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STEREOCHEMISTRY OF MANNICH BASES—V*

LITHIUM ALUMINIUM HYDRIDE REDUCTION OF α-ASYMMETRIC-β-AMINO PROPIOPHENONES AND RELATIVE CONFIGURATION OF THE CORRESPONDING AMINO-ALCOHOLS

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Abstract—The reduction by LAH of α-asymmetric-β-amino propiophenones is stereospecific and affords the erythro amino-alcohols as predominant diastereomers. The configurations of these amino-alcohols have been assigned by correlation of IR and NMR spectra, from which their preferred conformations have been also deduced.

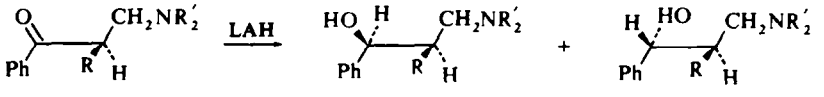
IT IS well known that in the reduction of α-asymmetric ketones bearing polar groups such as OH, OMe and NH_2 attached to the asymmetric centre, a "cyclic model" in many cases allows the prediction of the predominant diastereomer resulting from the reaction, on the basis of Cram's Rule of "Steric Control of Asymmetric Induction".[2, 3]

In the reduction of β-hydroxy and β-methoxy asymmetric ketones by means of organo-metallic compounds, Leitereg and Cram[4] correlated the results in terms of competition between "polar" and "open chain" models (for β-hydroxy compounds) and "cyclic" and "open chain" models (for β-methoxy compounds).

More recently, Jacques *et al.*[5] reported that in order to explain the results obtained in the LAH reduction of β-amino-ketones $\diagdown\!\!\diagup N{-}CH(R){-}C(R'')_2{-}COR'$, it would be necessary to take into consideration a particular model of the transition state in which not only steric factors are considered determinant.

The present paper reports the results of the LAH reduction of the α-asymmetric-β-amino propiophenones I–III (Chart 1 and Table 1) and the configurational assignment of the diastereomeric amino alcohols (IV–VI) by means of IR and NMR correlations.

CHART 1‡



I-III (a,b) erythro IV-VI (a,b) threo IV-VI (a,b)

I, IV: R = Me
II, V: R = CH_2Ph
III, VI: R = Ph

a: NR'_2 = NMe_2
b: NR'_2 = Piperidino

‡ Only one enantiomer of the racemic pair is here represented.

* Part IV, see Ref 1.

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The relative amounts of diastereomeric amino alcohols were determined on the crude reaction product by integration of H^1 NMR signal (Table 3). Erythro and threo amino alcohols have different chemical shifts for their H^1 peaks and these bands were used for the analyses.

TABLE 1. PERCENTAGE OF THE ERYTHRO ISOMER IN THE MIXTURE OF ERYTHRO AND THREO AMINO ALCOHOLS Ph—CH(OH)—CH(R)—$CH_2NR'_2$

Comp	R	NR'_2	% Erythro*
IVa	Me	NMe_2	60†
IVb	Me	Pip	58
Va	CH_2Ph	NMe_2	54
Vb	CH_2Ph	Pip	59
VIa‡	Ph	NMe_2	86
VIb‡	Ph	Pip	78

* ±3 for compounds IV and V; ±4 for compounds VI.
‡ Only the erythro forms were isolated.

The predominance of the erythro isomer, which is always observed, is predictable by the Cram's Rule if the "cyclic model" (6-membered chelated ring due to coordination between the reducing agent and the heteroatoms and approach of the entering group from the least hindered side of the carbonyl) is applied.

As, however, the "open chain" model for II and III also can lead to the same qualitative results (assuming the R groups, benzyl and phenyl, to be greater in effective bulk than $CH_2NR'_2$) it is questionable if any conclusions about the transition states can be drawn, in the absence of a better knowledge of the reagents and their behaviour.**

Configurations of amino-alcohols (IV–VI)

The absolute (and therefore also the relative) configurations of the amino alcohols (erythro-IVa and erythro- and threo-IVb) were reported in a previous paper.[6] In the present work the configurational assignment of the remaining compounds is based on the correlation of their IR and NMR spectra according to previous procedures.[5,9,10] Erythro-VIa is the only amino alcohol of known configuration[11] and its structure is here confirmed. Erythro-IVa[12] and erythro-VIb[13] are described in the literature but their configurations are not reported.

IR spectra (Table 2) show that such amino alcohols exist, in CCl_4, in intramolecularly H-bonded conformations: in fact, even at low concentrations ($\sim 5 \cdot 10^{-3}$M), it is possible to observe a band at 3617–3629 cm^{-1} attributable to "OH free" stretching and a broad band in the range 3250–3170 cm^{-1} attributable to "OH bonded" stretching.

† Erythro-IVa is not afforded in 100% yield as previously described,[6] but only as the predominant diastereomer. In this connection, the catalytic hydrogenation of α-methyl-β-dimethylamino and α-methyl-β-piperidino propiophenones Ia and Ib has been investigated to obtain a better understanding of the discrepancies observed with the data of other Authors[7] (Experimental).

** Work is in progress concerning the influence on the stereospecificity of such factors as concentration and nature of the reagents and presence of agents capable of complexing the metal hydride.

$\Delta\nu_{OH}$ and $\varepsilon_{OH(b)}/\varepsilon_{OH(f)}$ values are in agreement with the data previously reported for analogous compounds[5, 10b] and their correlation makes an unambiguous configurational assignment possible.

Since in the known compounds IVa and IVb, $\Delta\nu_{OH}$ and $\varepsilon_{OH(b)}/\varepsilon_{OH(f)}$ values are higher for the threo isomer, the threo configuration was attributed (for all the diastereomeric pairs) to the amino alcohol with higher $\Delta\nu_{OH}$ and $\varepsilon_{OH(b)}/\varepsilon_{OH(f)}$ values. This means

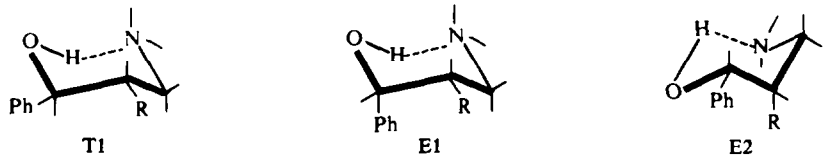
TABLE 2. IR DATA OF THE AMINO ALCOHOLS Ph—CH(OH)—CH(R)—$CH_2NR'_2$*

Comp	R	NR'_2	$\Delta\nu_{OH}$†	$\varepsilon_{OH(b)}/\varepsilon_{OH(f)}$	Conf
IVa	Me	NMe_2	377	2·3	erythro
			409	8·9	threo
IVb	Me	Pip	390	5·6	erythro
			436	15·9	threo
Va	CH_2Ph	NMe_2	383	3·0	erythro
			427	8·0	threo
Vb	CH_2Ph	Pip	394	6·1	erythro
			459	10·9	threo
VIa	Ph	NMe_2	388‡	2·9	erythro
VIb	Ph	Pip	399	5·1	erythro

* Spectra carried out in CCl_4 (conc 4·9 – 8·0 10^{-3}M) with quartz cells (thickness: 2 cm).
† Difference between "OH free" and "OH bonded" stretchings in cm^{-1}.
‡ Ref 11 reports 385 and 440 for erythro and threo VIa, respectively.

that threo H-bonded conformers must be more energetically favoured than the corresponding erythro conformers. This point of view is in fact confirmed by a simple inspection of the chelated species (as "quasi-chair" conformers) (Chart 2) which immediately reveals that T1, with R and Ph both in "quasi-equatorial" positions, has less severe steric interactions than E1 and E2, and is therefore energetically favoured.[10a] The assignment of threo configuration to the diastereomers with higher

CHART 2



$\varepsilon_{OH(b)}/\varepsilon_{OH(f)}$ values (i.e. with higher relative percentage of "bonded" species) is therefore justified.**

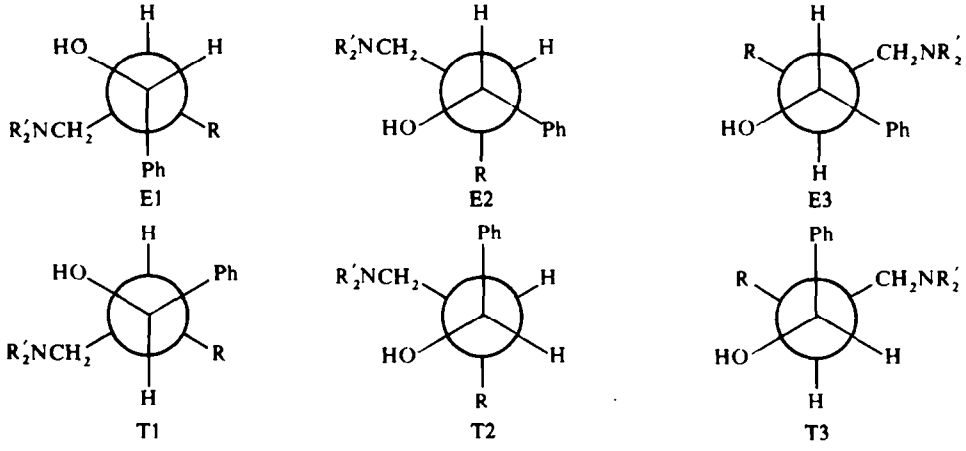
The same assignment, made on the basis of $\Delta\nu_{OH}$ values, although possible for such compounds, may not be equally correct, since the $\Delta\nu_{OH}$ value reflects the enthalpy of the H-bond and not strains existing in other parts of the molecule, or entropy effects in general.[9b]

** Portoghese and Smissman[14] assigned the threo configuration to that of the two epimeric 1(4-methoxyphenyl)-2-methylpropane-1,3-diols which was found to possess the higher $\varepsilon_{OH(b)}/\varepsilon_{OH(f)}$ value. See also Ref 5.

It is moreover noteworthy that IR spectra of compounds erythro-VIa and VIb show a third band at 3579 cm^{-1} attributable to intramolecular OH···π bonding between the OH group and the π electrons of the R (=Ph) group. Such behaviour was previously reported for the similar erythro-3-amino-1,2-diphenylpropanol (OH···π band at 3590 cm^{-1}),[11] erythro-2-amino and 2-methylamino-1,2-diphenylethanols (at 3590 and 3585 cm^{-1}, respectively)[11] and for the series erythro-2-morpholino, -piperidino, -pyrrolidino and -dimethylamino-1,2-diphenylethanols (at 3590, 3595, 3575 and 3590 cm^{-1}, respectively).[15] It is therefore necessary to take into account the participation of E3 (R = Ph) (Chart 3), in which the possibility of OH···π bonding exists, in the conformational equilibrium of erythro VIa and VIb.

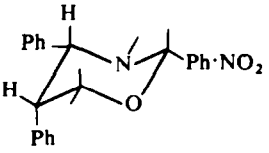
NMR spectra (Table 3) also allow an unequivocal configurational assignment. Since, in fact, the known compounds erythro-IVa and IVb show lower field resonance signals due to the H^1 proton and smaller $J_{H^{(1)}H^{(2)}}$ values than the corresponding threo-IVa and IVb isomers, erythro or threo configuration was consequently attributed to the remaining amino alcohols.* Such assignment is in agreement with the results obtained from the IR spectra.

CHART 3

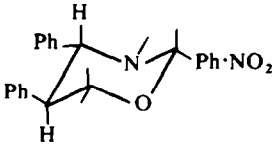


From the experimental J_{vic} values it is possible to argue *gauche* and *trans* relationships between H^1 and H^2 protons respectively in erythro and threo isomers. The "pure" J_g and J_t values previously used in order to determine in similar compounds the percentages of *gauche* and *trans* conformers were 2 and 12,[9e, 17] and 2·6 and 10·3[18] c/s. Since compounds IV–VI in the intramolecularly H-bonded conformations (Chart 2) are related to tetrahydro-1,3-oxazines as "model" molecules, it seems reasonable to assume that J_g and J_t for "bonded" conformers are close to 2 and 9 c/s, respectively, in agreement with the reported data for the oxazines VII and VIII in $CDCl_3$ (J_{ea} = 4·5 and J_{aa} = 10·2)[19] and IX and X in CCl_4 ($J_{3e4a} = J_{3e4e} = 3$; $J_{3a4e} \simeq 1$ and $J_{3a4a} = 8·5$).[20]

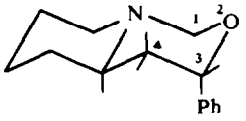
* Although the use of J_{vic} as a criterion for configurational assignment may be unreliable,[9d, e] owing to different conformational preferences, the correlation of J values seems reasonable for the above compounds, since they form a fairly homogeneous series.



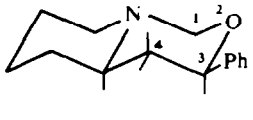
VII



VIII



IX



X

TABLE 3. NMR DATA OF THE AMINO ALCOHOLS $Ph-\underset{OH}{\underset{|}{CH^1}}\underset{R}{\underset{|}{CH^2}}-CH_2NR'_2$*

Comp	R	NR'_2	$\delta_{H^{(1)}}$	$J_{H^{(1)}H^{(2)}}$	Conf
IVa	Me	NMe_2	4·70	2·5	erythro
			4·25	8·3	threo
IVb	Me	Pip	4·66	3·0	erythro
			4·22	8·5	threo
Va	CH_2Ph	NMe_2	4·86	2·0	erythro
			4·43	7·2	threo
Vb	CH_2Ph	Pip	4·79	2·5	erythro
			4·40	7·5	threo
VIa	Ph	NMe_2	4·93	3·5	erythro
			4·7†	8·3†	threo
VIb	Ph	Pip	4·90	3·6	erythro
			4·7†	8·6†	threo

* Spectra carried out at 60 MHz in CCl_4 with TMS as internal standard. $\delta_{H^{(1)}}$ and $J_{H^{(1)}H^{(2)}}$ values in ppm and cps respectively.

† Approximate values obtained from spectra of the crude reaction product.

Therefore, from the results quoted in Table 3 it can be deduced that erythro-IV (a,b) and V (a,b) reside preferentially in the E1 and/or E2 "bonded" and "non-bonded" conformations (Chart 3), whereas for erythro compounds VIa and VIb the increase of J_{vic} is due to the participation in the equilibrium also of conformer E3 (H^1 and H^2 *trans*), in agreement with the IR results indicative of OH···π bonding.

In the threo series, on the contrary, rotamer T1 is to be considered the most populated. The lowering of J_{vic} for the benzyl derivatives V is attributable to an increase of the contribution of the "non-bonded" T2 conformer (more energetically favoured than T3) with *gauche* H^1 and H^2 protons.

EXPERIMENTAL

IR spectra were determined on a Perkin–Elmer Model 225 Spectrophotometer, NMR spectra on a Varian A-60A or on a Jeol C60-HL spectrometer, and optical rotations on a Bendix N.P.L. Automatic Polarimeter. M.ps are uncorrected.

α-Asymmetric-β-aminopropiophenones (I–III). Compounds Ia,[16] Ib,[16b], IIa and IIb,[21] IIIa[22] and IIIb[23] were prepared and purified as described.

General LAH reduction method of the α-asymmetric-β-aminopropiophenones I–III. Into a magnetically stirred suspension of LAH (about 0·02 mol) in dry ethyl ether (50 ml) an equimolecular amount of an ethereal soln of the amino ketone (100 ml) was added dropwise. The mixture was refluxed for 1 hr and then cooled in an ice-bath and cautiously hydrolysed with water. The ethereal layer, washed and dried, gave, after removal of the solvent, the crude mixture of diastereomeric IV–VI (yields ⩾ 90%).

The integrated areas ratios of the H^1 signals (Table 3) were obtained directly from the NMR spectra of the crude reaction products in CCl_4 (approximately 30% w/v). From such ratios the diastereomeric percentages were then determined.

The mixtures of amino alcohols were separated by fractional crystallization from light petroleum. Erythro isomers are less soluble and were always obtained first. A further purification was by crystallization of the hydrochlorides from EtOH, or EtOH–AcOEt, until the diastereomeric purity, checked by NMR, resulted within the error of the method employed. Table 4 reports characteristics and elemental analyses of the amino alcohols obtained.

TABLE 4. MPS AND ELEMENTAL ANALYSES OF THE AMINO ALCOHOLS Ph—CH(OH)—CH(R)—$CH_2NR'_2$

Comp	R	NR'_2	Conf.	free base m.p.	hydrochl. m.p.	Elem. anal. of hydrochl. C%	H%	N%
IVa	Me	NMe_2	erythro[a]	87–89°	168–170°	62·73	9·15	6·18
			threo	—	96–98°[b]	62·57	8·89	5·96
						calc 62·73	8·78	6·10
IVb	Me	Pip	erythro	50–51°	233–235°	66·47	9·03	5·10
			threo	—	171–173°	66·91	9·07	5·29
						calc 66·77	8·97	5·19
Va	CH_2Ph	NMe_2	erythro	136–137°	228–229°	70·99	7·95	4·64
			threo	62–63°	155–157°	70·39	7·97	4·62
						calc 70·68	7·91	4·58
Vb	CH_2Ph	Pip	erythro	98–99°	233–235°	73·18	8·16	4·11
			threo	104–105°	149–151°	73·20	8·25	4·11
						calc 72·91	8·16	4·05
VIa	Ph	NMe_2	erythro[c]	98–100°	213–214°	69·92	7·51	4·92
						calc 69·97	7·60	4·81
VIb	Ph	Pip	erythro[d]	91–92°	263–264°	72·57	7·85	4·31
						calc 72·37	7·90	4·22

[a] Lit.[12]: free base, m.p. 88–89°; hydrochloride, m.p. 170–171°.
[b] Very hygroscopic.
[c] Lit.[11]: free base, m.p. 97–98°.
[d] Lit.[13]: free base, m.p. 92·3–93·4°; hydrochloride, m.p. 264·5–265·5°.

Catalytic hydrogenation of optically active α-methyl-β-dimethylamino and α-methyl-β-piperidinopropiophenones (Ia and Ib). (−)-α-Methyl-β-dimethylaminopropiophenone dibenzoyltartrate[8] (optically impure), dissolved in dil HCl, was shaken with ethyl ether and the aqueous layer, containing (+) Ia hydrochloride, was reduced with PtO_2 and H_2 as described.[7] The reaction mixture was analyzed by NMR (erythro/threo

ratio: 65/35) and then submitted to fractional crystallization from light petroleum. The two epimers obtained were furtherly purified, as hydrochlorides, by crystallization from EtOH which afforded (+) erythro-IVa hydrochloride, m.p. 160–164°; $[\alpha]_D^{21}$ +22·5° (MeOH),* 0° (H_2O) and (−) threo-IVa hydrochloride (very hygroscopic), $[\alpha]_D^{21}$ −30·6° (MeOH), −29·5° (H_2O); dibenzoyltartrate: m.p. 168° (dec). (Found: C, 65·62; H, 5·91; N, 2·70. $C_{30}H_{33}NO_9$ requires: C, 65·32; H, 6·03; N, 2·54%).

Incidentally, being *S* and 1*R*,2*S* the configurations of (+) Ia hydrochloride[8] and of (+) erythro 1-phenyl-2-methyl-3-dimethylaminopropan-1-ol hydrochloride (IVa),[6] respectively, (−) threo-IVa hydrochloride has therefore the 1*S*,2*S* configuration.

The reduction of (+) Ib hydrochloride[8] afforded analogously (+) erythro-IVb hydrochloride (68%), m.p. 223–225°; $[\alpha]_D^{21}$ +21·7° (MeOH),[6] −4·5° (H_2O) and (−) threo-IVb hydrochloride (32%), m.p. 141–143°; $[\alpha]_D^{21}$ −20·9° (MeOH),[6] −32·2° (H_2O).

The incomplete stereospecificity of the reaction, the dependence of the magnitude of the optical rotations on the solvent and the opposite sign shown by erythro and threo isomers all can be factors responsible of the discrepant data reported in the literature (see footnotes on Ref 6).

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* The data reported in Ref 6 for the same compound were obtained from a starting material with higher optical purity.

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