FIRST ASYMMETRIC SYNTHESIS OF 4-PIPERIDONES. PREPARATION OF OPTICALLY ACTIVE DIASTEREOMERS OF 1-α-PHENYLETHYL-2-METHYL-4-PIPERIDONE

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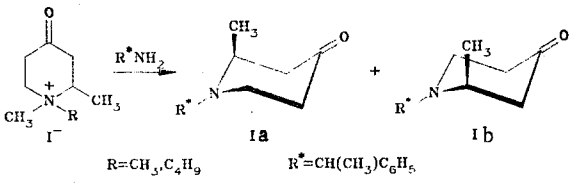
The fundamental possibility of carrying out the asymmetric synthesis of 4-piperidones on the basis of the transamination of 1-substituted 2-methyl-4-piperidone methiodides by optically active α-phenylethylamine was demonstrated; the optical yield of the asymmetric transamination is 50%. The occurrence of asymmetric synthesis was confirmed by the isolation of enantiomers of 2-methyl-4-piperidol by reduction of the individual diastereomers of 1-α-phenyl-ethyl-2-methyl-4-piperidone to the corresponding 4-piperidols with subsequent removal of the chiral substituent attached to the nitrogen atom.

The necessity of a search for methods for the asymmetric synthesis of 4-piperidones is explained by the fact that they are key substances for the preparation of a large number of biologically active and natural compounds. Among such compounds, prodine and promedol, which have neuro- and psychotropic activity that significantly exceeds the activity of morphine [1], are known. The literature does not contain data on the synthesis of optically active 4-piperidones or on attempts to separate them into optical antipodes by classical methods. In the present research we established the possibility of the asymmetric synthesis of 4-piperidones by means of the previously described method for the preparation of 1-alkyl-4-piperidones, which is based on the transamination of N-methyl-4-piperidone methiodides by primary amines [2]. We established that the reaction of 1,2-dimethyl-4-piperidone methiodide with (−)-α-phenylethylamine at room temperature in the presence of water leads, according to the results of chromatographic analysis, to the formation of two new compounds Ia (R_f 0.5) and Ib (R_f 0.3), which, according to the results of elementary analysis and mass spectrometry, are isomers of 1-α-phenylethyl-2-methyl-4-piperidone.



Isomers Ia and Ib were isolated in the individual state in 40% overall yield by means of column chromatography on silica gel. Diastereomer Ia is formed in larger amounts; the ratio of the isolated isomers Ia and Ib is 2.2:1, which corresponds to a diastereomeric excess of 37%. The structures of individual diastereomers Ia and Ib were confirmed by chromatographic mass spectrometry, the IR and UV spectra, and ^1H and ^{13}C NMR data. The primarily axial orientation of the 2-CH_3 group was established from ^{13}C NMR data, information regarding which will be reported in greater detail in a future paper. According to the PMR data, the diastereomeric purity of each of isomers Ia, b is 98%, and both of the isomers obtained are optically active. A positive Cotton effect at 300 nm, which is associated with the $n \rightarrow \pi^*$ transition of the carbonyl chromophore, is displayed for each isomer in the circular dichroism spectra; however, the intensities of the Cotton effects differ: θ + 650° for Ia, and θ + 2200° for Ib (Fig. 1).

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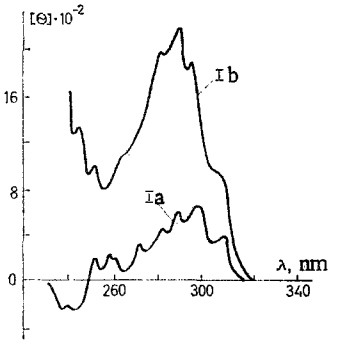


Fig. 1

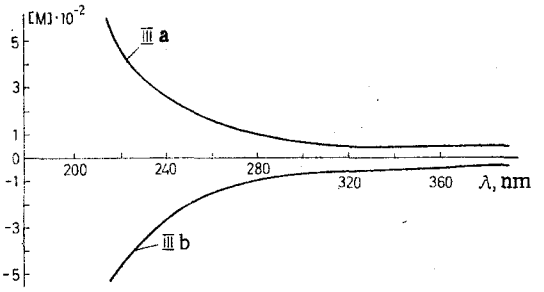
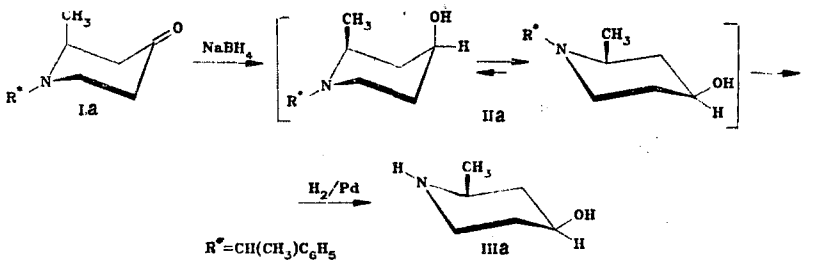


Fig. 2

Fig. 1. Circular dichroism curves for 1-α-phenylethyl-2-methyl-4-piperidones Ia and Ib in heptane.

Fig. 2. Optical rotatory dispersion curves of (+)-2-methyl-4-piperidol (IIIa) and (−)-2-methyl-4-piperidol (IIIb) in CH_3OH.

In order to shed some light on the question of the possibility of the occurrence of asymmetric synthesis from a molecule of each of isomers Ia, b one must remove the chiral α-phenylethyl substituent and compare the chiral-optical properties of the resulting 2-methyl-4-piperidones. However, the 2-methyl-4-piperidone that is formed in this case is an unstable and readily resinified compound [3]. Confirmation of the asymmetric synthesis was therefore carried out with stable 4-piperidols IIa,b, which were obtained by reduction of individual 4-piperidones Ia, b with sodium borohydride with subsequent removal of the chiral substituent attached to the nitrogen atom. The reduction of isomers Ia, b was carried out with $NaBH_4$ in aqueous ethanol at room temperature. The formation of two 4-piperidols with considerable preponderance of one of them was observed in each case by chromatographic monitoring of the reaction mixture. The corresponding 4-piperidols IIa (R_f 0.3) and IIb (R_f 0.1) were isolated in both cases in 94% and 93% yields by fractional crystallization from hexane and chromatographic separation of the residue with a column packed with Al_2O_3. According to the NMR data, the isolated isomers IIa, b are diastereomerically pure, and identical character of the fragmentation and virtually identical intensities of the fragment ions are observed for both isomers; this constitutes evidence for their identical chemical and spatial structures.



Only a band of stretching vibrations of a free hydroxy group at 3605 cm^{-1} is observed in the IR spectra of solutions of piperidols IIa,b (concentration 0.01 mole/liter). We used ^{13}C NMR spectroscopy to determine the spatial orientation of the OH and 2-CH_3 groups in isomeric piperidols IIa,b. The experimentally found chemical shifts and the values calculated by an additive scheme were compared. The calculated values of the ^{13}C chemical shifts for both piperidols IIa, b were obtained by means of data from the spectrum of 2-methylpiperidine with an equatorial orientation of the CH_3 group [4] and the averaged parameters of the equatorial hydroxy group for cyclohexanols and N-methyl-4-piperidol [5]. The calculated ^{13}C spectra for both piperidols IIa and IIb are in good agreement with the experimental spectra (Table 1), and consequently, both diastereomers have a diequatorial orientation of the substituents in the ring. The ^{13}C spectra calculated for isomers IIa,b with the aid of increments of the axial OH group [6] showed pronounced deviation from the experimental values. Thus stable cis-2-methyl-4-piperidols IIa,b are formed from piperidone isomers Ia,b which have primarily an axial 2-CH_3 group. Consequently, attack by the hydride ion at the carbonyl group of isomers

TABLE 1. Experimental and Calculated ^{13}C Chemical Shifts (δ, ppm) of 1-α-Phenylethyl-2-methyl-4-piperidol Isomers IIa,b

Spectrum*	Compound	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	2-CH_3	α-CH_3
ES	IIa	51,7	42,6	69,4	35,5	44,8	20,4	8,6
	IIb	51,7	43,6	68,7	35,5	44,7	20,7	19,0
CS (e-OH)	IIa	50,5	43,8	68,0	35,3	45,5	—	—
$\delta_{exp} - \delta_{calc}$	IIa	1,2	−1,2	1,4	0,2	−0,7		
	IIb	1,4	0,2	0,7	0,2	−0,8		
CS (a-OH)	IIb	46,1	42,9	61,9	35,9	45,1		
$\delta_{exp} - \delta_{calc}$	IIa	5,6	0,3	7,5	−0,4	−0,3		
	IIb	5,8	0,7	6,8	−0,4	−0,4		
	2e-Methylpiperidine [4]	53,0	35,5	25,8	27,0	57,9		23,5

*The experimental spectrum is indicated by ES, and the calculated spectrum is indicated by CS; the increment used is indicated in parentheses.

Ia,b occurs from the equatorial orientation and leads to the primary formation of the cis-2*a*,4*a* conformer, which is converted to the thermodynamically more favorable diequatorial conformer. The asymmetrizing α-phenylethyl substituent was removed in each of piperidols IIa,b by means of hydrogenolysis. According to the IR spectral data and the melting points, the 2-methylpiperidols IIIa,b obtained were identical and had identical mass spectra. Piperidols IIIa,b are optically active and are characterized by smooth optical rotatory dispersion (ORD) curves with antipodal trends vis-à-vis virtually identical intensities (Fig. 2); this confirms that asymmetric transamination occurs in the reaction of 1,2-dimethyl-4-piperidone methiodide with (−)-α-phenylethylamine. It must be noted that increases in the optical yield to 50% and in the chemical yield to 60% are observed in the transamination of 1-butyl-2-methyl-4-piperidone with α-phenylethylamine, i.e., it is further necessary to investigate the effect of various factors that lead to an increase in the optical yield of the reaction, viz., the nature of the substrate and agent, the solvents, and the temperature.

EXPERIMENTAL

The IR spectra of films, mineral oil suspension, or solutions in CH_2Cl_2 were recorded with UR-20 and Perkin-Elmer 457 spectrometers. The PMR spectra were measured with Varian T-60 and XL-100 spectrometers with tetramethylsilane (TMS) as the internal standard. The ^{13}C NMR spectra were recorded with a CFT-20 spectrometer; the chemical shifts are given on the δ scale relative to TMS. The mass spectra were obtained with MKh-1303 and Varian MAT-111 spectrometers equipped with a system for direct introduction of the samples into the ion source at a vaporization temperature of 100-150°C and an ionizing-electron energy of 50-60 eV. The UV spectra were recorded with Cary-15 and Specord UV-vis spectrophotometers. The circular dichroism and optical rotatory dispersion curves were recorded with a Jasco-20 spectropolarimeter at room temperature. Analysis by gas–liquid chromatography (GLC) was carried out with an LKhM-8MD chromatograph with a capillary column (30 m, SE-30 support).

1,2-Dimethyl-4-piperidone Methiodide. A solution of 9.3 ml (150 mmole) of methyl iodide in 10 ml of petroleum ether was added with stirring to 9.5 g (75 mmole) of 1,2-dimethylpiperidone [7] in 20 ml of petroleum ether (70-100°C), and the mixture was allowed to stand overnight. The resulting precipitate was removed by filtration and dried in vacuo to give 19.7 g (98%) of 1,2-dimethyl-4-piperidone methiodide with mp 162-163°C. Found: C 35.4; H 5.8; N 5.2%. $C_8H_{16}INO$. Calculated: C 35.6; H 5.9; N 5.2%.

1-Butyl-2-methyl-4-piperidone Methiodide. A mixture of 7 g (40 mmole) of 1-butyl-2-methyl-4-piperidone [8], 70 ml of dry acetone, and 5 ml (40 mmole) of freshly distilled CH_3I was refluxed in a stream of argon for 3 h, after which the resulting precipitate was removed by filtration and washed with acetone to give 7 g (54%) of 1-butyl-2-methyl-4-piperidone methiodide with mp 126-127°C (from acetone). Found: C 42.6; H 7.0%. $C_{11}H_{22}INO$. Calculated: C 42.4; H 7.1%.

1-α-Phenylethyl-2-methyl-4-piperidone Diastereomers (Ia,b). A) A mixture of 6.22 g (20 mmole) of 1-butyl-2-methyl-4-piperidone methiodide, 4 ml of (−)-α-phenylethylamine ($[\alpha]_D^{20}$ − 41°), and 1.4 ml (78 mmole) of water was stirred until it became homogeneous, after which it was allowed to stand at room temperature for 1.5 h. It was then saturated with potassium

carbonate and extracted with ether. The ether extracts were dried with potassium carbonate, the ether was removed, and the residue (2.7 g) was applied to a column packed with silica gel (40/100, Chemapol) in benzene. Elution was carried out with benzene–ethyl acetate (5:1) to give 0.52 g of isomer Ia in the form of an oil [R_f 0.7, Merck Silufol, benzene–acetone (5:1)], 0.24 g of crystalline isomer Ib, with mp 81-82°C (from pentane) [R_f 0.5, Merck Silufol, benzene–acetone (6:1)], and 0.04 g of a mixture of isomers Ia and Ib. The overall yield was 37%.

B) From a mixture of 6.22 g (20 mmole) of 1-butyl-2-methyl-4-piperidone, 4 ml of (–)-α-phenylethylamine, and 2 ml (100 mmole) of water under similar conditions, after separation with a column packed with silica gel and elution with benzene–ethyl acetate (3:1), we obtained 2.2 g (73%) of isomer Ia in the form of a light-yellow oil and 0.8 g (27%) of isomer Ib with mp 81-82°C (from pentane). The overall yield was 70%. Isomer Ia had M^+ 217 (calculated M 217). IR spectrum in mineral oil: 1730 cm^{-1} (C=O). Isomer Ia also had $[\alpha]_D^{20}$ –7.1° (c 17, CH_3OH), and $[\theta]_{307}$ + 423° (heptane). UV spectrum, λ_{max}, nm (ε): (in heptane) 300 (97), shoulders 256 (439), 262 (304), and 266 (224); (in methanol) shoulders 288 (152), 258 (963), 253 (1230), and 248 (1398). Isomer Ib had M^+ 217. IR spectrum in mineral oil: 1730 cm^{-1} (C=O). Isomer Ib also had $[\alpha]_D^{20}$ –19.7° (c 2.3, CH_3OH) and $[\theta]_{298}$ +1970° (heptane). UV spectrum, λ_{max}, nm (ε): (in heptane) shoulders 290 (185), 267 (404), 262 (516), and 256 (717); (in methanol) shoulders 300 (258) and 259 (1105). The picrate of a mixture of Ia,b had mp 144-145°C (from ethanol). Found: C 53.8; H 4.9; N 12.5%. $C_{14}H_{19}N \cdot C_6H_3N_3O_7$. Calculated: C 53.8; H 5.0; N 12.6%.

(+)-cis-1-(S-α-Phenylethyl)-2-methyl-4-piperidol (IIa). A solution of 0.11 g (3 mmole) of $NaBH_4$ in 10 ml of cold water was added at 0°C to a solution of 0.65 g (3 mmole) of piperidone Ia in 60 ml of ethanol, and the reaction mixture was stirred at room temperature for 2 h. An equal volume of water was added, and the aqueous mixture was extracted with chloroform. The chloroform extract was dried with magnesium sulfate, and the solvent was removed to give 0.56 g (93%) of a crystallizable oil. Chromatography on Al_2O_3 in benzene–ethyl acetate (7:3) demonstrated the presence of two compounds with R_f 0.5 (traces) and R_f 0.3. Fractional crystallization from hexane and chromatography of the residue with a column packed with aluminum oxide [elution with benzene–ethyl acetate (4:1)] gave 0.47 g (94%) of cis isomer IIa with mp 90-91°C (from hexane), M^+ 219 (calculated M 219), and $[\alpha]_D^{20}$ + 62° (c 0.5, CH_3OH). IR spectrum: (in mineral oil) 3400 cm^{-1} (OH); [in CH_2Cl_2 (c 0.01 mole/liter)] 3600 cm^{-1} (OH). PMR spectrum ($CDCl_3$): 1.26 (d, 3H, J = 6.6 Hz, CH_3 of the phenylethyl substituent), 1.28 (d, 3H, J = 6 Hz, 2-CH_3), 4.3 (q, 1H, J = 6.6 Hz, CH group of the phenylethyl substituent), and 7.3 ppm (m, 5H, C_6H_5). Found: C 77.0; H 9.6; N 5.9%. $C_{14}H_{21}HO$. Calculated: C 76.7; H 9.7; N 6.4%.

(–)-cis-1-(S-α-Phenylethyl)-2-methyl-4-piperidol (IIb). The reduction of 0.8 g (4 mmole) of piperidone Ib by a similar procedure gave 0.65 g (93%) of cis-4-piperidol IIb in the form of a clear oil with R_f 0.1 [Al_2O_3, benzene–acetone (4:1)] and M^+ 219. IR spectrum: (thin layer) 3350 cm^{-1} (OH); [in CH_2Cl_2 (c 0.01 mole/liter)] 3605 cm^{-1} (OH). PMR spectrum ($CDCl_3$): 1.24 (d, 3H, J = 6 Hz, 2-CH_3), 1.45 (d, 3H, J = 7 Hz, CH_3 group of the phenylethyl substituent), 4.1 (q, 1H, J = 7 Hz, CH group of the phenylethyl substituent), and 7.28 ppm (s, 5H, C_6H_5). The product had $[\alpha]_D^{20}$ –62° (c 0.4, CH_3OH). The picrate of IIb had mp 173-174°C (from ethanol). Found: C 53.8; H 5.5; N 12.3%. $C_{14}H_{21}NO \cdot C_6H_3N_3O_7$. Calculated: C 53.6; H 5.4; N 12.5%.

(+)-cis-2-Methyl-4-piperidol (IIIa). The hydrogenation of 0.27 g (1.2 mmole) of cis-piperidol IIa in 20 ml of absolute ethanol in the presence of 0.015 g of 10% Pd/C [up to complete disappearance of starting piperidol IIa, according to monitoring by thin-layer chromatography (TLC)] gave, after removal of the catalyst and evaporation of the solvent, 0.14 g (98%) of piperidol IIIa in the form of a light-yellow oil with M^+ 115 (calculated M 115). IR spectrum: [in CH_2Cl_2 (c 0.01 mole/liter)] 3595 cm^{-1} (OH). The product had $[\alpha]_D^{20}$ + 85.6° (c 0.93, CH_3OH). The hydrochloride had mp 189-190°C (from ethanol) and $[\alpha]_D^{20}$ –6.8° (c 1.16, CH_3OH). Found: C 47.8; H 9.1; N 9.3%. $C_5H_{13}NO \cdot HCl$. Calculated: C 47.5; H 9.3; N 9.2%.

(–)-cis-2-Methyl-4-piperidol (IIIb). As in the preceding experiment, the hydrogenolysis of 0.7 g (3.2 mmole) of cis-piperidol IIb gave 0.36 g (97%) of piperidol IIIb in the form of a clear oil with M^+ 115. IR spectrum: [in CH_2Cl_2 (c 0.01 mole/liter)] 3595 (OH) and 3310 cm^{-1} (OH). The product had $[\alpha]_D^{20}$ –85.0° (c 0.82, CH_3OH).

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$^{13}C-^{13}C$ SPIN-SPIN COUPLING CONSTANTS IN THE SPECTRA OF MONOSUBSTITUTED PYRIDINES

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The $^{13}C-\{^1H\}$ NMR spectra of pyridine and a number of monosubstituted pyridines for compounds with the natural percentage of the ^{13}C isotope were analyzed. The direct, geminal, and vicinal $^{13}C-^{13}C$ spin-spin coupling constants (SSCC) were determined. Linear relationships that link the $^{13}C-^{13}C$ SSCC in the spectra of monosubstituted pyridines and benzenes were obtained.

Researchers have recently become interested in $^{13}C-^{13}C$ spin-spin coupling constants (SSCC) for the study of structures and electronic structures [1-4]. The $^{13}C-^{13}C$ SSCC depend on the degree of hybridization of the coupling carbon atoms, the nature of the substituents, and the three-dimensional structure of the molecule and vary over a wide range from −20 Hz in the case of bicyclobutanes to +200 Hz in the case of acetylenes [4].

Systematic investigations of the $^{13}C-^{13}C$ SSCC have not been made for heteroaromatic compounds, and constants for only individual heterocycles (for example, furan, thiophene, pyrrole, and pyridine [5]) have been presented in the literature. Theoretical calculations of the $^{13}C-^{13}C$ SSCC in the spectra of aromatic compounds [6, 7] are in poor agreement with the experimental values, and this makes it necessary to use empirical rules that are frequently based on additive equations. Their effectiveness for nitrogen-containing heterocycles has been demonstrated in the case of $^{13}C-^1H$ SSCC [8].

The aim of the present research was to measure the $^{13}C-^{13}C$ SSCC in the spectra of monosubstituted pyridines and to search for empirical relationships between the constants for pyridines and benzenes.

The ^{13}C NMR spectrum of pyridine (with complete spin decoupling of the protons) is presented in Fig. 1. The set of lines in the vicinity of the principal signals of the ^{13}C isotopmers corresponds to the signals for molecules that contain two ^{13}C isotopes. In the general case the amplitude of the signals is on the order of 1/200 of the principal signal, and the $^{13}C-^{13}C$ SSCC are readily determined as the distances between the lines of the doublets.

The $^{13}C-^{13}C$ SSCC found for monosubstituted pyridines are presented in Table 1. In analogy with benzenes [4, 7], the direct and vicinal constants are assumed to be positive. The geminal ($^2J_{CC}$) constants were obtained only in some cases due to their small values (less than 3.5 Hz, except for $^2J_{2,6}$) and superimposition of the lines of these signals on the principal signal of the ^{13}C isotopomer. The $^2J_{2,6}$ values are two times greater than the geminal constants observed for benzenes.

The results of a comparison of the $^{13}C-^{13}C$ SSCC for monosubstituted pyridines and benzenes [7] (for the direct and vicinal constants) are presented in Table 2. For methyl benzo-

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