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1,3-ASYMMETRIC INDUCTION—VI[a,b]

STEREOCHEMISTRY OF THE REACTIONS BETWEEN ORGANO-METALS AND β-ASYMMETRIC AMINO-KETONES

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Abstract—The stereochemical course of the reaction between organo-metals and β-asymmetric amino-ketones has been investigated by varying the nature of the reagent and the substituents in the substrate, as well as the distance of the amino-group from the reaction center.

The relative configurations of the diastereomeric amino-alcohols obtained were assigned, thus determining the direction of the predominant attack by the nucleophile.

The stereoselectivity was found to be strongly dependent on the factors investigated, particularly on the nature of the amino-group and of the reagent.

No single model of asymmetric induction proved to be suitable for the prediction of the stereochemical results in the above reactions.

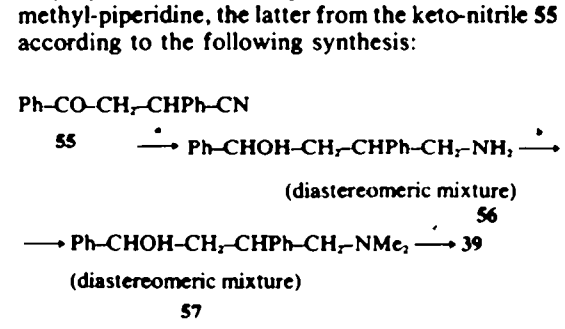
In a previous work[2] on 1,3-asymmetric induction, the reaction between LAH and a number of β-asymmetric β-amino-ketones was investigated. The stereoselectivity was found to be higher with the N,N-dialkylamino-derivatives than with N-monoalkylamino-derivatives which generally afforded diastereomeric ratios near one.

A significant point in the discussion of the above results concerned the role played by the aminic nitrogen on the stereochemical course of the reaction. We have therefore extended our research to the reactions between β-asymmetric amino-ketones and LAH or organo-metals, in order to observe the variation of stereoselectivity produced by varying both substrates (steric hindrance of the substituents, nature of the amino-group and distance of nitrogen from the reaction center) and reagent.

To this end, the substrates **1–16** and **39–42** were allowed to react with LAH, organo-lithiums and Grignard reagents (Scheme 1) giving rise, respectively, to the amino-alcohols **17–38** and **43–54**.

Each reaction proved to be stereoselective, affording a diastereomeric pair A and B which derived, respectively, from the attack on the opposite or the same side with respect to R', as depicted in Scheme 1.

Most of the amino-ketones **1–16** and **39–42** have already been described (Experimental) and were generally prepared by addition of the amine to the unsaturated ketone. A different method was adopted for the unknown compounds **42** and **39**, the former being obtained from ω-bromo-butyrophenone by nucleophilic substitution with 2-methyl-piperidine, the latter from the keto-nitrile **55** according to the following synthesis:

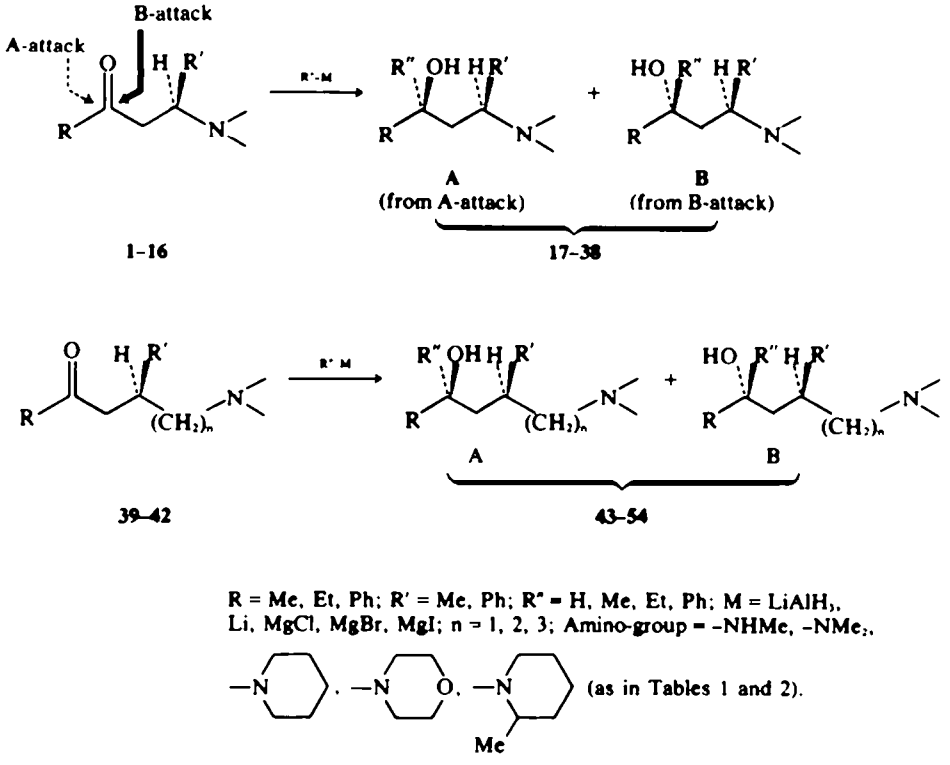


The reactions between amino-ketones and LAH or organo-metals (Scheme 1) were performed in refluxing diethylether (or at 0°, see Table 1) in the presence of excess of reagent (molar ratio, 1:3). The diastereomeric ratio of amino-alcohols was measured by GLC and/or NMR. The isomeric products were then generally isolated by fractional crystallization of their salts with the appropriate acid (Experimental).

Formation of enolates was noted, to a greater or lesser extent, in the reactions between organo-metals and amino-ketones. The starting material, as

*Note V, Ref 1.

*Note VIII of the series *Stereochemistry of Amino-carbonyl compounds*; Note VII, Ref 1.



SCHEME 1. (Only one enantiomer of the racemic pair is here represented.)

well as its decomposition products, was in fact obtained after hydrolysis in the reactions with β-amino-ketones. For the γ-, δ- and ε-amino-ketones, complete enolization was observed only with the Grignard reagents, the amino-ketone being completely recovered from the reaction.[3] In one case this was further confirmed by the Zerewitinoff method (Experimental).

Some of the aminoketones, scarcely soluble in ether, were added as a powder (or, with the same results, as a very dilute solution) to the reagent in ether. On the other hand, when THF was employed as solvent for these aminoketones, variations of the diastereomeric ratios resulted (Table 1).

Tables 1 and 2 report the percentages of A- and B-attack on, respectively, the β-amino-ketones **1–16** and on their homologous γ-, δ- and ε-derivatives **39–42**. The evaluation of the A/B ratios was made possible by the knowledge of the relative configuration of each diastereomer. Such configurational assignment (Table 3) was made by correlating the amino-alcohols with compounds of known configuration.

The NMR and GLC data of the pairs **23–24** and **29–30**, the configurations of which were previously determined by chemical methods,[1] were used for the configurational assignment to the series of 1,3-amino-alcohols **21–22**, **25–26** and **31–38**. We have in particular assigned the T structure (according to the conventional picture of Table 3) to the amino-alcohols with upfield NMR signals and lower retention times with respect to the corresponding diastereomer. IR spectroscopy was unable to distinguish between each diastereomer, owing to the too small differences between the spectral data ($\nu_{OH\ free} - \nu_{OH\ bonded}$ and $\epsilon_{OH\ free}/\epsilon_{OH\ bonded}$).

The N,N-dimethylamino-alcohols **27** and **28** were similarly correlated with the corresponding piperidino-derivatives already described.[2] The relative configurations of the N-methylamino-derivatives **17–20** were determined by chemical correlation (methylation of the secondary amino-group, see Experimental) with the corresponding N,N-dimethylamino-derivatives **23–26**.

The assignment of the absolute and relative configuration to the compounds **43–46** has been previously reported.[4]

It is noteworthy that the NMR and GLC data of the compounds, the configurations of which were determined by chemical methods, show the same trend (i.e. T-isomers with upfield NMR signals and lower retention times), thus confirming the reliability of the method employed.

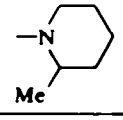
Compounds **47–54**, which are obtained with low stereoselectivity, were not submitted to any configurational assignment.

Table 1. A/B Ratios (± 2%) in the reactions between amino-ketones **1–16** and LAH or organometallic reagents

	Amino-group	R	R′	A/B Ratio: R″ = H, M = LiAlH₄	R″ = Me, M = Li	R″ = Me, = MgI	R″ = Et, M = MgBr	R″ = Ph, M = Li	R″ = Ph, = MgCl	R″ = Ph, – MgBr	R″ = Ph, – MgI
1		Me	Ph	46/54[a]	—	—		61/39		22/78	
2		Et	Ph	47/53			—	63/37		17/83	
3		Ph	Ph	50/50[a]	87/13[b]	53/47	33/67	—	—	—	—
4		Me	Me		—	—			78/22[c]	50/50[c]	70/30[d]
5		Me	Ph	34/66[a]	—	—		68/32		75/25	
6		Et	Ph				—	70/30		79/21	
7		Ph	Me	25/75		76/24[e]		—	—	—	—
8		Ph	Ph	25/75[a]	83/17[f]	70/30	85/15	—	—	—	—
9		Me	Me		—	—			28/72[c]	19/81[c]	13/87[c]
10		Me	Ph	40/60[a]	—	—		76/24		35/65	
11		Et	Ph				—	83/17		44/56	
12		Ph	Me	33/67[a]		80/20[e]		—	—	—	—
13		Ph	Ph	31/69[a]	83/17[f]	67/33[g]	85/15[h]	—	—	—	—
14		Me	Ph	50/50[a]	—	—		72/28		52/48	
15		Et	Ph				—	76/24		58/42	
16		Ph	Ph		73/27	43/57	49/51	—	—	—	—

[a] From Ref 2. [b] 50/50, Reaction in Et_2O/THF. [c] Reaction time, 2·5 h; the same results (± 1%) were obtained at 0°C. [d] 66/34, at 0°C. [e] 82/18, in Et_2O/THF; 86/14, in highly diluted ethereal solution. [f] 65/35, in Et_2O/THF. [g] 80/20, in Et_2O/THF. [h] 86/14, in Et_2O/THF.

Table 2. A/B Ratios (± 2%) in the reactions between amino-ketones **8**, **39–42** and LAH or organometallic reagents

	Amino-group	R	R′	n	R″ = H, M = LiAlH₄	M = Li	R″ = Me, = MgI	R″ = Et, M = MgBr
8				0	25/75[a]	83/17[a]	70/30[a]	85/15[a]
39				1	33/67	68/32	no reaction	no reaction
		Ph	Ph					
40				2	46/54	60/40 (or 40/60)	no reaction	no reaction
41				3	48/52	57/43 (or 43/57)	no reaction	no reaction
42		Ph	H	1			no reaction	no reaction

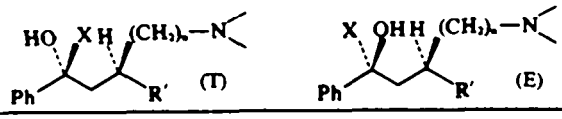
[a] From Table 1.

DISCUSSION

The stereochemistry of the nucleophilic attack on α-asymmetric ketones bearing OH or NH_2 bonded to the asymmetric center has been interpreted on the basis of a 5-membered cyclic model[3,4] in which the metal atom of the reagent links both the carbonyl oxygen and the heteroatom, the predominant attack coming from the less hindered side of the carbonyl plane. Such a model has demonstrated its applicability to the prediction of the diastereomeric predominance for a large number of substrates,[7] even if, in some cases, it has not proved to be completely effective.[8]

As regards the 1,3 asymmetric induction on β-hydroxy- or β-methoxy-ketones, three competing models, i.e. open-chain, polar, and cyclic, have

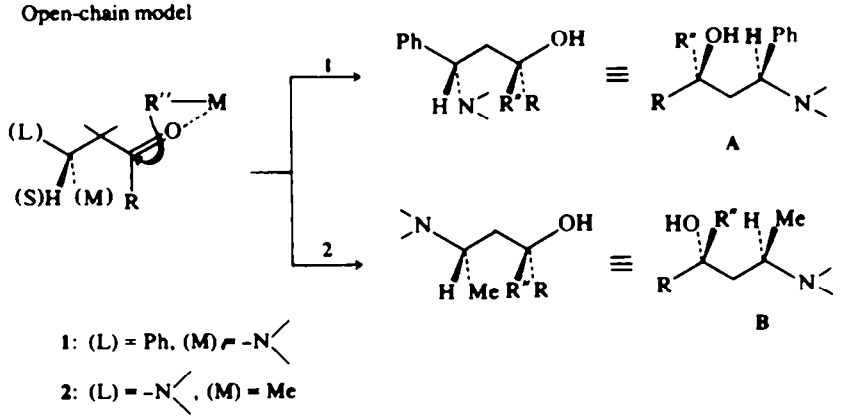
Table 3. Relative configurations, NMR, GLC and IR data of the amino-alcohols 17–38 and 43–54



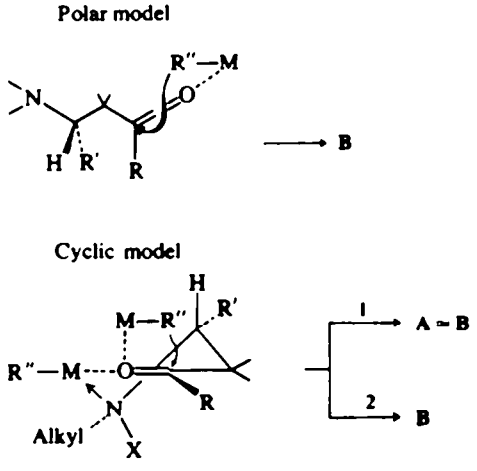
Amino-alcohols					NMR[a]				GLC[b]		IR[c]			
	Amino group	n	X	Configuration	CH₃–C–O	CH₃–N	H–C–N	CH₃–C–N	Column temp. (°C)	Retention times ratio E/T	free OH ν(cm⁻¹)	free OH ε	bonded OH ν(cm⁻¹)	bonded OH ε
17		0	Me	Ph	T	1·44	2·02	3·10	—	175	1·28	3640	4		
18					E	1·63	2·23	3·90	—			3600	3	3230	83
												3595	4·5	3250	72·5
												3570	6		
19		0	Et	Ph	T	—	2·02	3·16	—	150	1·25				
20					E	—	2·20	3·89	—						
21		0	Me	Me	T	1·32	2·02	2·30	0·67	180[d] or 173[e]	1·21				
22					E	1·45	2·10	3·10	0·80		1·57				
23′		0	Me	Ph	T	1·50	2·02	3·33	—	185	1·33	—	—	3180	80
24′					E	1·64	2·18	4·16	—			3570	3	3185	77
25		0	Et	Ph	T	—	2·02	3·39	—	185	1·29	—	—	3170	82
26					E	—	2·14	3·14	—			3640	4	3185	70
												3572	7		
27		0	H	Me	T	H–C–O ~4·9	2·20	~2·7	0·82	135→170[e]	1·06				
28					E	4·87	2·27	3·07	0·92						
29′		0	Me	Me	T	1·30	—		0·75	200[e]	1·65				
30′					E	1·42	—		0·90						
31		0	Me	Ph	T	1·52	—	3·40	—	198	1·39	—	—	3170	93
32					E	1·57	—	4·19	—			—	—	3170	86
33		0	Et	Ph	T	—	—	3·43	—	198	1·27	—	—		
34					E	—	—	4·15	—					3160	88
35		0	Me	Ph	T	1·55	—	3·42	—	200	1·29				
36					E	1·68	—	4·20	—						
37		0	Et	Ph	T	—	—	3·42	—	200	1·23				
38					E	—	—	4·25	—						
43		1	H	Ph	T	H–C–O 4·88	2·23	—	—			3608	16	3140	74
44					E	4·67	2·35	—	—			3590	15	3140	77
45		1	Me	Ph	T	1·42	2·10	—	—	195[e]	1·1				
46					E	1·54	2·32	—	—						
47		2	H	Ph	T or E[h]	H–C–O 4·50	2·01	—	—						—
48					E or T	4·28	2·03	—	—						
49		2	Me	Ph	T or E[h]	1·36	2·06	—	—	237[e]	1·0				
50					E or T	1·42	2·13	—	—						
51		3	H	Ph	T or E[h]	H–C–O 4·40	1·97	—	—						
52					E or T	4·21	1·99	—	—						
53		3	Me	Ph	T or E[h]	1·36		—	—						2·03
54					E or T	1·39		—	—						2·05

[a] Solvent, $CDCl_3$ (CS_2 for compounds 21–22 and 29–30. [b] Perkin–Elmer F7; column (1 = 2 m) SE 30 (1%) on Chromosorb G, unless otherwise stated. [c] Solvent, tetrachloroethylene. [d] Carlo Erba Fractovap GV; col. (1·5 m) SE 52 (5%) on Chromsorb W. [e] Idem; col. (1 = 2 m) Versamid (10%) on Chromosorb W. [f] See Ref 1. [g] Aerograph 200; col. (1 = 3 m) SE 30 (10%) on Chromosorb W. [h] Less abundant isomer.

been proposed.[9] Their application to our β-amino-ketones leads to the following Scheme 2 in which we have attributed, on the basis of the conformational energies in the cyclohexane systems, a decreasing effective steric hindrance in the series Ph > N(Alkyl)$_2$ > Me > H.



SCHEME 2



When the β-substituent R' is C_6H_5, the open-chain model would predict a predominance of the **A** isomer (1), whereas the **B** isomer would be obtained when R' = Me (2).

In the polar model, on the contrary, the **B** isomer is predicted regardless of the nature of the R' group.

The assignment of the predominant direction of attack in the cyclic model is less straightforward than in the substrates investigated by Cram,[9] as the less hindered side of the carbonyl plane is not immediately identifiable. This is evident particularly with the N-monomethylamino-ketones, whereas the N,N-dialkylamino-derivatives would appear to display less hindrance from the upper side (Scheme 2) of the carbonyl plane.

The comparison between predicted and observed (Table 1) results allows the following considerations to be made:

1. *In LAH reductions*, the diastereomeric predominance of isomer **B** agrees with either the polar or the cyclic model. However, as the latter can also explain the low selectivity observed in the reductions of the N-monomethyl-derivatives, this could be indicative of the applicability of the cyclic model to the LAH reductions. In this connection, it is noteworthy that similar ketones non-containing the aminic group afford inverted diastereomeric ratios as well as lower selectivity[10] than the dialkylamino-derivatives.

The low selectivity observed in the LAH reductions of γ-, δ- and ε-dimethylamino-ketones could also be attributed to a decreasing probability of ring formation, although the contribution of non-selective cyclic transition states cannot be excluded.

2. The large predominance of isomer **A** in the *reactions with organo-lithiums* which occurs regardless of the nature of both substrate and reagent cannot be explained on the basis of the above models. The predominance of isomer **A** is predicted only by the open-chain model and only when R' = Ph.

3. The stereochemistry of the *organo-magnesium additions* to β-amino-ketones appears to be affected by the nature of both substrate and reagent:

(a) *Nature of the substrate.* In the piperidino- and morpholino-ketones the *same isomer* is obtained on inverting the substituents on the carbonyl group and on the Grignard reagent (CO-Alkyl and PhMgBr *vs* CO-Ph and AlkylMgX) i. e. **9** *vs* **12**, **10** *vs* **13**, **14** *vs* **16**. In other words, the predominant direction of attack on the alkyl-ketones is reversed with respect to the aryl-ketones.

An inversion of the predominant isomer also occurs when the aminic substituent is changed (see, e.g. 4 *vs* 9 and 5 *vs* 10).

(b) *Nature of the organometallic reagent.* The A isomer slightly predominates in the reactions between the N-methylamino-ketones (compounds 1, 2 and 3 and MeMgI, whereas isomer B is the main product from the reactions with EtMgBr and PhMgBr.

Furthermore, very different results are afforded by phenyl-magnesium chloride, bromide and iodide with the N,N-dimethylamino-ketone 4 (or, to a lesser extent, with the piperidino-derivative 9).

We can therefore conclude that a prediction of the predominant isomer obtained from the reactions between the amino-ketones investigated and the various nucleophilic reagents is not possible on the basis of the proposed models, even when considering them as simple rules and not as schematic approximation of real transition states.*

The experimental results could be interpreted, of course, by taking into account all the factors (conformational situation, polar and steric effects, solvation and coordination abilities, etc) involved in each particular case, but this was not the purpose of this work.

EXPERIMENTAL

IR spectra were measured with a Perkin-Elmer Infracord 337 or with a Beckmann IR 5 spectrophotometer. M.ps were determined with a Kofler apparatus or a Perkin-Elmer DSC 1 microcalorimeter. NMR spectra were measured, at 60 MHz, with a Perkin-Elmer R 12 or a Jeol C-60 HL and, at 100 MHz, with a Varian HA 100 spectrometer (chemical shifts are given in δ (ppm) using TMS as internal reference). Elemental analyses were performed on a F&M Mod. 185 CHN Analyzer, or by the "Service Central de Microanalyse du C.N.R.S."; the elemental formula in the text identicates that the analyses resulted within the 0·2% of the calculated value.

Synthesis of amino-ketones

The β-amino-ketones 1, 2, 4, 5, 6, 9, 10, 11, 14, and 15 were identified by IR spectroscopy (C=O stretching at 1715–1720 cm^{-1}) which usually showed also the presence of unreacted vinyl-ketone (C=O stretching at 1670 cm^{-1}). In some cases the amino-ketones were characterised as picrates.

Amino-ketones 1, 3, 5, 8, 10, 13 and 14 (Ref 2 and Refs cited therein) as well as 7[12], 12[1,12], 40 and 41[13] are already described.

4-(N,N-Dialkylamino)-pentan-2-ones 4 *and* 9. The dimethylamino-derivative 4 was obtained from pent-3-en-2-one and 33% aqueous dimethylamine (molar ratio 1:4) in the presence of 10% NaOH aq (few drops). The mixture was stirred at room temp for 4 h and, after standing for 12 h, was made acidic with conc HCl at 0° and thoroughly extracted with Et_2O. The aqueous layer was made alkaline under ice cooling and again thoroughly ether extracted. The ethereal soln was dried and the solvent evaporated under reduced pressure at room temp (70% yield). Picrate, m.p. 157–158° (from EtOH), Anal: $C_{13}H_{16}N_4O_8$.

The piperidino-derivative 9 was prepared with the method already described[12] for β-piperidinobutyrophenone and isolated as above (75% yield), picrate, m.p. 120–122° (from EtOH/H_2O). Anal: $C_{16}H_{22}N_4O_8$.

5-(N-Methyl)- and 5-(N,N-dialkylamino)-5-phenylpentan-3-ones 2, 6, 11 *and* 15. The monomethyl- and dimethylamino-derivatives 2 and 6 were obtained as the above described amino-ketone 4 from 5 - phenyl - pent - 4 - en - 3 - one and the appropriate alkylamine (as 40% aqueous soln). They were identified as mentioned above and were reacted without further purification.

The piperidino- and morpholino-derivatives 11 and 15 were obtained by reaction between the vinyl-ketone and the alkyl-amine (in equimolar ratios) for several hours at room temp. The mixture was worked up in the usual manner. The amino-ketones containing some vinyl-ketone (see before) were not purified.

3 - Morpholino - 1,3 - diphenyl - propan - 1 - one 16. Compound 16 was prepared as the above described amino-ketones 11 and 15; m.p. 80–81° (from Et_2O) (84% yield), Anal: $C_{19}H_{21}NO_2$.

4 - (N,N - Dimethylamino) - 1,3 - diphenyl - butan - 1-one 39. Compound 39 was prepared by portionwise addition of the keto-nitrile 55[14] (7·1 g, 0·03 mol) to an ethereal soln (50 ml) of LAH (3·29 g, 0·087 mol). The mixture was refluxed for 18 h and hydrolysed under ice cooling by stepwise addition of water (15 ml). After filtration of the ppt, evaporation of the solvent afforded 5·9 g of material which was dissolved again in Et_2O. The ethereal soln was extracted with dil HCl and the crude amino-alcohols 56 were obtained in the usual way (4·2 g, 60%).

The amino-alcohols 56 (1·22 g, 0·0051 mol) were then refluxed for 28 h with formic acid (2·5 ml) and 30% aqueous formaldehyde (3 ml).[11] The reaction gave a mixture of the dimethylamino-alcohols 57 (1·044 g, 77%), which aere identified by NMR (the *erythro/threo* ration was 67/33 by integration of the N-methyl signals).

The amino-alcohols 57 (2·83 g, 0·0106 mol) in acetone (100 ml) were treated with Djerassi reagent[15] (5 ml). After 5 min some drops of MeOH were added and the ppt filtered out. The aqueous soln was then made alkaline and worked in the usual manner, 2·39 g (85% yield) of the title compound were obtained, m.p. 69° (from n-hexane), Anal: $C_{18}H_{21}NO$.

4 - (2' - Methylpiperidino) - 1 - phenyl - butan - 1 - one 42. Compound 42 was prepared from γ-bromobutyrophenone[17] (18 g, 0·08 mol) and 2-methyl-piperidine (11·8 g, 0·12 mol) in benzene (100 ml) under reflux (2 h). After standing at room temp for 12 h, the mixture was extracted with dil HCl and the aqueous soln treated with NaOH aq and ether extracted. The ethereal soln was evaporated under reduced pressure at 100° on a water bath in order to eliminate the excess of 2-methylpiperidine. The residue, dissolved in Et_2O and treated with dry HCl, afforded 42 hydrochloride (63% yield), m.p. 180–181° (from abs EtOH), Anal: $C_{18}H_{24}NOCL$.

Reactions with lithium aluminum hydride (LAH) or organo-metals and amino-ketones (General procedure)

LAH Reductions. Compounds 2, 7, 39, 40 and 41 were the only amino-ketones reduced in the present work and the procedure adopted was the same as for the compounds described in Ref 2. The crude diastereomeric amino-alcohols were obtained with yields varying from 78 to 100%.

Reactions with organo-metals. The amino-ketone (0·01 mol) dissolved in anhyd Et_2O (20 ml) (or as such in

*See, on this point, Cram's private communication reported by Salem.[11]

the case of low solubility) was slowly added, at room temp and under N_2, to a stirred ethereal soln (40 ml) of the organo-metal (0·03 mol) obtained from the appropriate phenyl- or alkyl-halide (0·03 mol) and Mg (0·033 mol) or Li (0·066 mol) (the amount of metal was in excess in order to avoid quaternization of the amine by the halide). The mixture was then refluxed for 1 h (in some cases for 2·5 h, see Table 1) and, after cooling, poured into saturated NH_4Cl aq and ether extracted. The neutral and basic products were separated in the usual way.

In the reactions on the β-amino-ketones **1–16**, a noticeable amount of neutral product was obtained which derived from the decomposition of unreacted (enolized) amino-ketone to give amine and unsaturated ketone. The yields in amino-alcohols were in the range 30–80% and appeared to be affected by both the rate of addition and the nature of the amino-ketones.

The crude mixture of amino-alcohols was finally dosed by GLC and/or NMR (Table 3).

Reactions, differing to some extent from this general procedure, are described below.

Reaction between 3 - *dimethylamino* - 1,3 - *diphenyl* - *propan* - 1 - *one* **8** *and* MeMgI. A ppt was formed after few min since the addition of the amino-ketone (2·53 g, 0·01 mol) to the Grignard reagent. After 1 h the ppt was separated from the ethereal soln and hydrolysed, thus affording 0·740 g of neutral product and 0·635 g of the crude amino-alcohols **23** and **24**, with a T(**23**)/E(**24**) ratio = 83/17. The ethereal soln gave 0·434 g of neutral material and 0·496 g of mixture with a T/E ratio = 54/46. The overall yield in amino-alcohols and the overall diastereomeric ratio resulted, respectively, 42% and 70/30. A second run treated in standard conditions according to the described above general procedure, gave a 43·5% yield and 71/29 diastereomeric ratio.

Reaction between **8** *and* EtMgBr. This reaction appeared to be similar to the one above described. From 0·01 mol of amino-ketone, the ppt gave 0·350 g of neutral material and 1·160 g of pure **25** (by NMR). The ethereal soln gave 0·412 g of neutral material and 0·390 g of diastereomeric amino-alcohols **25** and **26** in the ratio 60/40. The overall yield was thus 55% (T/E = 90/10). A second run in standard conditions gave 56% yield and T/E = 86/14.

Reaction between 5 - (N,N - *dimethylamino*) - 1,3 - *diphenyl* - *pentan* - 1 - *one* **40** *and* MeMgI. After the addition of the amino-ketone (0·22 g), a ppt was immediately formed which then disappeared. After 5 min, however, a crystalline ppt appeared again and was isolated after the reaction was completed. It was proved to be 5 - dimethylamino - 1,3 - diphenyl - pentan - 1 - one methiodide (0·055 g), m.p. 215° (from MeOH) (C=O stretching at 1670 cm^{-1}). Anal: $C_{20}H_{26}NOI$. The ethereal soln gave 0·129 g of unreacted amino-ketone.

In a second run the extent of enolization was evaluated by the Zerewitinoff method after treatment of the amino-ketone (2·95 g, 0·0105 mol) with excess of MeMgI, 230 ml (0·0102 mol) of CH_4 and 2·90 g of unreacted ketone were obtained.

Separation of the diastereomeric amino-alcohols

The procedure generally adopted was based on the treatment of the crude mixture with a suitable acid followed by fractional crystallization of the corresponding salts. The following acids were used: 3-hydroxy-2-naphthoic (HNA), *p*-nitrobenzoic (NBA), oxalic, picric and hydrochloric. The reported yields are to be considered as crystallization yields.

4 - (N - *Methylamino*) - 2,4 - *diphenyl* - *butan* - 2 - *ols* **17** *and* **18**. Diastereomer **17** was obtained by treatment of the crude mixture T(**17**)/E(**18**) = 53/47 with HNA. After 3 crystallizations from AcOEt, the salt had m.p. 159°, Anal: $C_{28}H_{25}NO_4$. The free base (6% yield) solidified on standing, m.p. 73°.

The mixture of diastereomeric amino-alcohols recovered from the mother liquors was treated with NBA and afforded a salt which was crystallized from AcOEt followed by MeOH; m.p. 183°. The so obtained free base (17% yield), resulted to be the isomer "*erythro*" **18**, m.p. 75–76° (from n-hexane). Anal: $C_{17}H_{21}NO$.

5 - (N - *Methylamino*) - 3,5 - *diphenyl* - *pentan* - 3 - *ols* **19** *and* **20**. The treatment of the crude mixture T(**19**)/E(**20**) = 85/15 with oxalic acid in AcOEt afforded predominantly the salt of isomer **20**. From the mother liquors almost pure **19** was recovered (76% yield) and was furtherly purified as NBA derivative by two crystallizations from AcOEt followed by acetone; m.p. 187°. The free base had m.p. 80° (from n-hexane). Anal: $C_{18}H_{21}NO$.

Isomer **20** was better obtained from a mixture T/E = 33/67 and oxalic acid. The oxalate was crystallized from AcOEt and, after digestion in MeOH, had m.p. 245° dec. Free base (58% yield) had m.p. 127° (from Et_2O). Purity determined by calorimetry.

4 - (N,N - *Dimethylamino*) - 2 - *phenyl* - *pentan* - 2 - *ols* **21** *and* **22**. The unreacted amino-ketone was eliminated from the reaction mixture by the method described[1] for the diastereomeric 4 - piperidino - 2 - phenyl - pentan - 2 - ols.

Pure **21** was obtained by treatment of the mixture T(**21**)/E(**22**) = 76/24 with dry HCl in Et_2O. The so obtained hydrochlorides were washed with a small amount of acetone and then crystallized from AcOEt/EtOH. Amino-alcohol **21** hydrochloride (40% yield) had m.p. 189–190°, Anal: $C_{11}H_{22}NOCl$.

Pure **22** was obtained as a picrate by fractional crystallization from a mixture of amino-alcohols T/(**21**)/E(**22**) = 30/70, m.p. 134·5–136° (from 95% EtOH) (30% yield). Anal: $C_{16}H_{24}N_4O_8$.

4 - (N,N - *Dimethylamino*) - 2,4 - *diphenyl* - *butan* - 2 - *ols* **23** *and* **24**. Pure **23** was obtained as described in Ref 1.

The diastereomer **24** was obtained from a mixture T(**23**)/E(**24**) = 25/75 by treatment with HNA in AcOEt. The salt had m.p. 190° dec. (from AcOEt followed by acetone). Free base (50% yield), m.p. 73° (from n-hexane) after vacuum drying. Anal: $C_{18}H_{21}NO$. NBA salt, m.p. 175° dec (from AcOEt).

5 - (N,N - *Dimethylamino*) - 3,5 - *diphenyl* - *pentan* - 3 - *ols* **25** *and* **26**. Hydrolysis of the ppt formed in the reaction between **8** and EtMgBr (see before) gave the pure amino-alcohol **25**, m.p. 63·5° (from n-hexane). Anal: $C_{19}H_{23}NO$.

Isomer **26** was obtained from a mixture T(**25**)/E(**26**) = 21/79 after treatment with NBA in AcOEt. The salt had m.p. 179° (from AcOEt/MeOH). The free base (oil) was obtained in 41% yield. Anal: $C_{19}H_{23}NO$.

3 - (N,N - *Dimethylamino*) - 1 - *phenyl* - *butan* - 1 - *ols* **27** *and* **28**. Any attempt to isolate the amino-alcohol **27** failed. For GLC and NMR data, see Table 3.

The amino-alcohol **28** was obtained by treatment of the mixture T(**27**)/E(**28**) = 25/75 with a slight excess (1:1·5 mol) of picric acid in a small amount of hot 95% EtOH. By cooling, **28**-picrate was obtained and purified

by several crystallizations from 95% EtOH, m.p. 126–128°, after drying. Anal: $C_{16}H_{22}N_4O_8$.

4 - *Piperidino* - 2 - *phenyl* - *pentan* - 2 - *ols* **29** *and* **30**. Amino-alcohol **29** was already described.[1]

Any attempt to isolate pure **30** failed. For GLC and NMR data, see Table 3.

4 - *Piperidino* - 2,4 - *diphenyl* - *butan* - 2 - *ols* **31** *and* **32**. The mixture T(**31**)/E(**32**) = 65/35 was treated with HNA in AcOEt. The resulting salt was crystallized from acetone/MeOH followed by MeOH, m.p. 195°, Anal: $C_{17}H_{15}NO_4$. From this salt, pure **31** was obtained (15% yield), m.p. 74° (from n-hexane) after vacuum drying.

The mother liquors of the first crystallization gave a mixture T/E = 36/64, which was treated with NBA. The salt was crystallized with acetone followed by MeOH, m.p. 186°. The free amino-alcohol **32** (8% yield) had m.p. 99° (from n-hexane) after vacuum drying, Anal: $C_{21}H_{27}NO$.

5 - *Piperidino* - 3,5 - *diphenyl* - *pentan* - 3 - *ols* **33** *and* **34**. Isomer **33** was isolated from a mixture T(**33**)/E(**34**) = 86/14 as HNA salt, m.p. 181° dec (from AcOEt). Free base (68% yield), m.p. 59·5° (by cooling at −20° in n-hexane) after vacuum drying, Anal: $C_{22}H_{29}NO$.

Isomer **34** was isolated as NBA salt, m.p. 170–171° (from AcOEt) from a mixture T/E = 17/83. Free base (31% yield), m.p. 73·5° (from n-hexane) after vacuum drying. Anal: $C_{22}H_{29}NO$.

4 - *Morpholino* - 2,4 - *diphenyl* - *butan* - 2 - *ols* **35** *and* **36**. Amino-alcohol **35** was isolated as HNA salt from a mixture T(**35**)/E(**36**) = 73/27. The salt had m.p. 192° (from AcOEt, followed by MeOH). Free base (46% yield), m.p. 80–90° (polymorphism) (from n-hexane), Anal: $C_{20}H_{23}NO_2$.

Pure **36** was obtained as NBA salt from a mixture T(**35**)/E(**36**) = 43/57, m.p. 157° (from AcOEt, followed by MeOH), Anal: $C_{27}H_{30}N_2O_8$. Free base 23% yield (oil).

5 - *Morpholino* - 3,5 - *diphenyl* - *pentan* - 3 - *ols* **37** *and* **38**. The mixture T(**37**)/E(**38**) = 32/68, treated with NBA, gave the salt of **38**, m.p. 130° (from AcOEt, followed by EtOH), Anal: $C_{28}H_{32}N_2O_8$. The free base (23% yield) was an oily product.

From the mother liquor of the first crystallization a mixture T/E = 61/39 was recovered and treated with HNA, thus obtaining the salt of **37**, m.p. 187° (from AcOEt, followed by EtOH), Anal: $C_{32}H_{34}NO_4$. The free base (oil) was obtained in 14% yield.

4 - (N,N - *Dimethylamino*) - 1,3 - *diphenyl* - *butan* - 1 - *ols* **43** *and* **44**. The amino-alcohol **44** was isolated and purified from a mixture T(**43**)/E(**44**) = 33/67 as a picrate, m.p. 165° (from AcOEt). Free base (24% yield), m.p. 96° (from n-hexane), Anal: $C_{18}H_{23}NO$.

From the mother liquor of the first crystallization a mixture T(**43**)/E(**44**) = 70/30 was recovered and submitted to preparative thin layer chromatography on Merck's F 254 silica gel, with a mixture of 1:1 n-hexane/AcOEt (15 ml) and 1:3 Me_2NH/benzene (50 ml) as eluent. The amino-alcohol **43** was more retained and was recovered in 58% yield, m.p. 60° (from n-hexane), Anal. $C_{18}H_{23}NO$.

5 - (N,N - *Dimethylamino*) - 2,4 - *diphenyl* - *pentan* - 2 - *ols* **45** *and* **46**. Isomer **45** was isolated from a mixture T(**45**)/E(**46**) = 68/32 as a salt with HNA, m.p. 153° after three crystallizations from AcOEt. Free base (20% yield), b.p. (0·2 mm Hg) 135–145°, n_D^{22} = 1·54488, Anal: $C_{19}H_{23}NO$.

The isomeric mixture recovered from the mother liquor of the first crystallisation was treated with NBA and afforded a salt which was crystallized from AcOEt (twice) followed by acetone/MeOH, m.p. 159°. The corresponding free base **46** (12% yield) had m.p. 56·5° (solvated) from n-hexane). After vacuum drying at 78°, Anal: $C_{19}H_{23}NO$.

5 - (N,N - *Dimethylamino*) - 1,3 - *diphenyl* - *pentan* - 1 - *ols* **47** *and* **48**. The mixture of amino-alcohols **47** and **48** (54/46 by NMR), obtained in 98% yield from LAH reaction, could not be separated by TLC.

6 - (N,N - *Dimethylamino*) - 2,4 - *diphenyl* - *hexan* - 2 - *ols* **49** *and* **50**. The mixture (60/40 by NMR), recovered in 99% yield from reaction with MeLi, was not separated by GLC. It did not contain unreacted amino-ketone (IR).

6 - (N,N - *Dimethylamino*) - 1,3 - *diphenyl* - *hexan* - 1 - *ols* **51** *and* **52**. The mixture (52/48 by NMR) was obtained in 98% yield from LAH reaction with the corresponding amino-ketone.

7 - (N,N - *Dimethylamino*) - 2,4 - *diphenyl* - *heptan* - 2 - *ols* **53** *and* **54**. The mixture (57/43 by NMR), obtained in 100% yield from MeLi reaction, did not contain unreacted amino-ketone (IR).

Dimethylamino-alcohols **23**, **24** *and* **26** *from the corresponding monomethylamino-derivatives* **17**, **18** *and* **20**

A preliminary experiment on diastereomer **24** showed that complete equilibration (as detected by GLC and NMR) occurred when the compound was kept for 15 h under the reaction conditions described[15] for the N-methylation with formaldehyde/formic acid. The reaction time being reduced to only 2 h, both the isomerizations **24** → **23** and **23** → **24** occurred to the extent of only 10% and 18%, respectively.

N-*Methylation of* **17**. The amino-alcohol **17** (0·054 g), 40% aqueous formaldehyde (0·4 ml) and formic acid (0·3 ml) were refluxed for 2 h. After the usual treatment, a mixture (0·054 g) of **23** and 3,6 - dimethyl - 4,6 - diphenyl - 1,3 - tetrahydrooxazine in the ratio 13/87 was obtained and analysed by GLC and NMR; GLC: (see footnote b in Table 3) col. temp, 175°; retention times ratio oxazine/amino-alcohol = 1·1. Tetrahydrooxazine, NMR (solv. $CDCl_3$): AB doublet, H_A = 3·98, H_B = 4·42 (J_{AB} = 8·65 Hz), N–CH_2–O; 3·4 (q), H–C–N; 1·93 (s), CH_3–N; 1·47 (s), CH_3–C.

Reduction of the mixture (0·052 g) with ethereal LAH afforded the pure (by GLC) **23** (0·050 g).

N-*Methylation of* **18**. The amino-alcohol **18** was allowed to react according to the above described procedure. The obtained product was a mixture (0·061 g) of **24** and of oxazine isomeric with the one above described, in the ratio of about 30/70. GLC: (see before), retention times ratio = 1·07. Tetrahydrooxazine, NMR (solv. $CDCl_3$): AB doublet, H_A = 4·49, H_B = 4·65 (J_{AB} = 9·3 Hz), N–CH_2–O; 3·66 (q), H–C–N; 2·12 (s), CH_3–N; 1·68 (s), CH_3–C.

Reduction of the mixture with ethereal LAH afforded **24** (0·06 g) contaminated by the diastereomer **23** (93/7, by GLC).

N-*Methylation of* **20**. The amino-alcohol **20** (0·144 g) was allowed to react in the usual manner. The obtained product was a mixture (0·131 g) of 3 - methyl - 6 - ethyl - 4,6 - diphenyl - 1,3 - tetrahydrooxazine and **26**. The ratio was 60/40 (by GLC and NMR) and became 25/75 after further methylation for 4 h under the same conditions. GLC: (see before), retention times ratio oxazine/amino-alcohol = 1·1. Tetrahydrooxazine, NMR (solv. $CDCl_3$): AB doublet, H_A = 4·32, H_B = 4·64 (J_{AB} = 9·3 Hz), N–CH_2–O; 3·66 (t), H–C–N; 2·11 (s), CH_3–N; 0·68 (t), $\underline{CH_3}$–CH_2.

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