Tetrahedron Vol. 37, pp. 2137 to 2142, 1981
Printed in Great Britain.

0040-4020/81/112137-06$02.00/0
Pergamon Press Ltd

STEREOCHEMISTRY OF AMINOCARBONYL COMPOUNDS—X[1]

THE INFLUENCE OF THE AMINE MOIETY ON 1-2, 1-5 AND 1-6 ASYMMETRIC INDUCTION IN GRIGNARD ADDITIONS AND HYDRIDE REDUCTIONS

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(*Received in UK 23 September* 1980)

Abstract—The stereoselectivity of the title reactions due to a hindering amino group in α-asymmetric aminoketones (**1** and **2**) and to an asymmetric center far away from the reaction center in β-(methylpiperidino)-ketones (**11–14**) has been studied. The aminoalcohols obtained (**3–8** and **15–22**) have been separated in most cases and the relative configurations attributed by NMR. Based on diastereomeric ratios, a N-coordinated cyclic transition state has been proposed and is, effective at least for the Grignard reactions on the β-aminoketone system.

A number of studies[2] have been devoted to the stereochemistry of the reaction between organometals or hydrides and chiral aminocarbonyl compounds, in order to synthesize diastereomeric aminoalcohols with relevant pharmacological interest. The configuration of these molecules and the parameters affecting the stereochemical course of their synthesis, are of great importance, owing to the well known stereoselectivity of the receptorial centers.

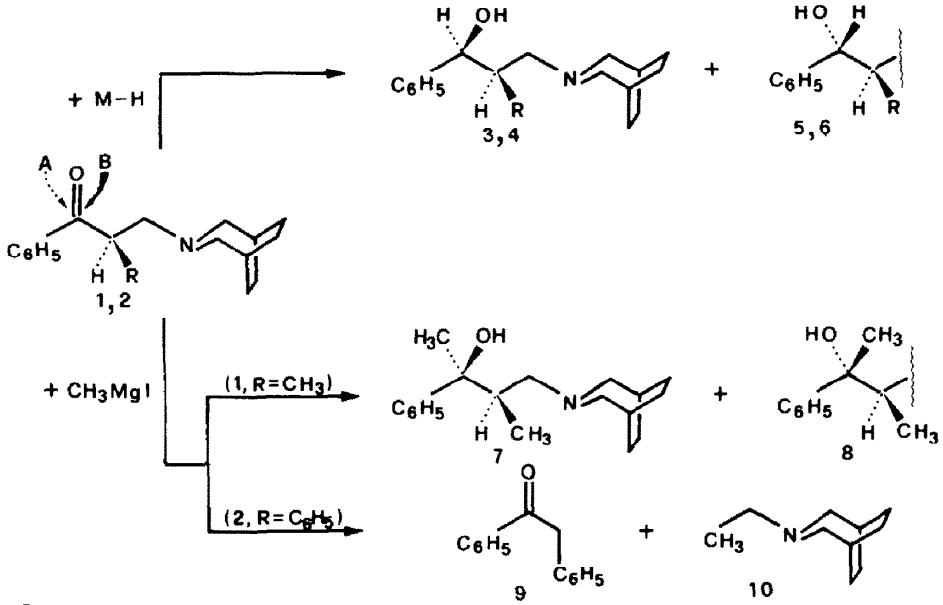
Among structural parameters, the nature of the amino group appears to be very important. Some examples of inversion of predominant attack due to changes in the amino group, as in the case of Grignard additions to β-chiral β-dimethylamino- and β-piperidinoketones,[3] or reduction and Grignard additions on various α-chiral α-dialkylaminoketones,[4] have been reported.

The aim of the present work is to obtain a better knowledge of the role played by the amino group in determining the diastereomeric ratios of the resulting aminoalcohols. To this end we have studied the α-chiral β-aminoketones (**1** and **2**) bearing the 3-azabicyclo[3.2.2]nonane group (ABN group), which should hinder the coordination of the nitrogen lone pair, and the β-(methylpiperidino)ketones (**11–14**) having the center of asymmetric induction far away from the reaction center, in order to observe its influence on stereoselectivity.

Hydride reductions and Grignard reactions

3 - ABN - 2 - methyl - 1 - phenyl- and 3 - ABN - 1,2 - diphenyl - propan - 1 - ones (**1** and **2**) have been reduced with various metal hydrides (Scheme I) affording the diastereomeric aminoalcohols **3**, **5** and **4**, **6** respectively. Diastereomers **3**, **4** and **5**, **6** are produced, respectively, by attack on the opposite (A) or the same side (B) with respect to R, in the extended conformation depicted in Scheme I. The results are reported in Table 1.

Aminoketones **1** and **2** were also allowed to react with MeMgI (Scheme I). The Me derivative **1** afforded the



1, 3, 5: $R = CH_3$
2, 4, 6: $R = C_6H_5$
$M–H = LiAlH_4$ (*LAH*), $HLiAl(OBu^t)_3$ (*TBH*), $LiBH_4$, $NaBH_4$

Scheme I[a,b]

[a]3, 4, 7, from A attack; 5, 6, 8, from B attack.
[b]Only one enantiomer of the racemic pair is represented.

Table 1. Hydride reductions of the aminoketones 1, 2 yielding aminoalcohols 3, 4 and 5, 6

Aminoketone	Hydride [a]	A / B ratio
3-ABN-2-methyl-1-phenyl-propan-1-one 1	LAH	50/50
	TBH	44/56 (47/53) [b]
	$LiBH_4$ [c]	48/52 (47/53) [c,d]
	$NaBH_4$ [e]	50/50 (46/54) [c,d]
3-ABN-1,2-diphenyl-propan-1-one 2	LAH	91/9
	TBH	85/15 [f]
	$LiBH_4$ [e]	95/5 (89/11) [c,d]
	$NaBH_4$ [e]	90/10 [g] (90/10) [c,d]

[a] Reactions carried out in refluxing THF for 1 hr, with quantitative yields, except when otherwise indicated. [b] For 3 hrs. [c] At room temp., for 48 hrs. [d] In diglyme. [e] Suspended hydride; at room temp. for 36 hrs. [f] For 24 hrs; 50 % yield. [g] 20–40 % of non aminic material recovered.

Table 2. Grignard reactions on the aminoketones 1, 2, 11–14, yielding aminoalcohols 7, 8 and 15–18

Aminoketone	Grignard	Yield % (A+B)	A / B ratio
3-ABN-2-methyl-1-phenyl-propan-1-one 1	CH_3MgI	75 [a]	50/50 [b]
3-ABN-1,2-diphenyl-propan-1-one 2	CH_3MgI	c	- [b]
3-(2'-Methylpiperidino)-1-phenyl-propan-1-one 11	CH_3MgI	25	55/45 (55/45) [d]
4-(2'-Methylpiperidino)-butan-2-one 13	C_6H_5MgI	60 (50) [d]	60/40 (60/40) [d]
3-(3'-Methylpiperidino)-1-phenyl-propan-1-one 12	CH_3MgI	66 (50) [d]	48/52 (48/52) [d]
4-(3'-Methylpiperidino)-butan-2-one 14	C_6H_5MgBr	68 (63) [d]	48/52 (50/50) [d]

[a] N-Ethyl-ABN 10 was recovered in a 13 % yield. [b] A/B ratios for the corresponding dimethylamino and piperidino derivatives were 100/0 (ref. [5]). [c] Deoxybenzoin 9 (98 % yield) and N-ethyl-ABN 10 (92 % yield) were recovered. [d] Reaction temperature, 0°C .

expected diastereomeric aminoalcohols **7** and **8** in 1:1 ratio (Table 2), whereas from the phenyl derivative **2**, deoxybenzoin **9**, and N-ethyl-ABN **10** were obtained.

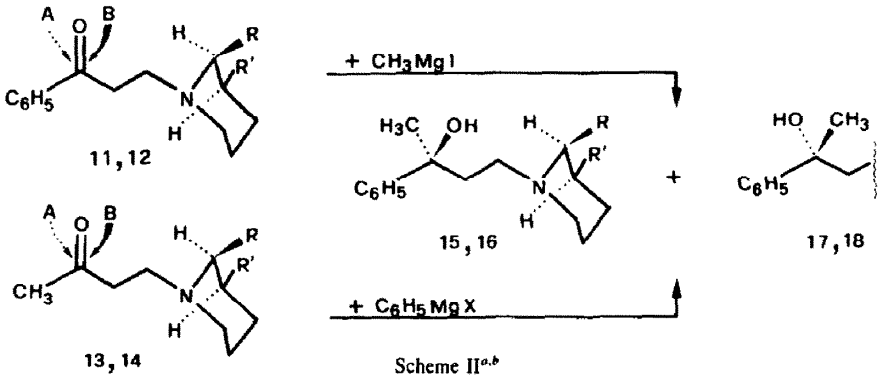
3 - (2'-Methylpiperidino) - and 3 - (3'-methylpiperidino) - 1 - phenyl - propan - 1 - one (**11** and **12**) gave with MeMgI the diastereomeric aminoalcohols **15, 17** and, respectively, **16, 18** (Scheme II). The same diastereomeric pairs were produced by the Methyl keto bases (**13** and **14**) with phenylmagnesium halides. The stereochemical results are reported in Table 2.

Methyl keto bases (**13** and **14**) were also reduced with $NaBH_4$ to the diastereomeric pairs 4-(2'-methyl-piperidino)- (**19, 20**) and, respectively, 4-(3-methyl-piperidino)-butan-2-ols (**21, 22**), in order to obtain NMR data useful for the configurational assignment to compounds **15–18**.

In most cases, the separation of one (pair **4, 6**) or of both the diastereomeric aminoalcohols (pairs **3, 5 7, 8 16, 18** and **19, 20**) was successful (Experimental).

Configurational assignment

The relative configurations of diastereomeric amino-alcohols (**3, 5** and **4, 6**) have been attributed by correlation of the H(1) NMR chemical shifts and $J_{1,2}$ with the corresponding piperidino derivatives of known configuration[3] (Table 3). The configurations of (**7** and **8**) were similarly assigned by comparing the Me(1) and Me(2)



Scheme II[a,b]

11, 13, 15, 17: R = CH_3, R' = H
12, 14, 16, 18, 21, 22: R = H, R' = CH_3
X = Br, I

[a]15, 16, from A attack on 11, 12, or from B attack on 13, 14.
[b]Only one enantiomer of the racemic pair is represented.

signals given by analogous, already known, piperidino derivatives[5] (Table 3).

The NMR spectrum of **15** and **17** shows a very low chemical shift difference ($\Delta\delta$ = 0.04 ppm) between Me(1) singlets and a $\Delta\delta$ of 0.35 ppm between the doublets due to the piperidine Me (Table 3), which can be attributed to a differential shielding effect of the phenyl group in the two disastereomers. In addition, the existence of intramolecular H-bonded structures for compounds **15–22**, previously observed in similar aminoalcohols,[6] has been confirmed by IR spectra carried out in CS_2 at increasing dilutions.

On this basis, models of the diastereomeric pairs I (SS/RR) and II (RS/SR) (Scheme III), which are the more stable among all possible H-bonded conformers, show that the possibility of a shielding effect by the phenyl group on the piperidino Me exists in II. To prove this, $NaBH_4$ reduction of **13** to give the aminoalcohols **19, 20**, in which the phenyl group is replaced by hydrogen (Scheme III), was carried out and NMR spectra measured: as expected, any chemical shift difference between piperidine methyls disappears, owing to the lack of the differential shielding effect of the phenyl. Since δ-Me(pip.) of **17** is highfield with respect to **15**, configuration I and II are therefore attributed to **15** and, respectively, **17**.

The same behaviour is shown also by the 3'-methylpiperidino pair **16, 18** (as compared with the corresponding pair **21, 22**) (Table 3), and the relative configurations have been accordingly assigned: in this case the larger distance of the piperidine Me from the phenyl group is responsible of the much lower ($\Delta\delta$ = 0.08 ppm) shielding effect of phenyl.

The relative configurations of **19, 20**, although non essential for our purposes, have been tentatively attributed on the basis of a likely deshielding effect of the nitrogen lone pair. Assuming that the preferred diastereomeric conformations are I and II (Scheme III), the distance from Me(1) to the N atom would be less (higher deshielding) in I than in II (lower deshielding), thus leading to superimposed Me signals in I and $\Delta\delta$ = 0.10 ppm between methyls in II, and therefore to the assignment reported in Table 3.

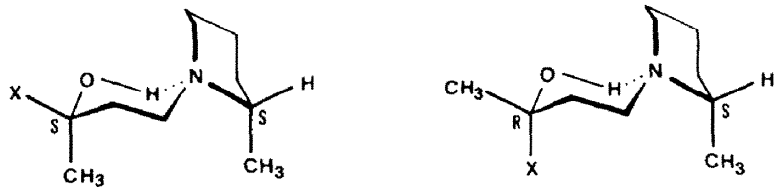
DISCUSSION

Reduction of 3 - ABN - 2 - methyl - 1 - phenyl - propan 1 - one (**1**) by various hydrides shows in every case very low stereoselectivity, whereas the same reactions on the corresponding α-phenyl substituted aminoketones (**2**) occurs with very high stereoselectivity. Such a behavioir is very similar to that of analogous dimethylamino- and piperidino-derivatives previously reported,[1] in which the diastereomeric A/B ratios ranged from 48/52 to 55/45 (α-Me derivatives) and from 87/13 to 90/10 (α-phenyl derivatives).

ABN-derivatives (**1** and **2**) behave differently, also when allowed to react with MeMgI: α-Me derivative **1** giving the expected addition to the carbonyl with production of the aminoalcohols **3, 5** in equal amounts (no stereoselectivity); α-phenyl derivative **2** behaving anomalously, with breakage of bond C_1–C_2 (corresponding to deaminomethylation of Mannich base[7]) and addition of the Grignard Me to the amine moiety, thus yielding N-ethyl-ABN **10**.

Grignard reactions on methylpiperidino ketones (**11–14**) show generally low stereoselectivities (Table 2), particularly those on 3-methylpiperidino derivatives (**12** and **14**), which are actually non stereoselective. As regards the reactions on 2-methylpiperidino derivatives (**11** and **13**), however, it must be noted that the accuracy of NMR determinations (the only ones which could be made for the corresponding aminoalcohols **15, 17**), is in any case modest.

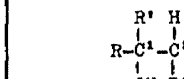
Examination of the results allows the following con-



15, 17: X = C_6H_5
19, 20: X = H

Scheme III

Table 3. NMR data and configurations of the diastereomeric aminoalcohols 3–8 and 15–22 (*δ*, in ppm; J, in Hz)



				Configuration RS/SR			Configuration RR/SS		
R	R'	R''	Aminogroup	Compound	NMR data		Compound	NMR data	
					δ-H(1) [a]	$J_{1,2}$		δ-H(1) [a]	$J_{1,2}$
C_6H_5	H	CH_3	Piperidino [b]	–	4.66 d	3.0	–	4.22 d	8.5
			ABN	3	4.77 d	3.0	5	4.30 d	8.8
C_6H_5	H	C_6H_5	Piperidino [b]	–	4.90 d	3.6	–	~4.70 d	~8.6
			ABN	4	5.20 d	3.7	6	~5.05 d	~8.8
					δ-CH_3(1) [c]	δ-CH_3(2) [c]		δ-CH_3(1) [c]	δ-CH_3(2) [c]
C_6H_5	CH_3	CH_3	Piperidino [d]	–	1.61 s	0.79 d	–	1.51 s	0.61 d
			ABN	7	1.62 s	0.78 d	8	1.54 s	0.60 d
					δ-CH_3(1) [e]	δ-CH_3(pip)		δ-CH_3(1) [e]	δ-CH_3(pip)
C_6H_5	CH_3	H	2-Methylpiperidino	17	(1.30 s)	0.65 d	15	(1.34 s)	1.00 d
H	CH_3	H	2-Methylpiperidino	19	0.95 d	1.05 d	20	1.02 d	1.02 d
C_6H_5	CH_3	H	3-Methylpiperidino	18	1.34 s	0.90 d	16	1.32 s	0.82 d
H	CH_3	H	3-Methylpiperidino	21 or 22	1.00 d	(0.84 d)	22 or 21	1.00 d	(0.86 d)

[a] In CCl_4. [b] Ref. [4]. [c] In $CDCl_3$. [d] Ref. [5]. [e] In CS_2.

siderations to be made:

(1) In the hydride reductions, replacement of the dimethylamino- or piperidino-group with ABN-group does not produce any substantial variation on the diastereomeric ratios. Presumably, such modification in structure of the amine moiety does not induce vovuations on the diastereomeric transition states and, therefore, does not allow to obtain further informations on the nature of such states. However, according to the conclusions of some authors (Ref. 1, and refs. cited therein) on the participation of coordination nitrogen to a cyclic transition state, it can be concluded that, if such a coordination occurs, it is not prevented even by the presence of the hindering ABN-group.

(2) In the Grignard reactions, introduction of the ABN-group induces, on the contrary, strong variations with respect to dimethylamino- and piperidino-derivatives (Table 2), leading to complete loss of stereoselectivity (α-Me substituted aminoketone) or to sharp change in the reaction behaviour (α-phenyl substituted aminoketone). In both cases, the presence of the ABN-group appears to disturb, or even to prevent a coordinated transition state. In fact, if we assume that the stereospecificity observed in the reactions on the dimethylamino- and piperidino-derivatives is due to a cyclic transition state with metal-coordinated nitrogen,[5] the ABN-group would then prevent such a coordination and force the molecule to react through a non-cyclic transition state, with presumably a very low stereoselectivity. In Fig. 1, a possible structure for the cyclic transition state, based on a reported four-centers mechanism[8,9] and adapted to our β-aminoketone systems, is represented. It can be observed that, when the amino-group is ABN, in both conformers strong interactions with the leaving ligand (e.g. Et_2O) of the magnesium reactant (conformation I) or with the methylene group in position 3 (conformation II) would take place.

(3) The results of the Grignard reactions performed on 2-methylpiperidino compounds (**11** and **13**) are not necessarily in contrast with the hypothesis of a cyclic transition state, even if a very low (if any) stereoselectivity has been found. If the above model is applied to **11** and **13**, the asymmetric induction center would be brought by the coordinated nitrogen in proximity of the reaction center, but the possibility of both the chelated cycle and the piperidine ring to assume several conformations should probably lead to balanced contributions of A and B attacks on the CO group.

The same considerations can be made also on the results afforded by the Grignard reactions on the 3-methylpiperidino derivatives (**12** and **14**) which are not stereoselective at all. In this case, the asymmetric induction center is further away from the reaction center even in the coordinated transition state. Therefore, it is unable to exert an influence in favouring either A or B attack.

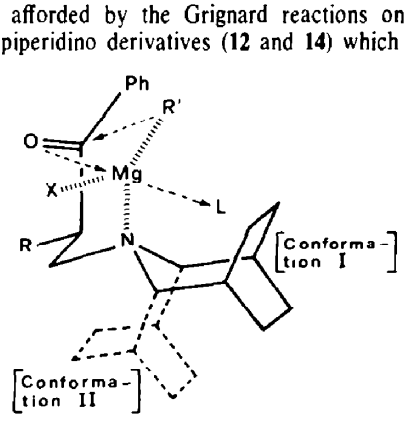


Fig. 1.

EXPERIMENTAL

IR spectra were measured with a Perkin–Elmer 577 Spectrophotometer, NMR spectra with a Jeol C-60 HL (chem shifts are given in δ ppm, using TMS as internal reference). Elemental analyses were performed on a F & M Mod. 185 CHN Analyser; the elemental formulas in the text indicate that the analyses resulted within the 0.3% of the calculated value. M.ps are uncorrected.

3 - *ABN* - 2 - *methyl* - 1 - *phenyl* - *propan* - 1 - *one*, **1**. To a refluxing soln of 3-azabicyclo[3.2.2]nonane hydrochloride (8.0 g, 0.05 mol) and propiophenone (6.7 g, 0.05 mol) in 13 ml of abs EtOH, trioxymethylene (2.25 g, 0.07 mol as CH_2O) was added in three portions together with a drop of conc HCl at intervals of 15 min. The mixture was gently heated for 4.5 hr, then cooled and Mannich base **1** hydrochloride precipitated with Et_2O. The crude product (11.5 g, 75% yield; m.p. 160–162°) crystallized from a small amount of abs EtOH: m.p. 161–162°. Anal. $C_{18}H_{26}NOCl$.

3 - *ABN* - 1.2 - *diphenyl* - *propan* - 1 - *one*, **2**. To a warm soln of deoxybenzoin (4.0 g, 0.02 mol) and 3-azabicyclo[3.2.2]nonane (2.5 g, 0.02 mol) in 10 ml EtOH, 1.5 ml 40% aqueous formaldehyde (0.02 mol) was added. The soln was gently heated without reflux for 15 min and then allowed to stand 1–2 hr at r.t. The ppt, 4.0 g (60%) of crude **2** (m.p. 102–107°), was crystallized from EtOH (m.p. 112–113°). Anal. $C_{23}H_{17}NO$. The corresponding hydrochloride (m.p. 180–183°) is very slightly soluble in water.

3 - (2' - *Methylpiperidino*) -, 3 - (3' - *methylpiperidino*) - 1 - *phenyl* - *propan* - 1 - *one* (**11, 12**) *and* 4 - (2' - *methylpiperidino*) -, 4 - (3' - *methylpiperidino*) - *butan* - 2 - *one* (**13, 14**). Mannich bases **11**,[10] **12**,[11] and **13**–**14**[12] were also prepared by addition of 2- or 3-methylpiperidine to the proper vinylketone (phenylvinylketone for **11** and **12**, methylvinylketone for **13** and **14**) according to the following general procedure:

Vinylketone (0.06 mol) was added dropwise to methylpiperidine (4.3 g, 0.043 mol) in toluene (20 ml) at 10°, and the mixture allowed to stand for 12 hr. The so obtained aminoketone was extracted with dil HCl. The acidic soln was then made alkaline and extracted with Et_2O to give the expected product. Compound **11** (66% yield): hydrochloride, m.p. 128–130°, from EtOH/Et_2O. Compound **12** (65% yield): hydrochloride, m.p. 170–171°, from abs EtOH (this compound can be prepared in good yields (73%) also through "normal" Mannich reaction by refluxing for 13 hr a mixture of acetophenone, trioxymethylene and methylpiperidine hydrochloride in abs EtOH). Compound **13** (56% yield): b.p. 760 mm Hg), 100–102°; picrate, m.p. 94–96° from EtOH. Compound **14** (70% yield): picrate, m.p. 115–117° from EtOH/H_2O (9:1).

General procedure for the hydride reductions of the aminoketones **1** *and* **2**. A 0.2 M soln of the aminoketone was added dropwise, under N_2, to a 0.2 M soln of the hydride (LAH/aminoketone molar ratio 1:1, or TBH/aminoketone = 4:1). The mixture was allowed to react at the conditions described in Table 1, then diastereomeric aminoalcohols isolated and their ratios determined by integration of NMR H–C^1 signals (chem. shifts, in Table 3), as described.[1]

General procedure for the Grignard reactions on the aminoketones **1, 2,** *and* **11–14** (see also Ref. 3). The aminoketone in anhyd Et_2O (25 ml) was slowly added to a stirred ethereal soln (40 ml) of the appropriate Grignard reagent (0.03 mol). The mixture was then refluxed for 3 hr and poured into sat NH_4Cl aq (procedure followed for aminoketones **1** and **2**), or into ice-cooled dil HCl (procedure for **11–14**). The aminoalcohol pairs were isolated and diastereomeric ratios determined as follows:

Reactions on Mannich bases **1** *and* **2**. The aqueous layer (NH_4Cl) afforded only N-ethyl-ABN **10**, which was identified as hydrochloride (m.p. 280–281°, from EtOH, unchanged when mixed with an authentic sample prepared as later described). The Et_2O layer gave the diastereomeric mixture **7** + **8** (from Mannich

base **1**), whereas only deoxybenzoin **9** was obtained from Mannich base **2**. Diastereomeric ratio **7**/**8** was finally determined by integration of NMR H–C^2 signals (chem. shifts in Table 3).

Reactions on Mannich bases **11–14**. Diastereomeric alcohols **15** + **17** were isolated in the usual way from the aqueous soln (HCl) and their ratio determined by integration of NMR methylpiperidine and aryl signals. The unreacted aminoketone **11** was estimated, when present, by integration of the signals due to the aromatic protons *ortho* to the CO group, which apper at lower field with respect to the remaining protons of the mixture.

Diastereomeric mixture **16** + **18** was purified from any unreacted aminoketone with hydroxylamine[13] and diastereomeric ratio determined by comparison of IR bands at 1010, 1025 cm^{-1} and 1210, 1280 cm^{-1} ($c = 0.12$ M, CCl_4).

Separation of aminoalcohols from the diastereomeric mixtures

3 - *ABN* - 2 - *methyl* - 1 - *phenyl* - *propan* - 1 - *ols* **3** *and* **5**. Aminoalcohol **3** was directly obtained by fractional crystallization of the crude product with pet. ether, m.p. 86–88°; Anal. $C_{18}H_{27}NO$. The aminoalcohols recovered from the mother liquor were then converted into the corresponding hydrochlorides and submitted to crystallization from abs. EtOH, thus obtaining **5** hydrochlororide, m.p. 206–208°, Anal. $C_{18}H_{28}NOCl$.

3 - *ABN* - 1,2 - *diphenyl* - *propan* - 1 - *ols* **4** *and* **6**. Aminoalcohol **4** was obtained from repeated crystallizations of the crude product with pet. ether, m.p. 85–87°, Anal. $C_{23}H_{29}NO$. Any attempt to isolate aminoalcohol **6** failed (NMR data in Table 3).

4 - *ABN* - 3 - *methyl* - 2 - *phenyl* - *butan* - 2 - *ols* **7** *and* **8**. The mixture of aminoalcohols **7** and **8**, as hydrochlorides, was submitted to fractional crystallization from EtOH/EtOAc thus obtaining diastereomer **7** (m.p. 204–206°; Anal. $C_{19}H_{30}NOCl$). Mother liquors were made alkaline, and the so obtained mixture submitted to preparative tlc (Allumina °F 254, typ T) with pet. ether/$CHCl_3$ (7:3) as eluent, thus recovering aminoalcohol **8**, which was further purified and characterized as hydrochloride: m.p. 196–197°, from EtOH/AcOEt, Anal. $C_{19}H_{30}NOCl$.

4 - (2' - *Methylpiperidino*) - 2 - *phenyl* - *butan* - 2 - *ols* **15** *and* **17**. Any attempt to separate this diastereomeric mixture by glc, tlc or fractional crystallization of various salts failed. Repeated treatments with warm acetone of the syrupy mixture of **15** and **17** hydrochlorides finally afforded a mixed salt (m.p. 146–148, Anal. $C_{16}H_{26}NOCl$), having a 2:1 (by NMR, chem. shifts in Table 3) **15**/**17** diastereomeric ratio.

4 - (3' - *Methylpiperidino*) - 2 - *phenyl* - *butan* - 2 - *ols* **16** *and* **18**. Diastereomeric aminoalcohols **16** and **18** were converted into the corresponding hydrochlorides and the resulting material treated with boiling acetone, which left the barely soluble **16** hydrochloride (m.p. 201–202°, from AcOEt/Abs. EtOH; Anal. $C_{16}H_{26}NOCl$). The hydrochloride mixture obtained by evaporation of the acetone liquor was then transformed into the oily free bases, from which diastereomer **18** slowly crystalized (m.p. 69–71°, from pet. ether, Anal. $C_{16}H_{25}NO$); hydrochloride, m.p. 169–170° from MeCOEt/abs. EtOH.

4 - (2' - *Methylpiperidino*) - *butan* - 2 - *ols* **19** *and* **20**. Aminoketone **13** (5.0 g, 0.03 mol) was reduced with $NaBH_4$ (1.9 g, 0.05 mol) in 90% MeOH (80 ml) with occasional stirring for 5 hr. The mixture, diluted with H_2O (80 ml), was submitted to evaporation under vacuum with gently heating and extracted with pet. ether, thus obtaining 3.7 g (75% yield) of diastereomeric aminoalcohols, which were dissolved in 30 ml EtOH/Me_2CO (1:2), containing an equimolar amount of conc HCl, to give the corresponding hydrochlorides. Diastereomer **19** slowly crystallized from the soln (m.p. 185–188°) and was further purified with EtOH (m.p. 190–192°, Anal. $C_{10}H_{20}NOCl$). Fractional precipitation with Me_2CO and then with Et_2O allowed to obtain from the mother liquor the more soluble isomer **20** (m.p. 132–139°) which was finally purified from EtOH/AcOEt (m.p. 138–140°, Anal. $C_{10}H_{20}NOCl$).

4 - (3' - *Methylpiperidino*) - *butan* - 2 - *ols* **21** *and* **22**. Aminoketone **14** was reduced with $NaBH_4$ as described for **13** (80% yield). Attempts to separate the diastereomeric mixture were unsuccessful. The crude product was then treated with an equimolar amount of picric acid in EtOH/H_2O (1:1) to give a picrate, m.p. 97–98° (from EtOH/H_2O, 1:1), Anal. $C_{16}H_{24}N_4O_8$. The aminic product obtained from this picrate was a mixture (by NMR) of compounds **21** and **22**.

N-Ethyl-ABN **10**. To 3-azabicyclo[3.2.2]nonane (2.0 g, 0.016 mol) in a small amount of anhyd benzene, an equimolar amount of diethyl sulphate was added under stirring. The reaction was carried out at 90° for 2 hr, left at r.t. for 24 hr and made alkaline with conc KOH aq (0.02 mol). The organic layer was extracted with Et_2O, and the ethereal soln dried over KOH and submitted to evaporation of the solvent. The residue gave by distillation 1.8 g (83%) of N-ethyl-ABN, b.p. 86.5° at 18 mm Hg. Hydrochloride, m.p. 280–281° (from EtOH), Anal. $C_{10}H_{20}NCl$.

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Acknowledgement—We thank C. N. R. (Rome) for financial support.