o-**Benzoylbenzoic acid** (75% yield, mp 127–129° from benzene–petroleum ether,[3] lit.[5] mp 128–129°) was prepared from *o*-bromobenzoic acid and methyl benzoate.

2-(*o*-Methylbenzoyl)benzoic Acid (16) and the Acid 23. A. The acidic product obtained as described for **7** by reaction of methyl *o*-toluate with the dianion prepared from *o*-bromobenzoic acid was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (70:30) as eluent] to give 2-(*o*-methylbenzoyl)benzoic acid (**16**), 59% yield, mp 107–109°[9] from benzene–petroleum ether.[3] No appreciable amount of **23** was isolated.

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; neut equiv, 240.02. Found: C, 75.03; H, 5.25; neut equiv, 238.

B. When *o*-toluoyl chloride was used instead of methyl *o*-toluate and the acidic product was chromatographed as in A the yield of **16** was 41% and the acid **23** was obtained in 19% yield, mp 240–242° from ethanol–water.

Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; neut equiv, 344.3. Found: C, 76.58; H, 4.89; neut equiv, 345.

2-(*o*-Bromobenzoyl)benzoic Acid (17) and the Acid 18. A. The acidic product obtained as described for **7** by reaction of methyl *o*-bromobenzoate (2.77 g, 0.125 mol) with the dianion prepared from *o*-bromobenzoic acid was recrystallized from methanol–chloroform to give **18** as a white solid, 29% yield, mp 284–286°.

Anal. Calcd for $C_{21}H_{13}BrO_4$: C, 61.63; H, 13.20; Br, 19.45; neut equiv, 409.2. Found: C, 61.43; H, 3.67; Br, 19.16; neut equiv 408.

The mother liquor obtained above was chromatographed on silica gel [preparative tlc, petroleum ether[3]–diethyl ether (60:40) as eluent] to give 2-(*o*-bromobenzoyl)benzoic acid (**17**), 45%, mp 134° from chloroform–petroleum ether.[3]

Anal. Calcd for $C_{14}H_9BrO_3$: C, 55.10; H, 2.97; Br, 26.19; neut equiv, 305.1. Found C, 54.89; H, 2.91; Br, 26.00; neut equiv, 304.

B. When *o*-bromobenzoyl chloride was used instead of methyl *o*-bromobenzoate, the yield of **18** was 27–30% and the yield of **17** was 40–44% (multiple runs including addition of the dianion at −75° to the acid chloride solution in hexane at room temperature, *i.e.*, reversed addition).

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Registry No.—**1**, 619-42-1; **3**, 51310-29-3; **4**, 51310-30-6; **5**, 618-89-3; **6**, 51310-31-7; **7**, 51310-32-8; **10**, 606-28-0; **16**, 5469-51-2; **17**, 51310-33-9; **18**, 5130-34-0; **23**, 51310-35-1; *n*-butyllithium, 109-72-8; methyl *o*-bromobenzoate, 610-94-6; *m*-bromobenzoic acid, 585-76-2; methyl benzoate, 93-58-3; *p*-bromobenzoic acid, 586-76-5; *o*-bromobenzoic acid, 88-65-3; methyl *o*-toluate, 118-90-1; *o*-toluoyl chloride, 933-88-0; *o*-bromobenzoyl chloride, 7154-66-7.

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Stereochemistry of Amino Carbonyl Compounds. IX.[1] Lithium Aluminum Hydride and Lithium Trialkoxyaluminum Hydride Reduction of α-Asymmetric β-Aminopropiophenones

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The stereochemical course of the reduction by lithium aluminum hydride ($LiAlH_4$), lithium trimethoxyaluminum hydride (TMH), and lithium tri-*tert*-butoxyaluminum hydride (TBH) of some α-asymmetric β-amino ketones has been investigated by varying hydride concentration, solvent, and reaction temperature. The stereoselectivity was found to be strongly dependent on the nature of the substrate and, to a lesser extent, on the other factors. Some considerations concerning the transition states are given.

Several papers concerning asymmetric induction of the reaction between acyclic asymmetric ketones bearing a heteroatom in the β position and nucleophilic reagents (organometallics and hydrides) have been published.[2] The discussion of the mechanism of such reactions is complicated, with respect to the corresponding substrates not containing heteroatoms, by the possibility of additional complexing and solvating effects which may affect the nature of the species involved.[3] In particular, an important question which arises whenever a rationalization of the stereochemical course of the reaction is attempted is concerned with the situation of the reducing species in the transition state.

In this connection we have investigated the role played by such factors as nature of the hydride, concentration of the reducing agent, solvent, and reaction temperature.

Results and Discussion

The reduction of the amino ketones **1–3** (Scheme I) was performed with hydride concentrations of about 0.01, 0.1, and 0.5 *M*, at 0° and at reflux in THF, and at 0° in Et_2O. The results are collected in Table I and graphically depicted in Figure 1.

The relative amounts of the obtained diastereomeric 1-phenyl-3-dialkylaminopropan-1-ols **4–6** were determined on the crude reaction mixture[4] by integration of the nmr signal due to the proton bonded to C-1, as described in a previous paper.[2h]

Most of the reaction yields were quantitative (nmr) in amino alcohols, except when the reduction was carried out with the alkoxy hydrides, particularly at low concentrations and at 0° (Table I). In such cases longer reaction times as well as higher temperatures (room temperature) were required in order to obtain appreciable amounts of product. The diastereomeric ratios, however, were not affected by the reaction time, thus confirming that no equilibration occurred under the adopted conditions.

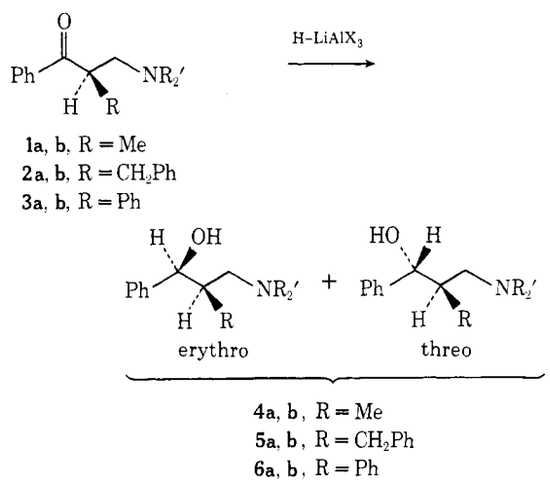
The experimental results show a general predominance of the erythro amino alcohols **4–6** and, in addition, allow the following observations to be made.

Table I
Per Cent of Erythro Amino Alcohols 4–6 by Reduction of the Amino Ketones 1–3[a]

Amino ketone	Reaction temp, °C	$LiAlH_4$ (Et_2O)[h] 0.01	0.10	0.45	$LiAlH_4$ (THF)[h] 0.01	0.09	0.44	TMH (THF)[h] 0.01	0.10	0.45	TBH (THF)[h] 0.01	0.10	0.45
1a	0	58	59	60	62	63	60	49	52	54	52[b] (70)	52[c]	53[d]
	Reflux				58	59[e]	54[e]	63	60	57	55[d] (36)	55	55
1b	0	57	55	55	53	52	55	51	50	48	45[b] (52)	45[c] (95)	46[d]
	Reflux				53	50[e]	53[e]	53	49	50	46[f] (55)	47	48
2a	0	67	71	69	67	67	64	82	78	79	79[b] (28)	79 (17) 81[c] (78)	85[d] (80)
	Reflux				61	61	61[e]	86	80	77	73 (42)	72	72
2b	0	60	57	57	46	49	46	*g*	62	61	63[b] (39)	66 (12) 66[c] (78)	68[d] (57)
	Reflux				48	49	51[e]	60	59	56	55[f] (28)	57	58
3a	0	87	89	89	97	94	94	99	98	98	*b, g*	92[d] (67) 92[f] (75)	95[c]
	Reflux				92	91	90 87[e]	97	95	95	85 (38)	91	90
3b	0	87	87	84	95	93	94	*g*	94	95	*b, g*	92[c] (47)	91[c] (93)
	Reflux				89	93	88[e]	95 (55)	97	93	85[f] (43)	88	90

[a] Limit error ±3%. When not quantitative, the reaction yields are reported in parentheses. Reaction time 1 hr, except when otherwise indicated. [b] 24 hr at room temperature. [c] Reaction time 8 hr. [d] Reaction time 3 hr. [e] Inverted addition of reactants (see Experimental Section). [f] Reaction time 5 hr. [g] No reaction. [h] Hydride (solvent) at various molar concentrations.

Scheme I[a]



a, $NR_2' = NMe_2$; b, $NR_2' = N(CH_2)_5$

X = H, lithium aluminum hydride ($LiAlH_4$)
X = OMe, lithium trimethoxyaluminum hydride (TMH)
X = $OCMe_3$, lithium tri-*tert*-butoxyaluminum hydride (TBH)

[a] Only one enantiomer of the racemic pair is here represented.

(1) The stereoselectivity is always higher with the dimethylamino derivatives than with the corresponding piperidino derivatives and increases, with only one exception, passing from R = Me to CH_2Ph to Ph.

(2) The alkoxy hydrides behave similarly, whereas $LiAlH_4$ in THF exhibits a different trend. In the $LiAlH_4$ reductions the change of solvent from THF to Et_2O causes in some cases relevant variations of stereoselectivity.

(3) The dependence of stereoselectivity on the hydride concentration is very small, usually within the error of determination.

(4) The general decrease of the predominant diastereomer which is observed when the reaction temperature is raised from 0° to the boiling point of the solution does not substantially affect the trend of Figure 1 (I and III *vs.* II and IV, respectively). This indicates that the diastereomeric transition states are not considerably altered.

For similar α- or β-asymmetric ketones bearing NH, OH, or OR in the β position, the stereochemical results deriving from the reactions with hydrides or organometals have been interpreted on the basis of various cyclic transition states in which the metal hydride is bonded to the β heteroatom,[2c] or links both carbonyl oxygen and β heteroatom.[2a,b,f,i] Further, a competition has been proposed between cyclic and open-chain models.[2b]

Our results enable us to discuss the behavior of the reactants involved, so as to throw some light on the diastereomeric transition states.

The variation of stereoselectivity, sometimes very pronounced, which is observed (Figure 1) passing from the dimethylamino to the piperidino derivatives is indicative of the presence in the transition state of coordinated nitrogen. The effective difference of steric requirements between $CH_2N(CH_3)_2$ and $CH_2N(CH_2)_5$ seems to us less important than the different availability for the coordination of the nitrogen lone pair. The 1-3 diaxial interactions between the piperidine ring and the coordinated group, which are absent in the dimethylamino derivatives, could in fact induce conformational changes of the ring, thus leading to other forms of transition state. In this respect it is noteworthy that the $LiAlH_4$ reduction of a series of asymmetric α-dialkylamino ketones affords large changes of stereoselectivity depending on the structure of the dialkylamino moiety.[5] Further evidence of the presence of N-coordinated transition states is given in the hydride reduction of some aziridinyl ketones[6] and 2-dialkylaminocyclohexanones.[7]

The influence of the R substituent on stereoselectivity can be related with the increasing steric requirements passing from R = Me to CH_2Ph to Ph, although such a trend is affected by the nature of the reducing agent. In the reactions with $LiAlH_4$ a deviation from the "regular" sequence observed with the alkoxy hydrides is afforded for the benzyl derivatives **2** and particularly when the piperidino group is also present in the substrate (**2b**).

The similar diastereomeric ratios afforded by TMH and TBH suggest that the alkoxy hydrides have comparable effective bulk, different from the one exhibited by $LiAlH_4$. Analogous behavior was observed in the reduction of some cycloalkanones with $LiAlH_4$ and with a large number of trialkoxy hydrides.[8] In particular, we have found that the alkoxy hydrides appear to be more selective ("larger") than $LiAlH_4$ when R = CH_2Ph, whereas generally smaller selectivities are observed when R = Me. This can be interpreted assuming that the alkoxy hydrides have a "long-range" larger hindrance and a "short range" similar or

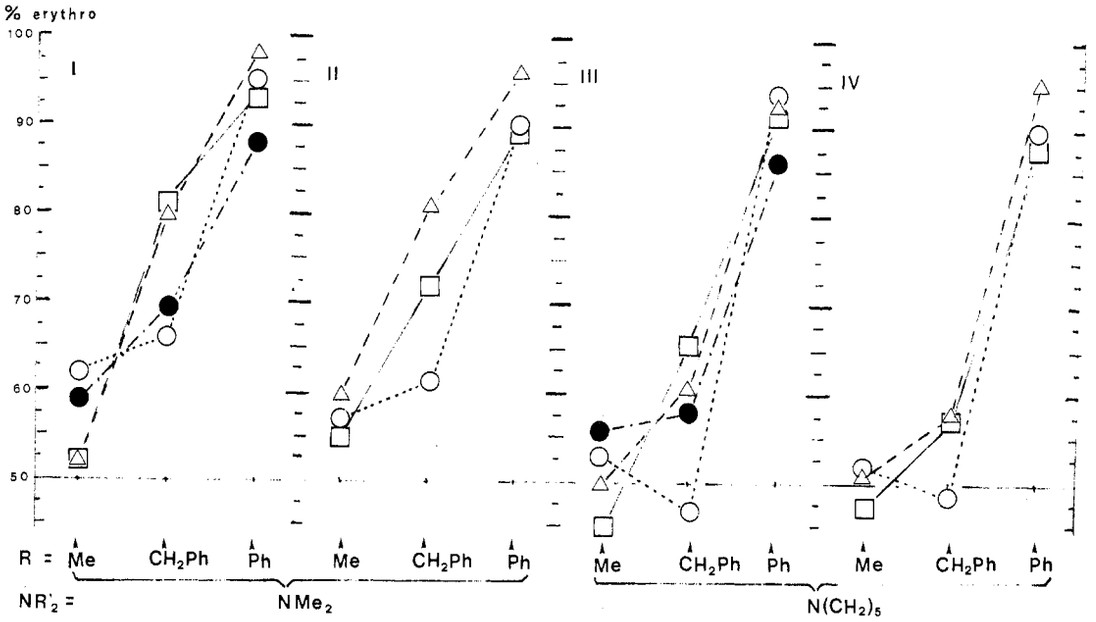


Figure 1. Dependence of stereoselectivity on the R substituent and NR_2' group in the hydride reductions of the amino ketones 1-3 (mean values from Table I) (I and III at 0°; II and IV at reflux): ●-·-·-·, $LiAlH_4$ in Et_2O; ○·····, $LiAlH_4$ in THF; □———, TBH in THF; △------, TMH in THF.

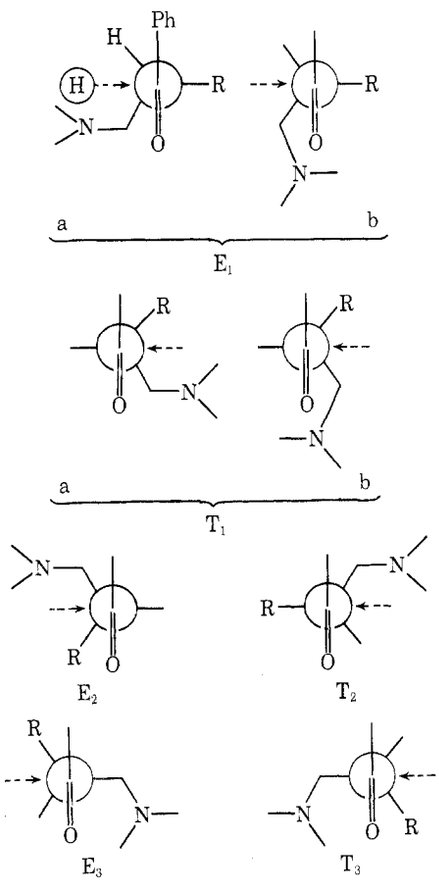
smaller hindrance with respect to $LiAlH_4$. Thus, when R = CH_2Ph (a large group at "long range") the alkoxy hydrides exhibit higher selectivity than $LiAlH_4$. When, on the contrary, R = Me (a smaller substituent) the alkoxy hydrides exhibit analogous or lower selectivity than $LiAlH_4$. The phenyl derivatives **3a,b** afford in all the cases high diastereomeric ratios owing to the large steric requirement of the phenyl group, which levels any difference among the reducing species.

Carbonyl systems containing heteroatoms are expected[3] to afford strong variations of stereoselectivity associated with changes of solvent. Such variations are observed in our $LiAlH_4$ reductions which resulted in effects largely dependent on the substituents. This is again particularly evident for the benzyl piperidino derivative **2b.**

We have also investigated how the stereoselectivity is affected by changes of the hydride concentration. It is known[9] that TBH in THF is monomeric over the entire range of concentrations investigated and that both $LiAlH_4$ and TMH display an increasing degree of association as the concentration increases. Our results (Table I) show very small selectivity variations with the dilution (usually within the limit error), thus demonstrating, reputing as unlikely an equal steric requirement by both monomeric and polymeric species, that the reactant in THF is always monomeric in the transition state. $LiAlH_4$ in Et_2O has been reported[10] as dimeric in the range 0.1-0.4 *M*. In this case we can only say that the reducing agent is always in the same state of aggregation, but it cannot be ascertained whether it is in the monomeric form or dimeric form.

A discussion on the diastereomeric transition states of the reduction should take in account the considerations above made, such as, mainly, (a) the participation, in some way, of coordinated nitrogen, (b) the monomeric state (at least in THF) of the reducing agents, and (c) the remarkable effects of the solvent. Such discussion would, however, require, to be well defined, the knowledge of several data which at the moment are unavailable. A first problem is, for example, whether the same molecule of reagent coordinates simultaneously both amino and carbonyl group and, in this case, whether one of both of the metal atoms are engaged. This would lead to stabilization of those conformations in which the nitrogen atom is close or far away, respectively, with respect to the carbonyl oxygen. Another problem is whether the hydride enters through an inter- or intramolecular mechanism.

If we assume that the torsional strain in the transition state tends to a minimum,[11] the following conformers of the substrate can be depicted.



(E and T forms afford erythro and threo diastereomers, respectively, according to the depicted direction of attack.)

Such forms allow either the coordination between nitrogen and carbonyl oxygen (in forms E_2 and T_2 the simultaneous participation of both Li and Al would be requested) or the anchimeric assistance by the coordinated nitrogen toward the entering species (E_{1a}, T_{1a}, E_2, T_2).

Although it is difficult to determine what forms are important in affecting the diastereomeric ratios, E_{1a} appears, however, to show the minimum of interactions both in the substrate and between the reacting species. It could be therefore responsible for the generally observed predominance of the erthro amino alcohols, but does not explain how the substituent R affects the stereoselectivity of the reaction. For this reason, it is necessary to envisage the participation to the transition state of other forms which allow for the possibility of interaction between R and entering species (*e.g.*, T_1, E_2, etc.).

Another important interaction can occur in some forms (*e.g.*, E_{1b}, T_{1a}, etc.) between R and the *N*-alkyl groups, particularly when in the molecule are present substituents as CH_2Ph and piperidino. Such groups could in fact strongly interact at long distance from the reaction center in rigid and "curled" conformations of the transition state. This could explain the deviations from the "regular" sequence observed in the $LiAlH_4$ reductions, especially when in the substrate are simultaneously present both benzyl and piperidino group. The above forms are therefore to be considered more important when R and/or the dialkylamino group have smaller steric requirements (*e.g.*, R = Me, amino group = NMe_2).

In conclusion it appears that the stereochemical course of the reaction cannot be interpreted on the basis of only one transition state. A number of different conformations could in fact be stabilized or destabilized by the concomitant intervention of steric and polar interactions and therefore participate with different weights in the overall diastereomeric balance.

Experimental Section[12]

Materials. The amino ketones **1–3** and the amino alcohols **4–6** were previously described and characterized.[2h]

Solvents diethyl ether and tetrahydrofuran (THF) were purified by refluxing over sodium wire, followed by distillation from lithium aluminum hydride under a nitrogen atmosphere.

The lithium aluminum hydride (Fluka A.G.) and lithium tri-*tert*-butoxyaluminum hydride (Fluka A.G.) solutions were prepared by stirring slurries for 1 day, followed by removal of solids by filtration. Lithium trimethoxyaluminum hydride in THF was prepared by slow addition of the calculated amount of absolute MeOH[13] to $LiAlH_4$ solutions of the required concentration in THF.[14]

The hydride solutions were then stored under a nitrogen atmosphere in the apparatus devised by Dillard,[15] from which the required aliquots may be exactly withdrawn, and titrated by the iodometric method described by Felkin.[16]

Reduction Procedure. A 0.2 *M* solution of the amino ketone was added by a dropping funnel, under a nitrogen flow, to the hydride solution (ratio hydride ion/amino ketone = 4:1, *i.e.*, molar ratio $LiAlH_4$/amino ketone = 1:1 or alkoxy hydride/amino ketone = 4:1). An inverted order of addition was found to be convenient when the required volume of hydride solution was so small as to prevent a regular reflux of the solvent.

The mixture was kept at the desired temperature (by ice cooling or refluxing the solvent) for 1 hr (for the exceptions see Table I) and then cautiously hydrolyzed with H_2O under cooling. After filtration of the inorganic material, the THF solutions were diluted with aqueous HCl and the organic solvent was evaporated under reduced pressure. The residual solution was then made alkaline with 10% aqueous NaOH and ether extracted. The ethereal solution was finally dried (Na_2SO_4) and evaporated to give the crude reaction mixture, which was submitted to nmr analysis.

Every reaction was repeated at least twice in order to check the reproducibility of the diastereomeric ratios.

Nmr Determinations. Nmr spectra were performed on a Jeol C60-HL spectrometer, using CCl_4 as solvent ($CDCl_3$ for the compounds **5a**) with TMS as internal standard.

The relative amounts of diastereomeric amino alcohols were directly determined by integration of the H-C(1) signals.[2h]

The amount of unreacted amino ketone was analogously dosed, when present, by integration of the signals due to the aromatic protons ortho to the carbonyl group, which appear at lower field with respect to all the remaining aromatic protons of the mixture. For the α-phenyl derivatives a complication arose, owing to superimposition between the resonance of the proton α to the carbonyl group of the unreacted amino ketone (**3a,b**) and the resonance due to the H-C(1) protons of the amino alcohols (**6a,b**). The determination was then made possible by repeated treatments, at room temperature for several hours, of the reaction mixture in THF with NaOD–D_2O, until complete deuteration of the α proton of the amino ketone was obtained.

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Registry No.—**1a,** 51371-02-9; **1b,** 51371-03-0; **2a,** 51293-59-5; **2b,** 51293-60-8; **3a,** 51293-61-9; **3b,** 51293-62-0; $LiAlH_4$, 16853-85-3; TMH, 12076-93-6; TBH, 17476-04-9.

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