ASYMMETRIC REDUCTION OF PHENYL α- AND β-DIALKYLAMINO KETONES BY TREATMENT WITH OPTICALLY ACTIVE ORGANOMAGNESIUM COMPOUNDS

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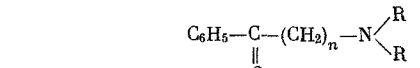
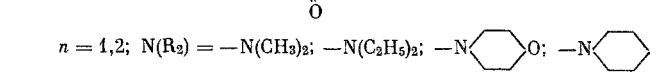
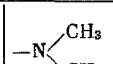
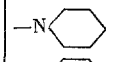
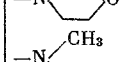
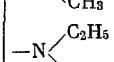
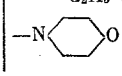
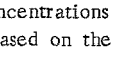
The synthesis and properties of some physiologically active amines, amino alcohols, and their derivatives, were studied in a number of papers [1]. Usually one of the antipodes has a greater physiological action, for which reason it is expedient to cleave the racemic modifications into the antipodes. In order to obtain the optically active amino alcohols we employed asymmetric synthesis via the reduction of the phenyl α- and β-dialkylamino ketones of general formula



$n = 1,2$; $N(R_2) = -N(CH_3)_2$; $-N(C_2H_5)_2$; 

by treatment with the optically active sterically hindered organomagnesium compounds: (+)-2-methylbutylmagnesium bromide and (–)-isobornylmagnesium chloride.

TABLE 1. Asymmetric Reduction of Phenyl α- and β-Dialkylamino Ketones to Amino Alcohols of General Formula $C_6H_5CH(OH)-(CH_2)_n-R$ under the Influence of Optically Active Organomagnesium Compounds

Compound No.	Obtained amino alcohol: n	Obtained amino alcohol: R	Reducing agent	Yield of crude product (hydrochloride), %	Yield of amino alcohol, %	Optical rotation of amino alcohol: $-\alpha_{350}^{23.5}$ (C, %)* (in abs. alcohol)	Optical rotation of amino alcohol: $-[\alpha]_{350}^{23.5}$	Optical rotation of amino alcohol: $-[\alpha]_{320}^{23.5}$
I	1		$C_5H_{11}MgBr$	60	17	0,88 (0,48)	184	270
			$C_{10}H_{17}MgCl$	58	10	0,76 (0,41)	185	290
II	1		$C_5H_{11}MgBr$	62	3	0,85 (0,30)	284	344
			$C_{10}H_{17}MgCl$	72	14	0,80 (0,22)	364	340
III	1		$C_5H_{11}MgBr$	76	24	0,14 (0,05)	280	500
			$C_{10}H_{17}MgCl$	58	5	0,74 (0,15)	490	660
IV	2		$C_5H_{11}MgBr$	50	38	0,09 (0,75)	12	20
			$C_{10}H_{17}MgCl$	75	22	0,48 (0,71)	675	130
			$C_{10}H_{17}MgCl$†	79	18	0,14 (2,80)	5	8
V	2		$C_5H_{11}MgBr$	51	3	0,07 (0,02)	350	—
			$C_{10}H_{17}MCl$	69	5	0,16 (0,02)	800	—
VI	2		$C_5H_{11}MgBr$	61	7	0,16 (0,09)	179	368
			$C_{10}H_{17}MgCl$	72	7	0,20 (0,07)	286	460

*The concentrations of the amino alcohols were calculated according to their yields (based on the UV spectra), and the total amount of unreacted amino ketone and obtained amino alcohol in the samples was 1-5%.

†Reduction of the amino ketone hydrochloride.

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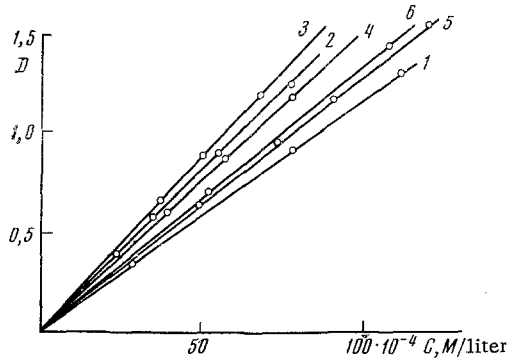


Fig. 1. Optical density at 253 nm as a function of the concentration for the amino ketones in 5% HCl solution: 1) α-dimethylaminoacetophenone; 2) α-piperidylacetophenone; 3) α-(4'-morpholino)acetophenone; 4) β-dimethylaminopropiophenone; 5) β-diethylaminopropiophenone; 6) β-(4'-morpholino)propiophenone.

The asymmetric activity of these reagents was discovered when 4'-nitro-2-acetamido-3-hydroxypropiophenone [2] and N-methylephedrone [3] were reduced. Consequently, it could be expected that these reagents will also prove to be effective in the reduction of the above-indicated amino ketones. It was interesting to ascertain the effect of the structure of the amino ketone on the degree of asymmetric reduction.

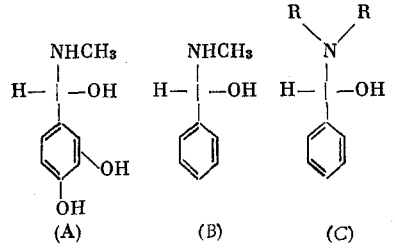
The Grignard reaction [4, 5] was run in solutions of either absolute ether or xylene as described in [6, 7]. The optimum ratio of the Grignard reagent and amino ketone was selected on the basis of the data given in [7, 8], and was 1 : 1 for (+)-2-methylbutylmagnesium bromide and 2.5 : 1 for (–)-isobornylmagnesium chloride. All of the α- and β-amino ketones were reacted as the free bases; reduction of the amino ketone hydrochlorides, for example, the hydrochloride of β-dimethylaminopropiophenone (Table 1) did not give satisfactory results.

The amino alcohols were not isolated from the reaction products. The degree of reduction was estimated spectrophotometrically: α-amino alcohols (λ_{max} 245-250 nm, log ε 2.1-2.15); β-amino alcohols (λ_{max} 253-260 nm, log ε 2.1-2.3). The amino ketones have absorption maxima in the same ranges of the wavelengths, log ε 3.8-4.1 (Fig. 1).* Based on the elemental analysis data, and also those of IR spectroscopy and TLC, addition products are not formed under the given conditions of the Grignard reaction.

As can be seen from Table 1, the total yield of amino alcohols when the phenyl α- and β-amino ketones are reduced with (+)-2-methylbutylmagnesium bromide and (–)-isobornylmagnesium chloride is low (3-38%). Catalytic asymmetric hydrogenation may apparently prove to be a more rational method for the synthesis of the investigated amino alcohols, since catalytic hydrogenation is at times more effective than reduction with asymmetric Grignard reagents [9]. Thus, when the hydrogenation is run on Pd the yields of the corresponding β-amino alcohols are 35-80%. It should be mentioned that when amino ketones are reacted with RMgX, the same as in the case of catalytic reduction, up to 20-50% of neutral substances is formed, which represent mainly desamination products of the starting compounds [10]. Grignard reagents evidently cause substantial desamination of amino ketones, independent of the length of their hydrocarbon chain [1]. The desamination is somewhat less when treatment is with isobornylmagnesium chloride.

The asymmetric reduction products were studied both polarimetrically and spectropolarimetrically. The observed optical rotation at 589 nm, equal to −0.02 to −0.09°, increased by 10-40 times when measured in the range 350-303 nm. As a result, it was shown spectropolarimetrically that the optically active phenyl α- and β-amino alcohols are formed in the asymmetric reduction of amino ketones by treatment with RMgX.

In order to determine the absolute configuration of the obtained amino alcohols we compared the optical rotation dispersion (ORD) curves [11] (Fig. 2) with the ORD curves of an (–)-amino alcohol of analogous structure with a known configuration. It is known that (–)-epinephrine (A), and also (–)-ephedrine have an R-(–)-configuration [12]. Epinephrine and phenylephrine (B) have one center of chirality and are analogs of the amino alcohols studied by us. From a comparison of the ORD curves it follows that the (–)-α- and β-aminocarbinols (C) obtained by us have the R-configuration



*The accuracy is at least ±0.5%.

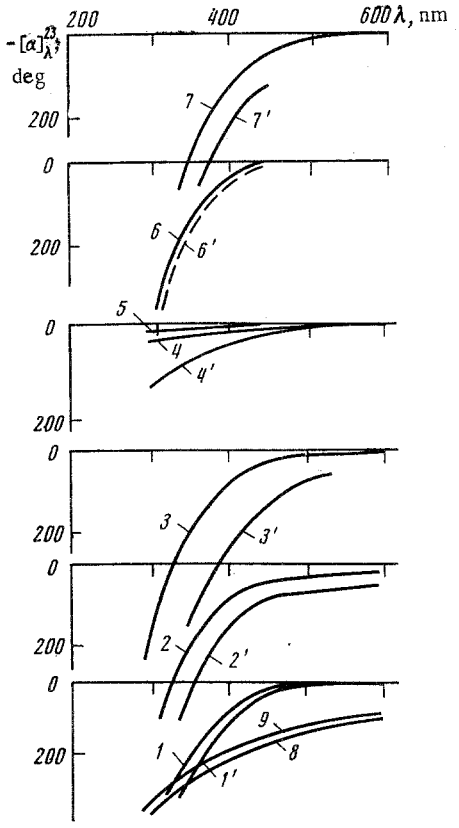


Fig. 2. Optical rotation dispersion (ORD) curves of reduction products of amino ketones by treatment with 2-methylbutylmagnesium bromide (1-7) and isobornylmagnesium chloride (1'-7'): 1) α-dimethylaminoacetophenone; 2) α-piperidylacetophenone; 3) α-(4'-morpholino)acetophenone; 4) β-dimethylaminopropiophenone; 5) hydrochloride of 4); 6) β-(4'-morpholino)propiophenone; 7) β-diethylaminopropiophenone; 8) ORD curve of ψ-(–)ephedrine from [12]; 9) ORD curve of (–)-epinephrine from [12].

For (–)-1-phenyl-2-dimethylaminoethanol (I) and (–)-1-phenyl-3-dimethylaminopropanol (IV) it proved possible to calculate the optical yield in the asymmetric reduction with organomagnesium compounds. Sufficiently reliable results are obtained by comparing the $[\alpha]_\lambda$ of the investigated compounds and of the optically pure isomers, which were obtained by us by the cleavage of the racemic bases [10]; for (I), $[\alpha]_D^{23.5}$ + 42.1°; for (IV), $[\alpha]_D^{23.5}$ + 78.8°. The optical yield when α-dimethylaminoacetophenone is reduced with (+)-2-methylbutylmagnesium bromide (p = 68 ± 7%) is close to the optical yield that is obtained when reduction is with (–)-isobornylmagnesium chloride (72 ± 8%). However, for β-dimethylaminopropiophenone it proved that (–)-isobornylmagnesium chloride was much more effective (p = 65 ± 15%) than when reduction was with (+)-2-methylbutylmagnesium bromide (11% when the free base of the amino ketone was reduced, and 4% when the hydrochloride was reduced). Apparently, the close proximity of the nitrogen atom to the carbonyl group facilitates the asymmetric reduction. The steric factors prove to be important for β-dimethylaminopropiophenone: in the given reaction the sterically large isobornyl radical promotes an increase in the degree of asymmetric conversion by 55% when compared with the action of (+)-2-methylbutylmagnesium bromide. Salt formation by the dimethylamino group of β-dimethylaminopropiophenone impedes the process of asymmetric reduction and the optical yield decreases by 2.5 times compared with the reduction of the free base.

As a result, the reduction of the phenyl α- and β-dialkylamino ketones by optically active Grignard reagents proceeds asymmetrically, in which connection the optical yield reaches 70% in some cases, which can be of practical interest.

EXPERIMENTAL METHOD

α-Dimethylaminoacetophenone [13], bp 94°C (3.5 mm); hydrochloride, mp 172-174°. α-(4'-Morpholino)acetophenone [14]; hydrochloride, mp 201°. α-Piperidylacetophenone [14], bp 153-155° (4 mm). β-Dimethylaminopropiophenone [15]; hydrochloride, mp 148-149°. β-Diethylaminopropiophenone [15]; hydrochloride, mp 108-110°, which was obtained as described in [15]. β-(4'-Morpholino)propiophenone; hydrochloride, mp 180-180.5°, which was obtained as described in [14, 15]. (+)-2-Methylbutyl bromide [4], which was obtained by the reaction of (–)-2-methyl-1-butanol with PBr_5. The optically active (–)-2-methyl-1-butanol (optical purity 94.5%) was isolated by fractional distillation from fermentation isoamyl alcohol. The (+)-2-methylbutyl bromide was obtained with $[\alpha]_D^{23.5}$ + 2.2, ($\alpha_D^{23.5}$ + 5.11; *l* 2; d_4^{20} 1.16), and an optical purity of 50%.

(–)-Isobornyl chloride was obtained from (–)-camphene via camphene hydrochloride, mp 124-124.5°, by the isomerization of the latter in ethyl bromide for 6 days [5]. The conversion was followed by GLC (0.7% of poly(ethylene glycol adipate) deposited on kieselguhr, 100-140°, flow rate of carrier gas 40-60 ml/min, retention time of isobornyl chloride 9.4-9.5 min). After two recrystallizations (first from n-amyl alcohol, and then from methanol), mp 152°; $[\alpha]_D^{23.5}-15°$; $(\alpha_D^{23.5}-0.3°$; C 1; *l* 2; absolute ethanol), and optical purity 44%.

Asymmetric Reduction of Amino Ketones with (+)-2-Methylbutylmagnesium Bromide. To the obtained Grignard reagent (0.024 M of Mg and 0.023 M of (+)-2-methylbutyl bromide in absolute ether) at 15° was added slowly in drops the free base of the amino ketone in absolute ether. After 2 h the complex was decomposed with 1:1 HCl solution. The acid aqueous layer was washed 10 times with ether, made alkaline with K_2CO_3 to pH 8.5-9, and the basic products were extracted with ether. The extract was dried over $MgSO_4$ and the filtrate was saturated with dry HCl gas. The hydrochlorides were recrystallized from absolute alcohol by the addition of ether (5:1). The reduction results are given in Table 1. The amino alcohols were not isolated from the mixtures, which contained the unreacted amino ketones. The absence of tert-aminocarbinols was qualitatively shown by the TLC method. In the IR spectra are also absent changes in the 2870-2940 cm^{-1} region, and the peaks of OH^- at 1150 cm^{-1}, which are identical to the corresponding peaks in the spectrum of the racemic amino alcohols. The yield of the amino alcohols was determined spectrophotometrically.

Asymmetric Reduction of Amino Ketones with (–)-Isobornylmagnesium Chloride. To the Grignard reagent (11.8 mM of Mg and 11.8 mM of isobornyl chloride in 118 ml of xylene) at 15° was added 4.9 mM of the amino ketone in xylene. After 2.5 h the reaction complex was worked up in the same manner as when reduction was with (+)-2-methylbutylmagnesium bromide. The neutral reaction products were extracted with benzene. Using the TLC method, in the system 1:5 ethanol–diethyl ether, it was shown that addition products are absent in the asymmetric reduction. The IR-spectroscopy measurements confirm the absence of tertiary phenyl-α- and β-amino alcohols.

CONCLUSIONS

1. When α-dimethylaminoacetophenone and β-dimethylaminopropiophenone are reduced by optically active organomagnesium compounds the asymmetric reduction proceeds with an optical yield of 65-70%.

2. The absolute configuration for the obtained amino alcohols was proposed on the basis of the optical rotation dispersion data.

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