ASYMMETRIC SYNTHESIS AND ABSOLUTE CONFIGURATION OF 1-α-PHENYLETHYL-2,5-DIMETHYL-4-PIPERIDONE ISOMERS

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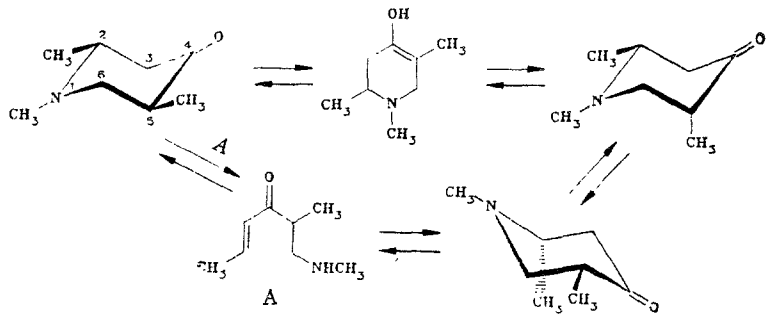
Reaction of the methyl iodide of trans-1,2,5-trimethyl-4-piperidone with S-α-phenylethylamine proceeds asymmetrically and leads in 66% optical yield to the formation of the cis- and trans-diastereomeric pair of 1-(α-phenylethyl)-2,5-dimethyl-4-piperidone, in which the new asymmetric centers possess the 2S,5S- and 2S,5R-configurations, respectively. According to x-ray structural analysis, the minor trans-1-(α-phenylethyl)-2,5-dimethyl-4-piperidone component possesses the 2R,5S-configuration. The occurrence of asymmetric synthesis accompanying transamination was confirmed via the preparation of enantiomers of trans-2,5- and trans-1,2,5-trimethyl-4-piperidones.

As part of our continuing studies [1, 2] of the stereochemical pathways of asymmetric syntheses of 4-piperidones and of the effect of substrate structure on optical yield, we have investigated the transamination of the methyl iodide of trans-1,2,5-trimethyl-4-piperidone derivatives is too complicated a model for study, due to the existence of cis- and trans-isomers, in a 5:95 ratio (^{13}C-NMR), as a result of keto-enol tautomerism of the carbonyl group. A second isomerization pathway would involve ring cleavage along the $C_{(2)}$–N bond.



These two processes, which can occur parallel to one another, could decrease the potential feasibility of an asymmetric synthesis. The selection of this model system is of practical importance for the preparation of optically active 1,2,5-trimethyl-4-piperidone, which itself is a valuable synthon for the directed preparation of a large series of synthetic drugs, among them promedole.

Treatment of equimolar amounts of the methyl iodide of trans-1,2,5-trimethyl-4-piperidone with S-α-phenylethylamine in the presence of water leads, according to TLC and GLC detection, to the formation of three new compounds, Ia-c, in a 3:2:1 ratio (Table 1). Based on elemental and mass spectral analysis, the three new compounds appear to be stereoisomers of 1-(α-phenylethyl)-2,5-dimethyl-4-piperidone. The mixture of stereoisomers Ia-c was isolated in 78% total yield of column chromatography on silica gel. The sparingly soluble isomer Ic was easily separated in crystalline form from the mixture after dissolution of the mixture in pentane.

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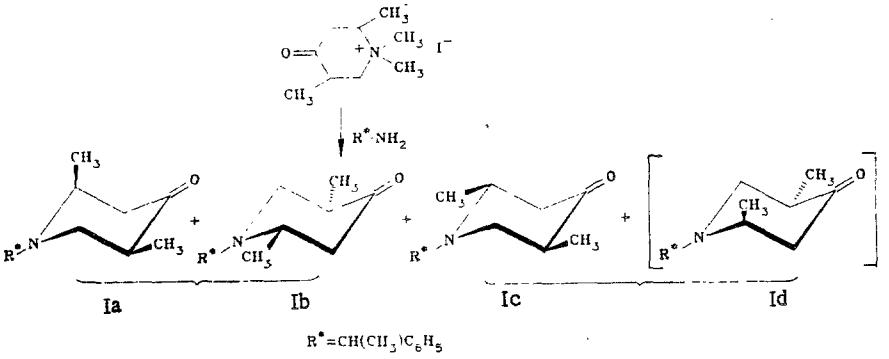
TABLE 1. Chromatographic Properties of 1-(α-Phenylethyl)-2,5-dimethyl-4-piperidone Isomers

Isomer	TLC*		GLC†	
	R_f	relative concentration	retention time, min	relative concentration
Ia	0,3	2,7	18,8	3,0
Ib	0,4	1,9	19,2	2,0
Ic	0,2	1,0	19,0	1,0

*The relative intensities of the spots were determined using a Joyce Loebl Scan Serus apparatus.
†50 m Capillary column, liquid phase SE-30, column temperature 170°C, pH_2 = 0.5 atm.



Based on PMR and ^{13}C-NMR* data, isomer Ic is the trans-1-α-phenylethyl-2e,5e-dimethyl-piperidone isomer, and its diastereomeric purity exceeds 98%. Chromatography of the purified 4-piperidone isomer Ic on Silufol was accompanied by partial conversion to the corresponding cis-isomer Id, whose chromatographic mobility is the same as that of the cis-isomer Ia. Conversion of the trans-isomer Ic to a mixture of the cis- and trans-isomers Ic, d was also observed by chromatographic analysis of a benzene solution of Ic in the presence of activity II grade Al_2O_3 after 3 h. It was not possible to separate the mixture of isomers Ia, b despite various attempts using different column and preparative chromatographic methods on silica gel and aqueous silicic acid, which always resulted in their mutual interconversion Based on ^{13}C-NMR analysis, isomers Ia, b occur in a 1.5:1 ratio; isomer Ia, which predominates in the mixture, appears to be the cis-isomer, with a preferred axial CH_3 group on $C_{(2)}$, and isomer Ib appears to be the trans-2e,5e-isomer.

The ratio of isomers Ia-c obtained in this reaction does not depend on whether the methyl iodide precursor used in the transamination reaction occurs as a mixture of cis- and trans-isomers, or as pure trans-1,2,5-trimethyl-4-piperidone. The results also did not differ when the reaction was carried out for 2, 5, or 20 h at 20°C, or in a water bath for 2 h. The transamination process thus results in the formation of a diastereomeric pair of 1-α-phenylethyl-2,5-dimethyl-4-piperidones (Ia, b), as well as the trans-isomer Ic in a (3:2):1 ratio, i.e., the optical yield of the transamination reaction is 66%. In order to interpret the steric effects directing the asymmetric synthesis, it is necessary, first of all, to establish the absolute configuration of the new asymmetric centers, at $C_{(2)}$ and $C_{(5)}$, in the piperidone products Ia-c. This was accomplished by performing an x-ray structural analysis of diastereomer Ic. The piperidone ring in trans-1-α-phenylethyl-2,5-dimethyl 4-piperidone (Ic) occupires an unsymmetrical chair conformation (Fig. 1). The N and $C_{(4)}$ atoms are deflected from the $C_{(2)}C_{(3)}C_{(5)}C_{(6)}$ plane (plane 1) by −0.677(6) and 0.540(8) Å, respectively, with an accuracy of 0.027(8) Å (the dihedral angles are 56.0° for plane 1/ $NC_{(2)}C_{(6)}$ plane and 43.3° for plane 1/$C_{(3)}C_{(4)}C_{(5)}$ plane). Bond lengths and bond angles are shown in Fig. 1. The torsional angles occurring in Ic are summarized in Table 2. The absolute configurations at $C_{(2)}$(R) and $C_{(5)}$(S) were unambiguously assigned based on the known S-configuration of the α-phenylethyl substituent attached to the nitrogen atom.

*A detailed investigation of the three-dimensional structures of all 4-piperidone derivatives prepared in this study, using NMR, will be reported in a separate publication.

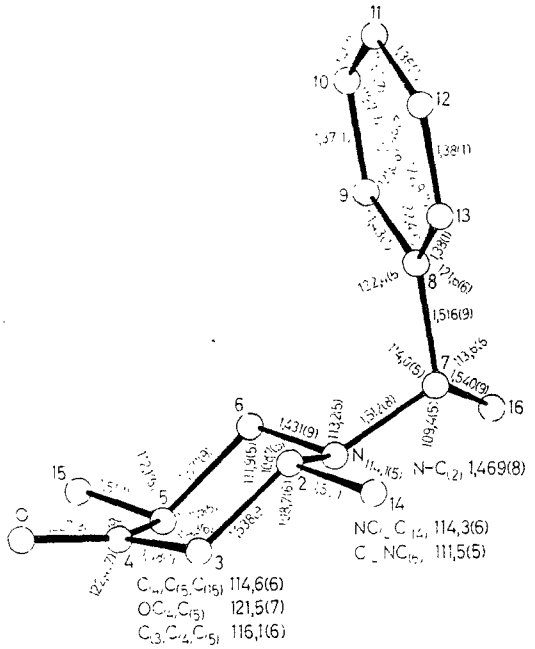


Fig. 1. X-ray structural data for trans-1-α-phenylethyl-2,5-dimethyl-4-piperidone (Ic).

TABLE 2. Torsional Angles τ (degrees) in a Molecule of Ic

Angle	τ	Angle	τ
N—C(2)—C(3)—C(4)	−48,7(7)	C(6)—N—C(2)—C(3)	58,8(8)
C(14)—C(2)—C(3)—C(4)	−174(1)	C(6)—N—C(2)—C(14)	−179,6(9)
C(2)—C(3)—C(4)—C(5)	46,5(8)	C(7)—N—C(2)—C(3)	−171,4(9)
C(2)—C(3)—C(4)—O	−131(1)	C(7)—N—C(2)—C(14)	−49,9(8)
C(3)—C(4)—C(5)—C(6)	−47,2(7)	C(2)—N—C(7)—C(8)	−66,9(8)
C(3)—C(4)—C(5)—C(15)	−172(1)	C(2)—N—C(7)—C(16)	164,7(9)
O—C(4)—C(5)—C(6)	131(1)	C(6)—N—C(7)—C(8)	62,0(8)
O—C(4)—C(5)—C(15)	6,2(7)	C(6)—N—C(7)—C(16)	−66,3(8)
C(4)—C(5)—C(6)—N	56,6(8)	N—C(7)—C(8)—C(9)	−77,3(8)
C(15)—C(5)—C(6)—N	−177,4(9)	N—C(7)—C(8)—C(13)	99,3(9)
C(5)—C(6)—N—C(2)	−65,5(8)	C(16)—C(7)—C(8)—C(9)	48,9(8)
C(5)—C(6)—N—C(7)	164,3(9)	C(16)—C(7)—C(8)—C(13)	−135(1)

It was not possible to apply a stereochemical correlation method based on CD data for isomers Ia-c, since all three of these isomers exhibited identical positive signs for the n → π* transition of the carbonyl group in their CD spectra. In order to determine the absolute configurations of the diastereomeric pair Ia, b; it was necessary to prepare 2,5-dimethyl- and 1,2,5-trimethyl-4-piperidone in optically active form. This was accomplished by removing the chiral substituent attached to the nitrogen atom in diastereomerically pure trans-Ic and in the mixture of cis- and trans-isomers Ia, b via hydrogenolysis in the presence of palladium black. This led in each case to the formation of optically active 2,5-dimethyl-4-piperidones, IIa, b, whose composition and structures were established by means of elemental analysis, mass spectrometry, and IR and PMR spectroscopy. The IR and PMR spectra of piperidones IIa, b were identical. The three-dimensional structure of isomer IIa, obtained from trans-Ic, corresponded to the trans-2e,5e-configuration, based on ^{13}C-NMR data, and isomer IIb also possessed the trans-2e,5e-structure. No isomerization about the $C_{(2)}$—N bond could be detected chromatographically during hydrogenolysis of isomers Ic and Ia, b, as had been observed to occur during hydrogenolysis of diastereomers of 1-α-phenylethyl-2-methyl-4-piperidone [3]. Reductive methylation of (−)-trans-2,5-dimethyl-4-piperidone (IIa) by treatment with paraformaldehyde in methanol in the presence of 10% Pd/C and anhydrous magnesium sulfate led to the formation of (−)-1,2,5-trimethyl-4-piperidone (IIIa) in 70% yield; (+)-IIIb was obtained in an analogous manner in 65% yield from (+)-trans-IIb. The structures of piperidones IIIa, b were documented by elemental analysis, IR and PMR spectroscopy, and by comparison with literature data for the corresponding racemates [4].

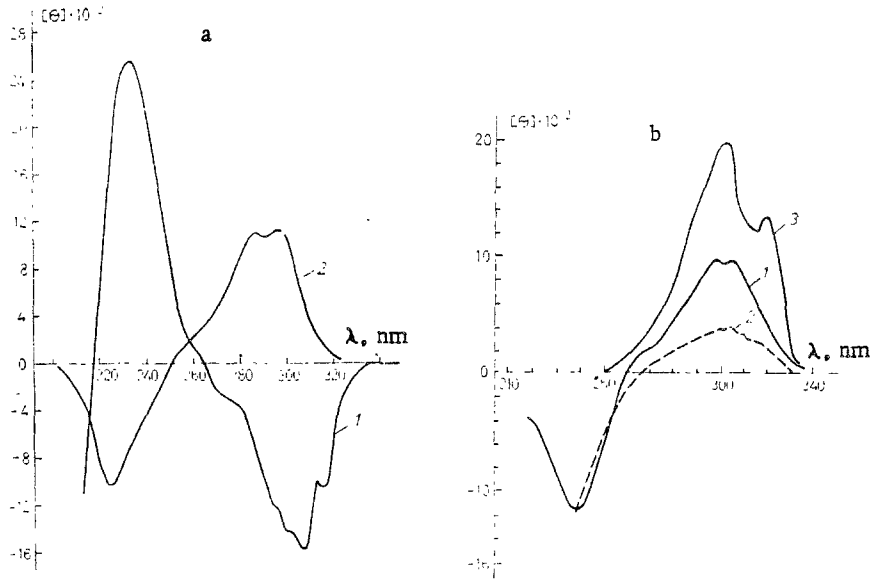
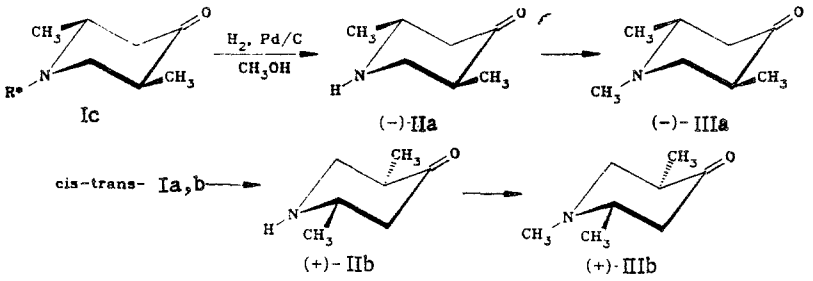
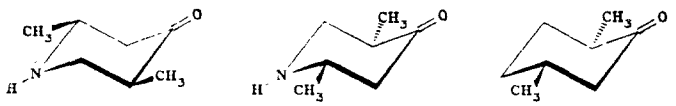


Fig. 2. CD curves (in heptane). a: 1) trans-2R,5S-dimethyl-4-piperidone (IIa); 2) (+)-2S,5R-dimethyl-4-piperidone (IIb). b: 1) trans-2S,5R-dimethyl-4-piperidone (IIb); 2) trans-1,2S,5R-trimethyl-4-piperidone (IIIa); 3) 3R-methylcyclohexanone in a mixture of ethanol and isoheptane.

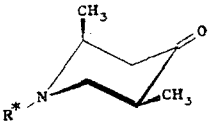


Consideration of the CD data for the trans-isomers IIa, b reveals that the CD curves in heptane have opposite signs (Fig. 2). However, the molecular ellipticity of the n → π* transition of the carbonyl group chromophore of piperidone IIa is more than twice as great as that of isomer IIb. This can be explained in terms of the presence of cis-isomer Id, of the second diastereomeric pair Ic, d, in the precursor diastereomeric pair, namely Ia, b. Nevertheless, piperidones IIa, b appear to be enantiomers, with opposite configurations at the $C_{(2)}$ and $C_{(5)}$ chiral centers. Similar absolute values of molecular ellipticity, which were opposite in sign, were observed in the CD spectra of heptane solutions of the 1,2,5-trimethyl-4-piperidone isomers IIIa, b (Fig. 2). We have also compared the chiroptical properties of the newly synthesized (+)-piperidones II and IIIb with those of (+)-3R-methylcyclohexanone and (+)-2R,5R-dimethylcyclohexanone, of known absolute configurations [5, 6]. Comparison of the CD curves of (+)-trans-IIb and IIIb in methanol indicated identical shapes and signs of the Cotton effects for the n → π* transition of the carbonyl chromophore (Fig. 2b). Based on these data, then, the absolute configurations of the $C_{(2)}$ and $C_{(5)}$ asymmetric centers in the (+)-trans-isomers IIb and IIIb must be the same as in (+)-2R,5R-dimethylcyclohexanone. The presence of a nitrogen atom in our compounds alters the priority values of the substituents groups, according to the R,S-nomenclature rules, and, as a result, the (+)-trans-isomers IIb and IIIb must possess the 2S,5R-configuration, whereas the (−)-trans-isomers IIa and IIIa possess the 2R,5S-configuration

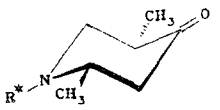


(−)-2*R*,5*S*-IIa (+)-2*S*,5*R*-IIb 2*R*,5*R*- dimethylcyclohexanone

Based on these data, trans-1-α-phenylethyl-2,5-dimethyl-4-piperidone (Ic), the precursor of trans-2R,5S-dimethyl-4-piperidone (IIa), must also possess the 2R,5S-configuration, which is consistent with the x-ray structural analysis. The cis-trans-diastereomeric pair Ia, b which gave trans-2S,5R-dimethyl-4-piperidone IIb after removal of the chiral nitrogen substit ent, exhibit the following absolute configurations:

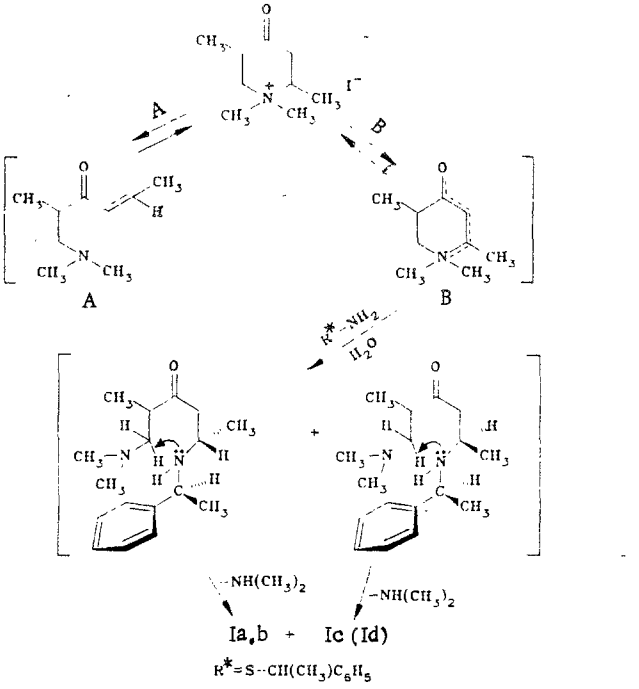


cis-1-α-phenylethyl-2S,5S-dimethyl-4-piperidone (Ia)



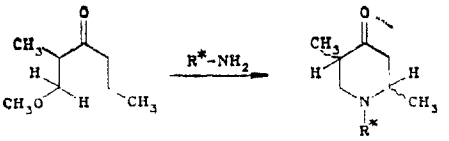
trans-1-α-phenylethyl-2S,5R-dimethyl-4-piperidone (Ib)

Comparison of the results of transamination of the methyl iodides 1,2-dimethyl-4-piperidone (37% optical yield) [3], and of 1,2,5-trimethyl-4-piperidone with S-α-phenylethylamine reveals that introduction of a second asymmetric center, at $C_{(5)}$, to the piperidone ring increases the optical yield to 66%. The relatively high degree of optical purity reflects, in our view, the course of the asymmetric transamination reaction, namely that it proceeds not via the open-chain α,β-unsaturated aminoketone form (path A), as has been previously [7] postulated but, instead, via a "quasicyclic" transition state, B:



In support of this hypothesis, we offer not only the magnitude of the optical yields for these reactions, but also the observation that the UV and NMR spectra do not seem to indicate the presence of the potential α,β-unsaturated aminoketone intermediate A in the reaction mixture. Furthermore, based on the results obtained for the absolute configurations of diastereomers Ia-c, and also upon consideration of molecular models, it is concluded that attack of the prochiral $C_{(2)}$ atom with a pro-R-face in the quasicyclic intermediate B by S-α-phenylethylamine is sterically hindered, and that, as a result, attack at the pro-S-face can take place much more readily, which leads to the predominant formation of a 4-piperidone with the S-configuration at the newly created $C_{(2)}$ asymmetric center. The other possible transamination pathway for the methyl iodide of 1,2,5-trimethyl-4-piperidone, which would involve cleavage of the $C_{(6)}$—N bond of the piperidone ring, would also be expected, based on molecular model examinations, to lead to the predominant formation of diastereomers with an S-configuration at $C_{(2)}$.

In conclusion, we would like to point out that direct reaction of S-α-phenylethylamine with 1-methoxy-2-methylhexen-4-one leads, in 14% yield, to the formation of a mixture of two diastereomeric pairs of 1-α-phenylethyl-2,5-dimethyl-4-piperidone derivatives (Ia, b and Ic, d), which could be separated by column chromatography on silica gel; they were obtained in a 1:1 ratio, i.e., asymmetric induction during the synthesis was not observed.



R^*=CH(CH$_3$)C$_6$H$_5$ Ia-d

EXPERIMENTAL

IR spectra were recorded on a UR-20 spectrophotometer, PMR spectra on T-60 and XL-100 spectrometers, UV spectra on a Cary-15 spectrophotometer using solutions in heptane and methanol, mass spectra on an MX-1303 mass spectrometer, and CD curves were obtained on a Jasco-20 spectrometer. GLC analyses were carried out on an LKhM-8MD(3) chromatograph using a 50 m capillary column with SE-30 liquid phase.

1-α-Phenylethyl-2,5-dimethyl-4-piperidone Diastereomers (Ia-c). A mixture of 18 g (65 mmole) of the methyl iodide of 1,2,5-trimethyl-4-piperidone (mp 185°C [8]), 8 g (64 mmole) of (−)-α-phenylethylamine, $[\alpha]_D^{20} = -41°$ (in the absence of solvent), and 5 ml (280 mmole) of water was stirred while heating at 30°C until the mixture was homogeneous, and was then allowed to stand overnight at 20°C. The mixture was saturated with potassium carbonate, extracted with 10 × 10 ml of ether, dried over anhydrous magnesium sulfate, concentrated to remove ether, and the residue (10.2 g) was dissolved in 30 ml light petroleum ether; the resulting precipitate was removed by filtration and washed with cold petroleum ether to give 0.2 g (1%) of trans-1-α-phenylethyl-2e,5e-dimethyl-4-piperidone (Ic), Rf 0.5 (silufol, 5:1 benzene–acetone), mp 126-127°C (from pentane), $[\alpha]_D^{21} = -36.6°$ (conc. = 1.9, benzene). IR spectrum (Vaseline mull): 1710 cm^{-1} (C=O). UV spectrum, $\lambda_{max}(\varepsilon)$ (in heptane): 257 (408, shoulder), 263 (254, shoulder), 298 nm (28). PMR spectrum ($CDCl_3$): 1.05 (3H, d, J = 6 Hz, 5-CH_3); 1.55 (3H, d, J = 6.6 Hz, C_6H_5–CH–CH_3), 3.03 (1H, m, 2-H), 4.07 (1H, q, J = 6.6 Hz, C_6H_5–CH–CH_3), 7.37 ppm (5H, s, C_6H_5–CH–CH_3). The remainder of the reaction mixture was added to a silica gel column and eluted with the following petroleum ether–ether solvent systems, 20:1, 15:1, 10:1, and 5:1. Chromatographically uniform fractions were (I) combined to give 5.8 g (39%) of a mixture of cis-1-α-phenylethyl-2a,5e-dimethyl-4-piperidone (a) and trans-1-α-phenylethyl-2e,5e-dimethyl-4-piperidone (Ib), Rf 0.8 and 0.7 (silufol, 5:1 benzene–acetone). IR spectrum (thin film): 1720 cm^{-1} (C=O). UV spectrum, $\lambda_{max}(\varepsilon)$ (in heptane): 250 (562), 257 (440), 263 (293), 291 (nm (81). PMR spectrum ($CDCl_3$): 0.73-1.05 (m), 1.23-1.40 (m), 3.37 (1H, q, J = 6 Hz), 4.36 (1H, q, J = 6.6 Hz), 7.27-7.53 ppm (5H, m, C_6H_5–CH–CH_3). Also isolated was 1 g (7%) of diastereomer Ic, Rf 0.5, mp 126-127°C (from peptane). Picrate salt of the mixture of diastereomers Ia-c, mp 150-153°C (from ethanol). Found, %: C 54.8, H 5.3, N 11.4. $C_{15}H_{19}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 54.8, H 5.2, N 12.2.

X-Ray Structural Analysis of Diasteriomer Ic. Crystals of Ic were rhombohedral; at −120°C, a = 5.654(1), b = 11.816(4), c = 19.260(7) Å, d_{calc} = 1.194 g/cm^3, Z = 8, $P2_12_12_1$ space group. Experimental cell parameters and intensities of 685 independent reflections with $F^2 \geq 2\sigma$ were measured on a Syntex $P2_1$ automated four-circle diffractometer (λ Mo K_α radiation, graphite monochromator, θ/2θ scanning, θ ≤ 25°). The structure was solved by direct methods using the MULTAN program and was refined by full matrix least squares, with initially isotropic, and later anisotropic (thermal) parameters (Table 3). All hydrogen atoms, which were directly observed in the difference synthesis, were included in the final refinements with fixed positions and temperature factors (B_{iso} = 5.0 Å^2). The final R factor was 0.047 (R_w = 0.052). All calculations were carried out on an Eclipse S/200 computer using an INEXTL program [9].

TABLE 3. Coordinates of Nonhydrogen Atoms (× 10^4)

Atom	x	y	z	Atom	x	y	z
N	1097(10)	9053(4)	6483(2)	$C_{(10)}$	5378(13)	11438(6)	5118(4)
$C_{(2)}$	1212(13)	8007(6)	6073(3)	$C_{(11)}$	4889(15)	11108(7)	4429(4)
$C_{(3)}$	1794(13)	7017(6)	6563(3)	$C_{(12)}$	2925(16)	10482(6)	4296(4)
$C_{(4)}$	3820(15)	7229(6)	7034(3)	$C_{(13)}$	1434(15)	10164(6)	4826(3)
$C_{(5)}$	3829(15)	8348(6)	7400(3)	$C_{(14)}$	−1012(14)	7734(6)	5688(4)
$C_{(6)}$	3281(13)	9271(5)	6835(3)	$C_{(15)}$	6078(14)	8603(6)	7794(3)
$C_{(7)}$	185(12)	10066(6)	6085(3)	$C_{(16)}$	−500(13)	11009(6)	6600(3)
$C_{(8)}$	1818(13)	10460(6)	5509(3)	O	5439(10)	6548(4)	7107(2)
$C_{(9)}$	3905(13)	11103(6)	5643(3)				

trans-2R,5S-Dimethyl-4-piperidone (IIa). Hydrogenolysis of 1.3 g (5.6 mmole) of trans-isomer Ic on palladium black (0.01 g) in glacial acetic acid, followed by solvent removal in vacuo, gave 0.85 g (80%) of a white crystalline substance, acetate IIa, which was extremely hygroscopic. Found: M^+ (free base) 127. Calculated: M 127. The free base IIa was isolated after workup of a concentrated aqueous solution of the acetate with solid potassium carbonate, and extraction of the resulting oil with ether, and was dried over 4-Å molecular sieves. Ether evaporation gave 0.5 g (86%) of compound IIa as a yellow oil. IR spectrum (thin film): 1710 (C=O), 3250 cm^{-1} (N–H). PMR spectrum (CCl_4): 0.86 (3H, d, 5-CH_3), 1.1 ppm (3H, d, 2-CH_3). UV spectrum (in heptane): λ_{max} 292 nm. CD spectrum, $[\theta]_{290} = -1660°$ (heptane).

trans-2S,5R-Dimethyl-4-piperidone (IIb). In an analogous manner, hydrogenation of 0.9 g (3.8 mmole) of the mixture of isomers Ia, b, followed by catalyst and solvent removal, gave 0.56 g (77%) of crystalline acetate IIb, mp 90-92°C (sublimation). Found: M^+ (free base) 127. Calculated: M 127. The aqueous solution of acetate IIb was basified with potassium carbonate, extracted with ether, dried over $MgSO_4$, and concentrated to remove ether; 0.32 g (84%) of 4-piperidone IIb was isolated as a yellow oil. IR spectrum (thin film): 1710 (C=O), 3250 cm^{-1} (N–H). PMR spectrum (CCl_4): 0.86 (3H, d, 5-CH_3), 1.1 ppm (3H, d, 2-CH_3). UV spectrum (in heptane): λ_{max} 292 nm. CD spectrum $[\theta]_{290} = +780°$ (heptane).

(–)-1,2,5-Trimethyl-4-piperidone (IIIa). A solution of 1.15 g (5 mmole) of trans-isomer Ic in 20 ml methanol was hydrogenated in the presence of 0.5 g of 10% Pd/C. After completion of the hydrogenolysis reaction (as detected by chromatographic control for the presence of piperidone IIa on Silufol, with chloroform saturated with ammonia, Rf 0.2), the reaction mixture was treated with 1 g of paraformaldehyde, 0.5 g anhydrous magnesium sulfate, and 0.5 g 10% Pd/C. Hydrogenation was continued until the complete disappearance of piperidone IIa was observed chromatographically. The catalyst was filtered, methanol was evaporated under vacuum, and 0.46 g (65%) of compound IIIa was obtained, Rf 0.5 (Silufol, chloroform, saturated with ammonia), $[\alpha]_D^{20} = -49.2°$ (conc. 0.76, heptane). IR spectrum (thin film): 1725 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 0.78 (3H, d, J = 6 Hz, 5-CH_3), 0.94 (3H, d, J = 6 Hz, 2-CH_3), 2.0 (3H, s, N–CH_3), 1.82-2.16 (s), 2.26-2.51 (m), 2.72-2.9 ppm (m). Picrate, mp 170-172°C (from benzene). Found, %: C 44.5, H 4.9, N 15.0. $C_8H_{15}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 45.4, H 4.9, N 15.1.

(+)-1,2,5-Trimethyl-4-piperidone (IIIb). In an analogous manner, 1.15 g (5 mmole) of a mixture of isomers Ia, b gave 0.5 g (70%) of compound IIIb, Rf 0.5 (Silufol, chloroform, saturated with ammonia). $[\alpha]_D^{20} = +47.1°$ (conc. 0.85 heptane). IR spectrum (thin film): 1725 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 0.78 (3H, d, J = 6 Hz, 5-CH_3), 0.94 (3H, d, J = 6 Hz, 2-CH_3), 1.82-2.16 (m), 2.0 (3H, s, N–CH_3), 2.26-2.51 (m), 2.72-2.9 ppm (m). Picrate, mp 170-172°C (from benzene). Found, %: C 45.3, H 4.9, N 14.9. $C_8H_{15}NO \cdot C_6H_3N_3O_7$. Calculated, %: C 45.4, H 4.9, N 15.1.

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