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STEREOCHEMISTRY OF MANNICH BASES—IV

STEREOSPECIFIC SYNTHESIS AND CONFIGURATIONS OF DIASTEREOISOMERIC 3-AMINO-PROPAN-1-OLS*

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Abstract—Reactions between Grignard reagents and a number of α-asymmetric β-amino-ketones were found in all cases to be highly stereospecific. All the phenylketo-bases reacted with methylmagnesium derivatives yielding only one of the two possible diastereoisomeric 1-phenyl-1-methyl-3-amino-propan-1-ols, while the corresponding methylketo-bases reacted with phenylmagnesium halides yielding in very high prevalence the other diastereoisomer.

The diastereoisomer ratios were determined and the steric configurations were assigned. The results are discussed on the basis of a cyclic model.

MANY investigators have studied the reaction between β-amino-ketones and Grignard reagents in order to obtain 3-aminopropanol derivatives, which often exhibit pharmacological properties.[1] Stereospecificity of the reactions involving asymmetric β-amino-ketones was frequently observed and the steric configuration of the products was occasionally determined.[1e]

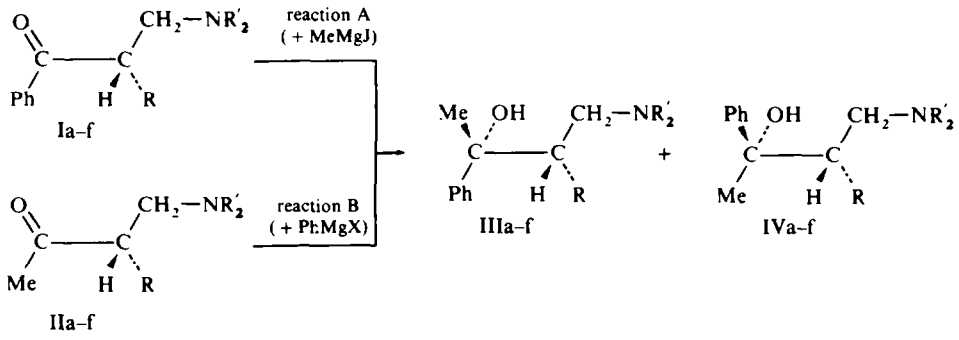
In our previous paper,[2] we studied the stereospecific synthesis of diastereoisomeric 1-phenyl-1,2-dimethyl-3-dimethylamino-propan-1-ols (IIIa and IVa) by the reaction of suitable Grignards on α-methyl-β-dimethylamino-propiophenone (Ia) or amino-butanone (IIa). These reactions showed a stereospecificity not commonly detectable in analogous derivatives, and the steric configurations of the resulting diastereoisomeric amino-alcohols were found to be in agreement with the hypothesis of a cyclic model.

In the present work we examined a series of analogous α-asymmetric-β-amino-ketones to study the effects of substituents on the reaction stereospecificity and to determine the steric configurations of the products.

The reactions on dimethylamino- and piperidino-phenylketo-bases (Ia–f) containing various substituents α to the carbonyl-group were carried out with methylmagnesium iodide (reaction A); analogous reactions on the corresponding methylketo-bases (IIa–f) were then carried out with phenylmagnesium bromide to obtain in both cases the same pair of possible diastereoisomers. Phenylmagnesium chloride and iodide were also used with the methylketo-bases (IIa and IIb), to see whether variations in the Grignard reagent affects the stereoselectivity (reaction B).

The results are collected in Tables 1 and 2.

* Part III, by L. Angiolini and G. Gottarelli, *Tetrahedron* **26**, 421 (1970)



R = Me, CH_2–Ph, Ph; NR'_2 = NMe_2, $N(CH_2)_5$ (as in Table 1).
X = Cl, Br, J (as in Table 2).
Note—Only one enantiomer of the racemic pairs is here represented.

Table 1 shows that all the phenylketo-bases (I) gave a completely stereospecific reaction, yielding amino-alcohols (III). The methyl-keto-bases (II) also gave in general a very high, although not complete, stereospecificity, yielding mainly amino-alcohols (IV), diastereoisomeric with III. Furthermore, in the series of phenylketo-bases (Ia–f), variation either of the substituent at the asymmetric center or of the alkylamine group did not affect the reaction stereospecificity. In the series of the methylketo-bases (IIa–f) variation of the substituent R and of the alkylamine group did have a small effect: except for the benzyl derivative (IIc), phenyl-substituted Mannich bases (IIe, f) gave in general higher diastereoisomer ratios than the corresponding methyl and benzyl derivatives (IIa, b, d), and no differences between dimethylamine and piperidine derivatives were observed.

Finally, a change of the halogen in the Grignard reagent, which affected strongly the stereochemistry of the reaction in other analogous systems,[3] in this case gave only a very small variation in diastereoisomer ratios (Table 2).

The steric configurations of the diastereoisomeric amino-alcohols (IIIb–f and IVb–f) were assigned by correlation with the amino-alcohol (IIIa) and the amino-alcohol (IVa) respectively.[2] In the IR spectra of all the compounds (IIIb–f), as in the spectrum of IIIa, two characteristic bands appear near 910 and 925 cm^{-1}. Analogously, all the compounds IVb–f, like IVa, show one characteristic band near 900 cm^{-1} (Fig. 1). Although not assigned, these bands seem suitable for the purpose, being slightly affected by changes in the substituents R and R′ of the amino-alcohols.

It follows that the amino-alcohols (IIIa–d) have a *R,S/S,S*, and IIIe, f a *R,R/S,S* configuration, while the amino-alcohols (IVa–d) have a *R,R/S,S* and IVe, f a *R,S/S,R* configuration.

Examination of the diastereoisomeric ratios reveals that variations either in the amino-ketone or in the organomagnesium reagent did not give rise to strong variations in the reaction stereospecificity; on the other hand, examination of the steric configurations of the predominant diastereoisomer demonstrates that either in reactions A or B, the organic group always approaches the carbonyl group from the same side of the C—CO—C plane.

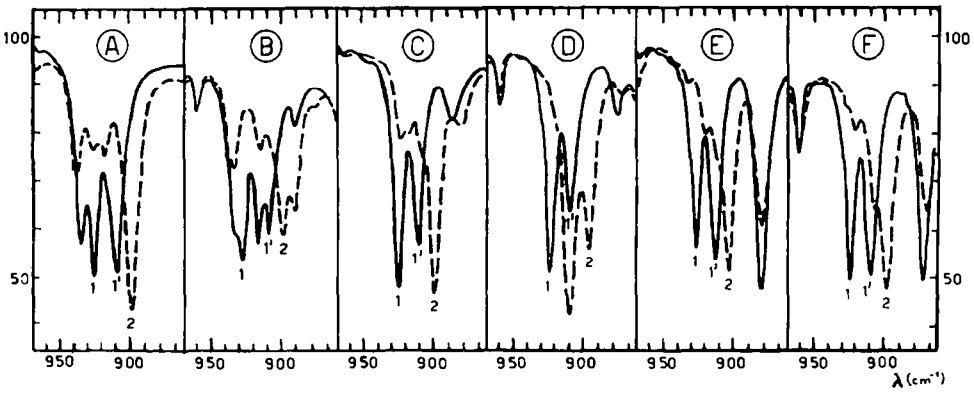
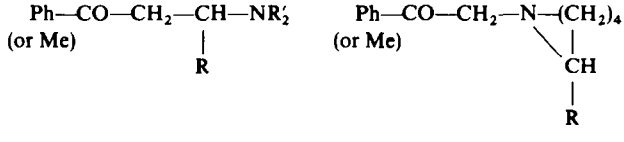


FIG. 1. IR spectra of the amino-propanols (III) ——— and (IV) – – –; characteristic bands of the diastereoisomers are indicated:

	Comp.	bands 1, 1' (cm^{-1})	Comp.	band 2 (cm^{-1})
(A)	(IIIa)	910, 926;	(IVa)	900
(B)	(IIIb)	909, 927;	(IVb)	899
(C)	(IIIc)	910, 925;	(IVc)	900
(D)	(IIId)	910, 925;	(IVd)	896
(E)	(IIIe)	912, 926;	(IVe)	901
(F)	(IIIf)	910, 925;	(IVf)	898

These facts seem to be in agreement with the hypothesis of a cyclic model in which the Mg atom of the Grignard coordinates both the carbonyl oxygen and the amine nitrogen; the entering organic group then approaches the carbonyl from the side opposite to the R group. An open-chain model, on the contrary, does not explain the observed results. For example, in the case R = CH_2—Ph, the R group and the CH_2—NR'_2 group would have a similar bulk, and the very high stereospecificity observed for the benzyl-substituted keto-bases (Ic, d) and (IIc, d) would be very difficult to explain. Moreover, an open-chain model in which the amine group is coordinated to a second molecule of the Grignard reagent is not in accord with our results. Thus, the CH_2—NR'_2(Mg-complex) should be always the large-group among H, R, CH_2—NR'_2(Mg-complex), for any R substituent; but such a model would result in opposite diastereoisomeric ratios to those observed in this work (see also Cram *et al.*[3, 4]).

In order to confirm the hypothesis of the cyclic model and to examine closely the stereochemistry of these reactions, we have also begun to study amino-ketones (V and VI), in which the inducing asymmetric center is in the β-position or, further away from the reactive center, in the alkylamine group:



V VI

The first results show a high stereospecificity (diastereoisomer ratios 0·5–0·15),* in general not lower to that observed in the α-asymmetric methyl-keto-bases (IIa–f).

* Unpublished data; This work is still in progress.

TABLE 1. DIASTEREOISOMERIC RATIOS OF 1-PHENYL-1-METHYL-3-AMINO-PROPAN-1-OLS (III) AND (IV), MADE BY THE ADDITION OF ORGANOMAGNESIUM DERIVATIVES TO 3-AMINO-PROPIOPHENONES (I) OR 4-AMINO-BUTAN-2-ONES (II)

	Keto-base	Organo-magnesium reagent	Diastereoisomer amino-alcohols (III) and (IV)				
			% Yield (III) + (IV)[a]	% (III) in the mixt.[b]	% (IV) in the mixt.[b]	(III)/(IV)	Analytical method[c]
(a) R = Me, $NR'_2 = NMe_2$	I	MeMgI	92	100	0	> 32	GLC
	II	PhMgBr	70	14	86	0·16	GLC
(b) R = Me, $NR'_2 = N(CH_2)_5$	I	MeMgI	91	100	0	> 32	GLC
	II	PhMgBr	72	14	86	0·16	GLC
(c) R = CH_2—Ph, $NR'_2 = NMe_2$	I	MeMgI	94	100	0	> 32	IR
	II	PhMgBr	80	0	100	< 0·03	IR
(d) R = CH_2—Ph, $NR'_2 = N(CH_2)_5$	I	MeMgI	88	100	0	> 32	IR
	II	PhMgBr	60	12	88	0·14	IR
(e) R = Ph, $NR'_2 = NMe_2$	I	MeMgI	96	100	0	> 32	IR
	II	PhMgBr	65	8	92	0·09	IR
(f) R = Ph, $NR'_2 = N(CH_2)_5$	I	MeMgI	92	100	0	> 32	IR
	II	PhMgBr	66	6	94	0·06	IR

[a] Calculated after elimination of the unreacted keto-base, when present.
[b] ± 3%.
[c] For GLC conditions, and IR analytical bands, see Experimental.

TABLE 2. DIASTEREOISOMER RATIOS OF 1-PHENYL-1,2-DIMETHYL-3-AMINO-PROPAN-1-OLS (IIIa, b) AND (IVa, b), BY ADDITION OF PHENYLMAGNESIUM REAGENTS TO 3-METHYL-4-AMINO-BUTAN-2-ONES (IIa) AND (IIb)

Keto-base	Phenylmagnesium reagent PhMgX	Diastereoisomer amino-alcohols (III) and (IV)			
		% Yield[a] (III) + (IV)	% (III) in the mixt.[b]	% (IV) in the mixt.[b]	(III)/(IV)
IIa	X = Cl	75	11	89	0·12
IIa	X = Br	65	14	86	0·16
IIa	X = I	60	12	88	0·14
IIb	X = Cl	71	12	88	0·14
IIb	X = Br	72	14	86	0·16
IIb	X = I	42	18	82	0·22

[a] Calculated after elimination of unreacted keto-base.
[b] ± 3%; analytical methods, as indicated in Table 1.

EXPERIMENTAL

The IR spectra were determined on 0·1 M solns in CCl_4 (0·4 mm cell) using a Beckmann IR 5 spectrophotometer. GLC determinations were made using a Fractovap Mod. GV gas chromatograph. The m.p. are uncorrected.

Mannich bases Ia–f *and* IIa–f. Mannich bases Ia and Ib,[5] Ic and Id,[6] Ie,[7] If,[8] IIa,[9] IIb,[10] IIc,[11] IIe and IIf[12] were prepared and purified as described in the literature; IId[13] was better prepared as described for the corresponding IIc[11] and, analogously, was separated from the isomeric 1-phenyl-5-piperidino-pentan-3-one by fractional crystallization of the corresponding picrates from ethanol. The picrate of IId had a m.p. of 129–130° (from EtOH). (Found: C, 55·5; H, 5·7; N, 11·8. Calc. for $C_{22}H_{26}N_4O_8$: C, 55·7; H, 5·5; N, 11·8%).

TABLE 3. 1-PHENYL-1-METHYL-3-AMINO-PROPAN-1-OLS (III) AND (IV) AND (OR) THEIR DERIVATIVES

Compound	m.p. (°C)	Crystn. solvent	Ref.	Analytical data (Calc/Found)		
				C%	H%	N%
IIIa	47–48	*a*	2			
IIIa hydrochl.	184–185	*b*	2			
IIIa picrate	188–189	*b*	2			
IIIb hydrochl.	202–204	*b*		67·7/67·8	9·25/9·2	4·95/4·95
IIIb picrate	142	*b*		55·45/55·65	5·9/6·05	11·75/11·7
IIIc	120–121	*b*		80·5/80·3	8·9/9·3	4·95/4·85
IIId	126–127	*b*		81·7/81·9	9·05/9·55	4·35/4·4
IIIe hydrochl.	197–198	*c*		70·7/69·4	7·9/8·05	4·6/4·6
IIIe picrate	176–177	*b*		57·8/58·2	9·55/9·05	11·25/11·65
IIIf	102–103	*b*	1*b*			
IVa hydrochl.	176–177	*c*	2			
IVa picrate	162–163	*b*	2			
IVb hydrochl.	164–165	*c*		67·7/67·8	9·25/9·45	4·95/5·0
IVc	58–59	*a*		80·5/80·3	8·9/9·0	4·95/4·75
IVd	80–81	*a*		81·7/82·05	9·05/9·15	4·35/4·2
IVd hydrochl.	228–229	*c*		74·4/73·75	8·4/8·7	3·9/3·8
IVe	78–79	*a*		80·25/80·1	8·6/8·75	5·95/5·45
IVe picrate	202–203	*b*		57·8/58·35	5·25/5·4	11·25/11·35
IVf	83–84[d]	*a*		81·9/81·9	9·55/9·9	4·4/4·6
IVf hydrochl.	211–213	*c*	1*b*			

[a] Light petroleum. [b] 95% ethanol. [c] Ethyl-acetate/abs. ethanol. [d] In Ref 1*b* is described as an oil.

The structure of the keto-base was finally confirmed by a positive iodoform test and by comparison of the IR spectrum with those of the corresponding IIc and of the isomers 1-phenyl-5-amino-pentan-3-ones.

Grignard reactions on the keto-bases Ia–f *and* IIa–f

Reaction A. A soln of I (0·01 mole) in Et_2O (30 ml) was added over 30 min to an ethereal soln (40 ml.) of MeMgI (0·025 mole). The mixture was then refluxed for 90 min, poured into 200 ml dil HCl, and extracted with ether. The aqueous layer, made alkaline, was extracted several times with ether. The organic layer was washed with water, dried, and freed from the solvent under reduced press. In the crude amino-alcohols no presence of unreacted keto-base was detected by the IR spectra.

Reaction B. These reactions were carried out as described above for the phenyl-keto-bases, using II and PhMg reagents (PhMgCl was prepared by refluxing Mg with a moderate excess of PhCl for 20 h and then diluting the mixture with ether).

The crude amino-alcohol mixtures sometimes contained unreacted keto-base, which was revealed by IR spectra. In such cases the unreacted ketone was removed by adding 1000–1500 ml water to the mixture, exactly neutralizing with HCl, and distilling; about 500 ml water were collected, and the residue was acidified with HCl and washed with ether. From this soln, made alkaline, the amino alcohol mixture was obtained in the usual manner.

Separation of diastereoisomers III *and* IV *from the mixtures.* Diastereoisomeric amino-alcohols III were easily obtained from the crude products of reactions A carried out on the phenylketo-bases I; when they were liquid, the products were characterized as hydrochlorides. The solvents used for crystallization are listed in Table 3.

Diastereoisomeric amino-alcohols IV were obtained from the mixtures deriving from reactions B carried out on the methylketo-bases II. Amino-alcohols IVa,[2] IVb, IVd and IVf were isolated by treating the mixtures with dry HCl in ether, followed by fractional crystallization of the resulting hydrochlorides. IVa can also be separated by fractional crystallization of the picrates; IVe, and sometimes IVd, can be obtained directly by crystallization of the amino-alcohol mixtures. Compound IVc, being the only reaction product, required no separation.

The crystallization solvents, uncorrected m.p., and analytical data are listed in Table 3.

Determination of diastereoisomeric ratios. Reaction mixtures of amino-alcohols IIIa/IVa and IIIb/IVb were evaluated by GLC, using Versamid 10% on Chromosorb W, He as the carrier gas, and temperatures of 180 and 210° respectively.

The other amino-alcohol mixtures were evaluated by their IR spectra, using the following bands (cm^{-1}): IIIc/IVc mixt, the 910, 925, 3150 bands of IIIc and the 900, 3150 bands of IVc; IIId/IVd mixt, the 700, 925, 1150, 1280 bands of IIId and the 700, 896, 1125 bands of IVd; IIIe/IVe mixt, the 912, 926, 995, 1140, 1160 bands of IIIe and the 901, 1125 bands of IVe; IIIf/IVf mixt, the 910 925, 1140 bands of IIIf and the 898 band of IVf.

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