholino (**3** and **6**).

The effects of the LAH/(−)-menthol molar ratio, the temperature, and the alkylamino residue on the optical yield of the reaction and the configuration of the alcohol obtained were investigated.

The reagent was prepared by the addition of (−)-menthol in various molar ratios to a standardized 0·1 M solution of LAH in ether, followed by the addition of an equimolar quantity of the β-aminoketone to this solution.

The reduction yield was nearly always quantitative. However, incomplete reduction was found in some cases when the LAH/(−)-menthol ratio in the reagent was 1/3. This was presumably due to the loss of strength of the solution of LAH in ether. When an excess of reagent was used, on the other hand, the reduction was complete, and there were no appreciable variations of the optical yield.

The results obtained, which are summarized in Table 1, show that the optical yield increases considerably as the ratio β-aminoketone/LAH/(−)-menthol is changed from 1 : 1 : 1 to 1 : 1 : 3.

A temperature rise, on the other hand, leads to a decrease in the optical yield, in agreement with kinetic control of the reaction.

Variation of the alkylamino residue of the β-aminoketone leads to pronounced variations of the optical yield, which is found to be greater for the dimethylamine derivative than for the piperidine derivative, while it is distinctly lower for the morpholine compound.

The sign of the enantiomer of the alcohol that predominates is always positive under the experimental conditions used and for the β-aminoketones investigated.

The absolute configurations of (−)-**4**, (+)-**4**, and (−)-**5** were determined by Horeau's method;[5] the alcohols (+)-**4** and (+)-**5** obtained in the asymmetric reduction were found to be *R*. It was not possible to make an assignment of the absolute configuration of (+)-**6** in the same manner, since a sample of sufficient enantiomeric purity was not available.

However, it was possible to find the absolute configuration of (+)-**6** by comparison of the circular dichroism spectra with those of the two γ-amino alcohols (−)-**4** and (−)-**5**, whose absolute

[a]Translated by Express Translation Service London.

Table 1. Asymmetric reduction of $C_6H_5COCH_2$-CH_2-NR_2 1–3 by LAH 0·1 M in ether in presence of (−)Menthole

-NR_2	Temp. °C	LAH (O-Menth) $[\alpha]_D$	LAH (O-Menth) Optical yield %	LAH $(O\text{-Menth})_2$ $[\alpha]_D$	LAH $(O\text{-Menth})_2$ Optical yield %	LAH $(O\text{-Menth})_3$ $[\alpha]_D$	LAH $(O\text{-Menth})_3$ Optical yield %	Enantiomeric purity[a]	Configuration
-NMe_2 (4)	0°	+0·37	1·3	+4·8	17·4	+20·2	73·2	77·5	*R*
	35°	+0·30	1·1	+1·2	4·4	+14·8	53·6		
 (5)	0°	+0·65	2·2	+5·6	19·1	+19·9	67·9	66·0	*R*
	35°	+0·47	1·6	+1·6	5·5	+13·3	45·4		
 (6)	0°	+0·24	2·1	+3·8	33·3	+6·7	58·7	58·7	*R*
	35°	+0·18	1·6	+2·6	22·8	+4·4	38·6		

[a]Determined by Mislow-Raban method.

configuration is known to be *S*. As can be seen from the Fig 1, the free bases *S*(−)-**4** and S(−)-**5** in various solvents, and their hydrochlorides, exhibit a negative Cotton effect at 210–220 mμ and a multiple positive Cotton effect in the range 250–270 mμ, which are attributable to an aromatic chromophore.[6] On the other hand, the spectra of (+)-**6** exhibit equal but opposite Cotton effects in the same ranges, and this enables us to assign the *R* configuration to this compound.

No appreciable changes are observed in the spectra on variation of the solvent and on protonation of the amino group.

The enantiomeric purity of the optically active γ-amino alcohols examined was checked by the Raban-Mislow ^{1}H-NMR method.[7]

Table 2 shows the chemical shifts of the protons of the diastereoisomeric (−)O-methyl mandelates used for the determination of the two enantiomeric forms. From a comparison of these values, it can be seen that the signals for the diastereoisomers containing the alcohols having the *R* absolute configuration are always situated at higher fields than those of the other diastereoisomers; this course is similar to that found by other workers[8] for diastereoisomers of O-methyl mandelates of other series of compounds.

It can be seen from Table 1 that within the limits of the experimental error, perfect agreement exists between the enantiomeric purity values and the optical yields; this rules out the presence of any by-products in the γ-amino alcohols examined.

The determination of the enantiomeric purity of the (+)-**6** enabled us to find the absolute specific rotation, from which the optical yields reported were found.

The results show the possible preparative value of this type of asymmetric reduction in view of the high induction values obtained.

Since achiral ketones similar to the compounds investigated by us do not undergo induction in the reduction under similar conditions, we believe that the nitrogen of the keto-base may be assumed to play a fundamental part in the reaction mechanism.

We intend to check this in further studies, in which the range of application of the reagent studied here will also be examined.

EXPERIMENTAL

M.ps are uncorrected. IR spectra were measured using a Beckman IR 5 spectrophotometer. ^{1}H-NMR spectra were determined on a Jeol C60-HL spectrometer in $CDCl_3$ (10% w/w) using TMS as internal standard. CD spectra were recorded on a Russel-Jouan II Dichro-

Table 2. Chemical shifts (τ) non equivalence of diastereotopic protons in (−)O-methylmandelates of S- and R- C_6H_5—CH(OH)—CH_2—CH_2—NR_2

Config NR_2	-OMe *S*	-OMe *R*	-OMe $\Delta\nu$[a]	H-C-OMe *S*	H-C-OMe *R*	H-C-OMe $\Delta\nu$[a]
-NMe_2	6·630	6·657	1·6	5·202	5·239	2·2
-Pip	6·607	6·634	1·6	5·202	5·239	2·2
-Morf.	6·620	6·645	1·5	5·199	5·235	2·2

[a]In Hz at 60 MHz.

graphe; optical rotations were measured on a Bendix NPL 143 C Automatic Polarimeter ($c = 1{\cdot}5$–3 MeOH and for little rotations $c = 10$ MeOH).

β-Dialkylamino propiophenones (1–3)

The hydrochlorides of compounds 1–3 were synthesized following previous procedure.[9] The free bases

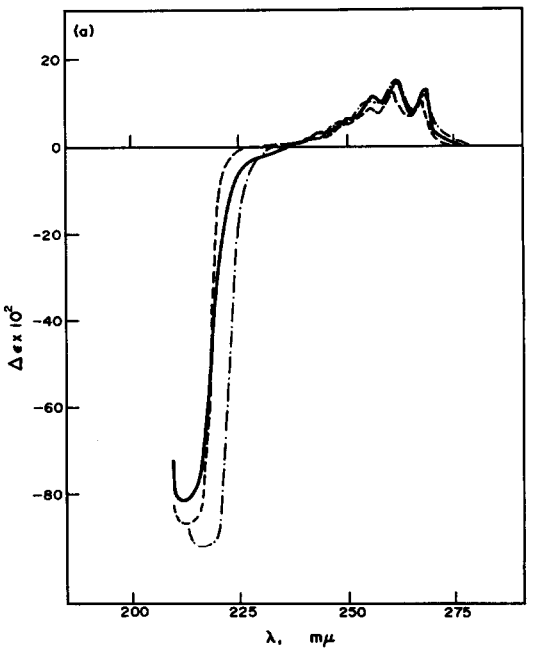


Fig 1(A).

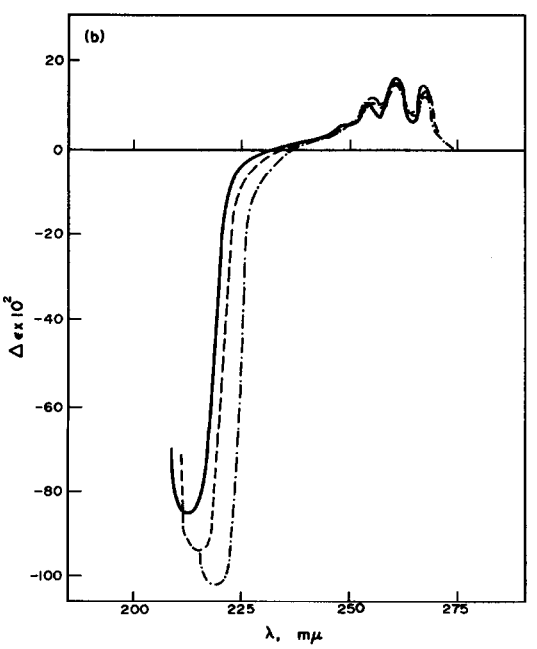


Fig 1(B).

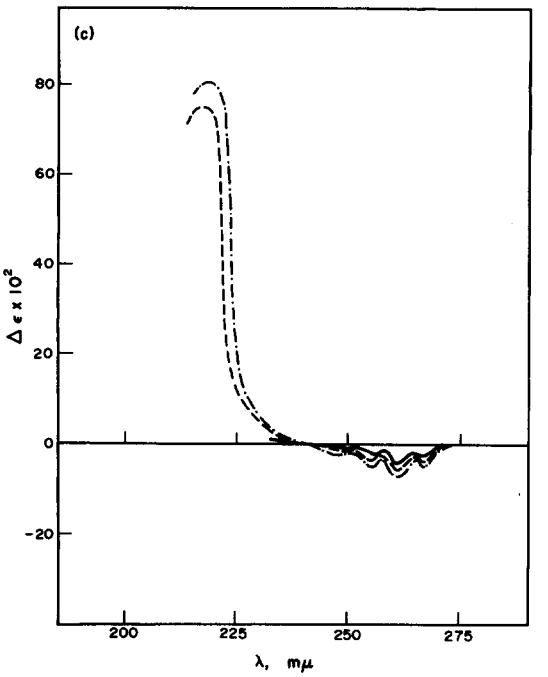


Fig 1(C).

Fig 1. CD curves of: (A) (−)-1-phenyl-3-dimethylamino-propan-1-ol, (B) (−)-1-phenyl-3-piperidino-propan-1-ol, (C) (+)-1-phenyl-3-morpholino-propan-1-ol. (–·–·–·– in cyclohexane, – – – – – in MeOH, ——— hydrochlorides in MeOH).

1–3 were obtained from hydrochlorides at 0° by treatment with N NaOH. ^{1}H-NMR spectra show:

(1) τ 1·9–2·2 (2H, m, aromatics); 2·4–2·8 (3H, m, aromatics); 6·6–7·0 (2H, m, CO-CH_2); 7·0–7·4 (2H, m, -CH_2-N); 7·65 (6H, s, NMe_2).

(2) τ 1·9–2·2 (2H, m, aromatics); 2·4–2·7 (3H, m, aromatics); 6·6–7·0 (2H, m, CO-CH_2); 7·0–7·4 (2H, m, CH_2-N), 7·4–7·8 (4H, m, $N(CH_2)_2$); 8·1–8·8 (6H, m, $(CH_2)_3$).

(3) 1·9–2·2 (2H, m, aromatics); 2·4–2·8 (3H, m, aromatics); 6·2–6·5 (4H, m, $O-(CH_2)_2$); 6·6–7·0 (2H, m, CO-CH_2); 7·0–7·4 (2H, m, CH_2-N); 7·4–7·7 (4H, m, $N(CH_2)_2$).

1-*Phenyl*-3-*dialkilamino-propan*-1-*ols* (4–6)

(±) 1-Phenyl-3-dimethylamino-propan-1-ol (4) was obtained by reduction of 1 with LAH in dry ethyl ether; it was crystallized from light petroleum m.p. 54–55°;[10] ^{1}H-NMR spectrum shows: τ 2·4–2·9 (5H, m, aromatics); 3·6 (1H, s, OH); 5·1 (1H, t, CHOH); 6·3–6·6 (2H, m, C-CH_2); 7·7 (6H, s, NMe); 8·0–8·4 (2H, m, CH_2-N).

(±) 1-Phenyl-3-piperidino-propan-1-ol (5) was prepared as described from 2, it was crystallized from light petroleum m.p. 68–9°;[11] ^{1}H-NMR spectrum shows: τ 2·5–2·9 (5H, m, aromatics); 3·0 (1H, s, OH); 5·1 (1H, t, CHOH); 7·2–7·8 (6H, m, CH_2-$N(CH_2)_2$); 8·0–8·7 (8H, m, -C-CH_2, $(CH_2)_3$).

(±) 1-Phenyl-3-morpholino-propan-1-ol (6) was prepared as described from 3, it was cristallized from light petroleum, m.p. 64–5° (Found: C, 70·53; H, 8·58; N, 6·38. $C_{13}H_{19}O_2N$ required: C, 70·55; H, 8·65; N, 6·33%);

^{1}H-NMR spectrum shows: τ 2·4–2·9 (5H, m, aromatics); 3·9 (1H, s, OH); 5·1 (1H, t, CHOH); 6·1–6·4 (4H, m, $O(CH_2)_2$); 7·1–7·8 (6H, m, CH_2-N-$(CH_2)_2$); 7·9–8·4 (2H, m, C-CH_2).

Resolution of the (±)-1-*phenyl*-3-*dialkylamino-propan*-1-*ols* (4–6)

(+)- *and* (−)-1-*phenyl*-3-*dimethylamino-propan*-1-*ols*, (+)- *and* (−)-(5). A soln of 15 g of (±) 4 in 75 ml dry Me_2CO was added to a soln of 31·5 g of (−) dibenzoyltartaric acid in 75 ml dry Me_2CO. The precipitated salt was crystallized from Me_2CO-EtOH (95/5), m.p. 107–8° (dec). (Found: C, 64·35; H, 6·16; N, 2·74. $C_{29}H_{31}O_9N$, required: C, 64·80; H, 5·81; N, 2·61%). The free base showed $[\alpha]_D = +27·6°$ ($c = 1·61$, MeOH).

By adding ethyl ether to mother liquors the other diasteroisomeric salt was obtained, it was crystallized from Me_2CO-EtOH (95–5) and showed m.p. 142–3° (dec) (Found: C, 64·50; H, 5·82; N, 2·74. $C_{29}H_{31}O_9N$, required: C, 64·80; H, 5·81; N, 2·61%). The free base, showed $[\alpha]_D = -28·2$ ($c = 2·14$ MeOH).

(−) 1-*Phenyl*-3-*piperidino-propan*-1-*ol* (−)-(5). Working as described above a diastereoisomeric salt was obtained, m.p. 112–3° (dec). (Found: C, 66·23; H, 6·55; N, 2·40. $C_{33}H_{35}O_9N$, required: C, 66·54; H, 6·11; N, 2·43%). The free base showed $[\alpha]_D = -29·3$ ($c = 1·9$ MeOH).

Attempts to resolve the (±) 6 with some optical active acids [(−) dibenzoyltartaric, (−) tartaric, (+) camphorsulfonic] were unsuccessful.

Absolute configuration of the optical active γ-*amino alcohols by the method of Horeau*[5]

The determination was performed on (−) 4 ($[\alpha]_D = -28·2$) using 0·11745 g of amino alcohol and 0·63221 of α-phenylbutiric anhydride (esterification yield: 96%, optical yield of (−)α-phenylbutiric acid: 10%).

The determination was performed on (+)-4 ($[\alpha]_D = +27·6$) using 0·10855 g of amino alcohol and 0·58983 g of α-phenylbutyric anhydride (esterification yield: 96%, optical yield of the (+)α-phenylbutyric acid: 17%). The determination was performed on (−)4 ($[\alpha]_D = -29·3$) using 0·16485 g of amino alcohol and 0·41755 g of α-phenylbutyric anhydride (esterification yield: 96·1%, optical yield of the (−)α-phenylbutyric acid: 15%).

General reduction method of compounds 1–3 *with* LAH *in presence of* (−)*menthol*

To a magnetically stirred 0·1 M solution of LAH[12] in ether was added (−)-menthol at suitable molar ratio (LAH/(−)menthol 1:1; 1:2; 1:3). To this soln was added dropwise an equimolecular amount of an ethereal soln of the amino ketone. The mixture was stirred for 2 hr and cautiously hydrolysed with 2N HCl: (−) menthol was eliminated by extraction with ether. From the soln, treated with 2N NaOH, the γ-amino alcohols (+)-4-(+)-6 were then extracted with ether.

(−)-O-*Methyl mandelates of optical active* γ-*amino alcohols*

These were synthesized, as described[7], from $2·0 \cdot 10^{-3}$ mol of γ-amino alcohols and $2·6 \cdot 10^{-3}$ mol of (−) O-methyl mandelyl chloride.[13]

^{1}H-NMR spectra of (−)O-methyl mandelic ester of (−)-4 $[\alpha]_D = -28·2$, (+)-4 $[\alpha]_D = +27·6$ and (−)-5 $[\alpha]_D = -29·3$ showed the presence of only one diastereoisomer.

The determination of enantiomeric purity of (+)-4, (+)-5 and (+)-6 obtained by asymmetric reduction, was performed on the crude products.

Acknowledgement—Thanks are due to the Consiglio Nazionale delle Ricerche (Roma) for a grant.

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