INFLUENCE OF TEMPERATURE OF THE STEREOSPECIFIC REDUCTION OF (−)-α-DIMETHYLAMINOPROPIOPHENONE (METHYLEPHEDRONE) UNDER THE ACTION OF OPTICALLY ACTIVE 2-METHYLBUTYL MAGNESIUM BROMIDE

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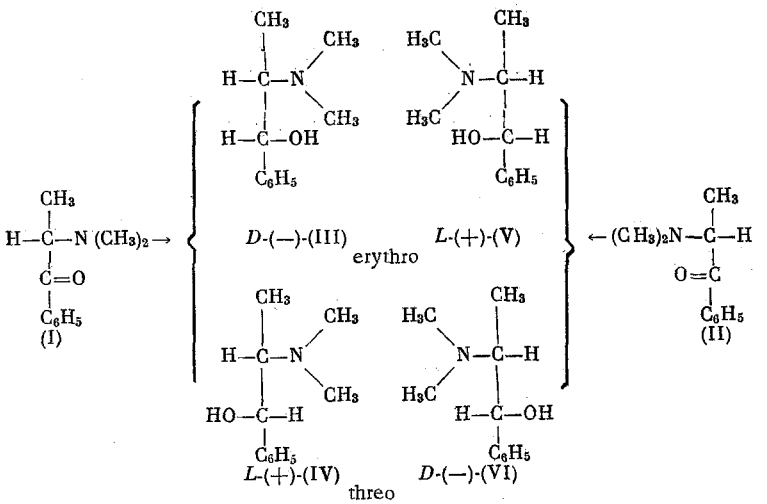
In [1-3] it was shown for the reaction of ketones with alcohols and amines that as the temperature of the reaction changes, not only the magnitude, but also the sign of the optical rotation of the reaction product changes. In this case the optical yield increases sharply if the reaction is conducted at low temperature (up to −180°); when the temperature is raised, the specificity drops [1]. At the same time, we have shown that the temperature has little influence on the asymmetrical synthesis of atrolactic acid, formed in the interaction of the methyl ester of phenylglyoxylic acid with methyl magnesium bromide [4]. In connection with this we were interested in studying the influence of temperature on asymmetric synthesis for other examples, in particular, for the reduction of (−)-α-dimethylaminopropiophenone under the action of an optically active organomagnesium complex in order to produce the practically important optically active methylephedrine.

The reduction of α-dimethylaminopropiophenone can lead to threo- and erythro-amino alcohols; however, according to the Kram rule of steric control we should expect the predominant formation of the threo-isomer (IV), (VI)



The use of organomagnesium complexes as the reducing agent promotes the formation primarily of the threo-isomer [5]. We might expect an increase in the optical selectivity of the process, which is of considerable interest, since it permits the synthesis chiefly of threo-methylephedrine, the properties of which in contrast to the ephedrine series, have been little studied.

The reduction of optically active (−)-α-dimethylaminopropiophenone (II) (produced by resolution of the racemic α-aminoketone) under the action of (+)-2-methylbutyl magnesium bromide was conducted in ether

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TABLE 1. Separation of Racemic α-Dimethylaminopropiophenone into Optical Isomers

Compound	No. of crystallizations	Yield, % of amino ketone taken	Mp of salts [bp of bases], °C	$[\alpha]_D$, deg; 21; abs. ethanol (α_D; C, %)
(±)-Amino ketone	—	—	Hydrochloride 205, [88—90 (2 mm)]	—
Dibenzoyl-(−)-tartrate of (−)-amino ketone	1	48	138—139	—
	2	35	138	−81 (−0,68; 0,84)
	3	19	138	−80,7 (−0,242; 0,30)
	4	—	138	−79,9 (−0,675; 0,845)
(−)-Amino ketone hydrochloride	From 3	17,4	195±0,5	−47,2 (−0,46; 0,975)
(+)-Amino ketone hydrochloride	From filtrates	46,5	199—201	+3,53 (+0,111; 3,14)*

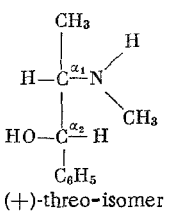
*Optical purity 7.5%.

at the temperatures −95 to +35°. The composition of the reaction mixture was analyzed by the methods of gas–liquid chromatography and UV spectroscopy. In addition, the reaction products were analyzed by IR spectroscopy and elemental analysis.

Dibenzoyl-D-tartaric acid was used for the resolution of (±)-α-dimethylaminopropiophenone, since according to [6] the dibenzoyl derivative of tartaric acid forms a diastereoisomeric salt, which crystallizes better than the salt of (+)-tartaric acid. The resolution was performed analogously to [6] by fractional crystallization of the diastereoisomeric salt in acetone. We determined the optically active amino ketone in the form of the hydrochloride and the base. The results of the separation are cited in Table 1. As can be seen from the data cited, two to three successive crystallizations of the dibenzoyltartrate in acetone are sufficient to obtain a salt with a constant melting point and practically the same specific rotation, i.e., an optically pure salt. Elemental analysis shows that the diastereoisomeric salt is the acid dibenzoyltartrate $C_{11}H_{15}NO \cdot C_{18}H_{14}O_8 \cdot H_2O$. The optically active (−)-α-dimethylaminopropiophenone, ($[\alpha]_D^{23.5}$ −28.3°), produced by decomposition of the salt, was converted to the hydrochloride with mp 195°; $[\alpha]_D^{23.5}$ −47.2°. Calculated on the basis of the amino ketone taken, the yield of the pure (−)-methylephedrone hydrochloride was 16%. A spectropolarimetric investigation of the sample indicated that the compound is characterized by a smooth negative curve of the optical rotatory dispersion.

The reduction of (−)-methylephedrone was conducted under the action of optically active 2-methylbutyl magnesium bromide in abs. ether at temperatures of +15 to −95°. The total yield of the bases was 71-78% (Table 2). It was shown chromatographically that the remaining 22-29% of the initial α-amino ketone was subjected under the reaction conditions to deamination to acetophenone and propiophenone. No products of addition according to the Grignard reaction were detected. The composition of the reaction mixture was quantitatively analyzed by gas–liquid chromatography and UV spectrophotometry at 246 nm (in the latter case, the amount of unreacted ketone was determined). The discrepancy in the results according to the two methods does not exceed 3% (see Table 2). As a result of the stereospecific reduction of (−)-methylephedrone under the action of (+)-2-methylbutyl magnesium bromide at 15°, (−)-methylephedrine is formed. By comparing the retention times of the product obtained with the retention times of ephedrine (erythro-isomer) and specially synthesized threo-ephedrine according to [7], it was shown that (−)-methylephedrine has a threo-configuration.

The values of the specific rotations of the threo-methylephedrine formed, cited in Table 2, were calculated on the basis of the summary specific rotation of a mixture containing methylephedrine and methylephedrone. The specific rotation of optically pure methylephedrine can be estimated on the basis of the principle of optical superposition. Thus, for the ephedrine series we have $[\alpha]_D$ 62.0° for the threo-isomer and $[\alpha]_D$ −34.4° for the erythro-isomer. Consequently, the increments of the specific rotations of the asymmetrical centers α_1 and α_2 are equal to +13.8 and +48.2°, respectively.


(+)-threo-isomer

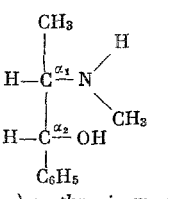

(−)-erythro-isomer

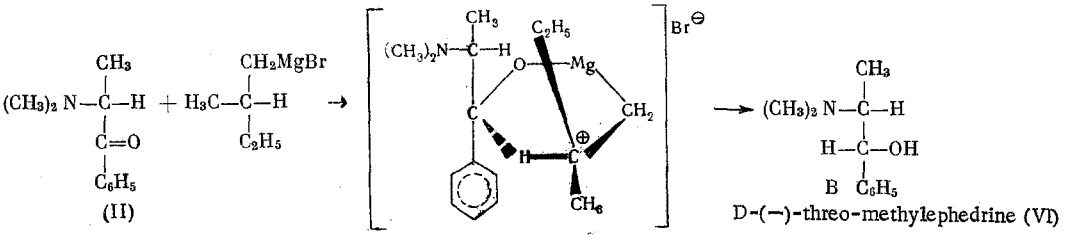
TABLE 2. Stereospecific Reduction of (−)-α-Methylaminopropiophenone by Optically Active 2-Methylbutyl Magnesium Bromide

T, °C	Amino alcohol and unreacted amino ketone obtained, % of initial	Yield of methylephedrine, % of initial amino ketone	Composition of reaction mixture, %				Mp of threo-alcohol hydrochloride, °C	N, %*	Summary optical rotation of catalyzate $[\alpha]_D^{23}$	$[\alpha]_D$ of threo-m-thylephedrine
			threo-methylephedrine		methylephedrone					
			Gas–liquid chromatography	UV spectroscopy	Gas–liquid chromatography	UV spectroscopy				
−95	75	16,1	21,5	22	78,5	78	188	6,46	−50° (α_D^{23} −0,25, *C* 1, *l* 0,5)	−63,4°
−32	71,5	37,2	52	51,4	48	48,6	187	6,66	−65,4° (α_D^{23} −0,327°, *C* 1, *l* 0,5)	−56°
0	73,7	53,8	70,5	73	29,5	27	187–188	6,56	−50,4° (α_D^{23} −1,12°, *C* 4,45, *l* 0,5)	−50,8°
15	78,0	61,5	76,2	79	23,8	21	186	6,50	−28,05° (α_D^{23} −0,3°, *C* 1,07, *l* 1)	−22,1

* $C_{11}H_{17}NO \cdot HCl$. Calculated: N 6.51%

It is known that for *l*-methylephedrine (erythro-isomer) the difference $(\alpha_1 - \alpha_2) = -29.8°$ [8, 9]; therefore $\alpha_1 = -29.8 + 48.2 = +18.4°$. From this the specific rotation of threo-methylephedrine is equal to $(\alpha_1 + \alpha_2) = 18.4 + 48.2 = 66.6°$. The same value (66.4°) is also obtained by extrapolation of curve 1 (Fig. 1) to p = 100%. Using the value found for the specific rotation of (−)-threo-methylephedrine, we calculated the optical yields (p) of threo-ephedrine, which apparently indicate partial rotation of the configuration with respect to both centers, which is intensified with increasing temperature. The data obtained permit a determination both of the (−)-methylephedrine formed and of the initial (−)-methylephedrone.

In accord with the reaction scheme suggested in [10], in the reduction of ketones a six-membered cyclic transition state (A) is formed



As is shown by the models, this should lead to the predominant formation of the threo-isomer (B), which is also observed experimentally. On the basis, the configuration D-(II) should be ascribed to the initial (−)-α-dimethylaminopropiophenone.

EXPERIMENTAL METHOD

Gas–liquid chromatography was conducted on a "Khrom-3" chromatograph with a flame-ionization detector at the temperature 200° and carrier gas velocity 60 ml/min in a stainless steel column 3 m long, 6 mm in diameter, filled with Celite-545, 30-60 mesh, preliminarily treated with 5% KOH and 10% polyethylene glycol-20,000. At a nitrogen volocity of 60 ml/min, the retention time of (−)-, (+)-, and (±)-methylephedrone is 10.2 min. Under the conditions of chromatography, the peak corresponding to the closest homolog of methylephedrine, *l*-ephedrine (erythro-isomer) (19.6 min), also emerged later than threo-ephedrine (18.0 min). The latter compound was produced by isomerization of *l*-ephedrine in HCl according to [7] for 15 h; mp 182°; $[\alpha]_D^{23.5}$ +61.90° ($\alpha_D^{23.5}$ + 0.86°; C 1.39; *l* 1; water). For purposes of identification we synthesized erythro-methylephedrine according to [9]. The retention time of threo-methylephedrine was 13.9-14.0 min, that of erythro-methylephedrine 15.9-16.0 min.

(−)-α-Dimethylaminopropiophenone (II) was produced by resolution of the racemic α-amino ketone by fractional crystallization of the salt of dibenzoyl-D-tartaric acid (mp 91.92°; $[\alpha]_D^{20}$ −116°).

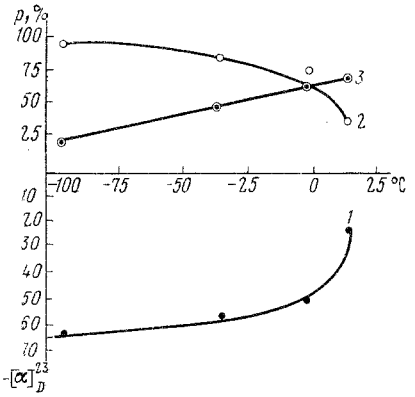


Fig. 1. Dependence of the optical rotation $[\alpha]_D$ (1), optical yield p (2), and yield of the amino alcohol (3) in the redution of (−)-methylephedrone under the action of 2-methylbutyl magnesium bromide on the temperature of the reaction.

A 177 g portion of racemic α-amino ketone with bp 88-90° (2 mm) was mixed in an acetone solution (8 liters) with 450 g of dibenzoyl-D-tartaric acid. The solution was mixed until crystallization at the temperature 20° and for another 18 h. The solid precipitate was filtered off, washed with acetone, and dried in air for 72 h. We obtained 250 g of the product, mp 138-139° (according to Allen). After recrystallization from abs. acetone, we obtained 180 g of the product; mp 138°; $[\alpha]_D^{20}$ −81° (α_D^{20} −0.68°; C 0.84; *l* 1; abs. ethanol); after the second recrystallization of acetone we obtained 10.5 g of a product with mp 138°; $[\alpha]_D^{20}$ −80.7° (α_D^{20} −0.242°; C 0.30; *l* 1; abs. ethanol). Subsequent crystallization gave a salt with the same melting point and $[\alpha]_D^{20}$ −79.9° (α_D^{20} −0.675°; C 0.845; *l* 1; abs. ethanol). Found: N 2.66, 2.60%. $C_{11}H_{15}NO \cdot C_{18}H_{14}O_8$. Calculated: N 2.65%.

A 100 g portion of dibenzoyl (−)-tartate of (−)-α-dimethylaminopropiophenone was treated with 38 ml of 28% NH_3 in 240 ml of water. (−)-α-Dimethylaminopropiophenone was extracted with 100 ml of ether; the solution was washed with 50 ml of water and dried with calcined $MgSO_4$. A stream of anhydrous HCl was passed through the ether solution and the precipitated hydrochloride filtered off. We obtained 30.8 g (91%) of a substance with $[\alpha]_D^{20}$ −41° (C_2H_5OH). After recrystallization from a mixture of abs. ethanol with diethyl ether (1 : 3), we obtained 28.1 g of the purified (−)-amino ketone hydrochloride with mp 195 ± 0.5°; $[\alpha]_D^{20}$ −47.1° (α_D^{20} −0.46°; C 0.975; *l* 1; abs. ethanol).

In an investigation on an SPU-E photoelectric spectropolarimeter, the sample showed a smooth curve of the optical rotatory dispersion: $[M]_{546}^{20}$ −151.0°; $[M]_{434.7}^{20}$ −266°; $[M]_{404.7}^{20}$ −266°; $[M]_{404.7}^{20}$ −340°; $[M]_{366}^{20}$ −790°. The yield of the pure product was 16% converted to the initial (±)-amino ketone or 32%, calculated on the basis of one isomer.

(+)-α-Dimethylaminopropiophenone ·HCl was isolated from the combined filtrates and wash waters by treatment analogous to the preceding; mp 199-201°; $[\alpha]_D^{20}$ +3.53° (α_D^{20} +0.111°; C 3.14; *l* 1; abs. ethanol); p (optical purity) 7.5%; yield 93% of the theoretical (calculated on the basis of one isomer). Found: N 6.50%. $C_{11}H_{15}NO \cdot HCl$. Calculated: N 6.50%. A spectropolarimetric investigation from 589 to 365 nm indicated a smooth path of the optical rotatory dispersion curve.

Optically active 2-methylbutyl bromide was produced according to [8] by the action of PBr_5 on (−)-2-methyl-1-butanol, isolated from amyl alcohol by fermentation; bp 128-128.5°; $[\alpha]_D^{20}$ −5.1°; (+)-2-methylbutyl bromide had bp 120°; $[\alpha]_D^{23.5}$ +2.2° (p 50%).

Stereospecific Reduction of (−)-Methylephedrone by Optically Active 2-Methylbutyl Magnesium Bromide. The Grignard reagents were prepared over a period of 4-5 h in absolute diethyl ether in an atmosphere of anhydrous nitrogen. The ratio amino ketone: Grignard reagent equals 1 : 1.1. The amino ketone (0.0049 mole) was introduced into the reaction over a period of 30 min at the corresponding temperature and exposed for 1-5 h. After this the reaction complex was decomposed with diluted HCl, the ether layer removed, the hydrochloric acid solution of nitrogen-containing compounds washed 10 times with ether, then alkalinized to pH 9-9.5 according to universal indicator, and the basic reaction products extracted. The ether extract was dried with freshly calcined $MgSO_4$, the ether distilled off, and the content of the basic substances determined (71-78%).

The reduction products were analyzed by the methods of gas–liquid chromatography and UV spectrophotometry in solutions of 5% HCl at 246 nm (see Table 2). Hydrochlorides were produced from the basic amino compounds by the action of HCl in abs. ether; the hydrochlorides were purified by recrystallization from methanol in abs. ether (1 : 3). Hydrochloride: mp 186-188°. Chromatographic analysis of the neutral products indicated the presence of acetophenone (5.5-10%) and propiophenone (3-5%). Elemental analysis, gas–liquid chromatography, and the IR spectra confirmed the anomalous course of the Grignard reaction.

CONCLUSIONS

1. The temperature dependence of the stereospecfic reduction of (−)-methylephedrone was investigated.

2. The reaction proceeds with strict selectivity, with the formation only of threo-(−)-methylephedrine. The optical yield can be increased by lowering the temperature.

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