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STERIC CONTROL OF THE ASYMMETRIC SYNTHESIS OF N-SUBSTITUED 2-METHYL-4-PIPERIDONES

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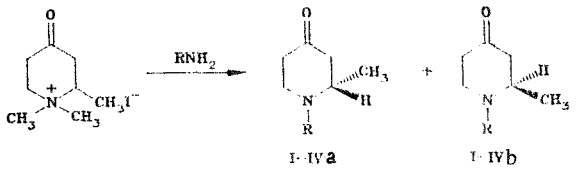
UDC 547.822.3:535.56

Transmission of the iodomethylate of 1,2-dimethyl-4-piperidone by (S)-sec-butylamine gives 1-(S-sec-butyl)-2S-methyl-4-piperidone in 33% optical yield while transamination by (S)-1-methyl-2-phenylethylamine gives a 1:1 diastereomeric mixture of 1-(1-methyl-2-phenylethyl)-2-methyl-4-piperidone. The decrease in the optical yield is related to the facile opening of the piperidone ring at the C–N bond with subsequent recyclization. The ^{13}C NMR data indicate that all the diastereomers of the 4-piperidones obtained are in the chair conformation with predominantly equatorial orientation of the methyl group at $C_{(2)}$. The chiral optical properties were studied and the absolution configurations of the 4-piperidones obtained were established.

We studied the reaction of the iodomethylate of 1,2-dimethyl-4-piperidone with (S)-(+)-sec-butylamine and (S)-(+)-1-methyl-2-phenylethylamine in order to determine the sterochemical features of this asymmetrical synthesis and expand the series of chiral 4-piperidones [1] which are synthones for the preparation of many biologically active compounds. The action of equimolar amounts of 1,2-dimethyl-4-piperidone iddomethylate with 1-methyl-2-phenylethylamine in the presence of excess water at room temperature gives a 48% yield of 1-(1-methyl-2-phenylethyl)-2-methyl-4-piperidone (I), which was shown to be a 1:1 mixture of isomers Ia and Ib by thin-layer chromatography on Silufol plates and gas liquid chromatography on a glass capillary column.



I R = $CH(CH_3)CH_2C_6H_5$; II R = $CD(CD_3)CD_2C_6H_5$; III R = $CH(CH_3)C_2H_5$; IV R = $CH(CH_3)C_6H_5$

In the light of the very slight difference in the chromatographic mobility ($\Delta R_f < 0.1$) isomers Ia and Ib could be separated only using preparative chromatography on Silufol plates.

M. V. Lomonosov Moscow State University, Moscow 117234. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1648-1655, December, 1985. Original article submitted July 5, 1984; revision submitted July 2, 1985.

0009-3122/85/2112-1355$09.50

TABLE 1. ^{13}C NMR Chemical Shifts of Diastereomers of 1-(1-Methyl-2-phenylethyl)-4-piperidone Ia and Ib and the Isotopomers IIa and IIb (δ, ppm, in $CDCl_3$)

Compound	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	2-CH_3	1′-CH_3	1′-CH	1′-CH_2
Ia	53,8	50,0	42,2	43,4	19,8	11,6	54,5	41,9
IIa	53,7	49,8	41,8	43,3	19,7	—	—	—
Ib	54,2	50,0	42,1	42,9	19,3	18,4	55,5	41,9
IIb	51,0	49,8	41,9	42,9	19,2			

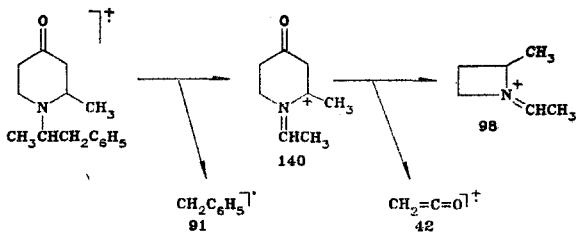
TABLE 2. Experimental CS (in $CDCl_3$) and Calculated ^{13}C CS of 1-(1-Methyl-2-phenylethyl)-2-methyl-4-piperidone Diastereomers Ia and Ib

Spectrum	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$
Experimental for isomer Ia	53,82	49,96	42,21	43,42
Experimental for isomer Ib	54,22	50,04	42,06	42,94
1-(1-Methyl-2-phenylethyl)-4-piperidone	47,84	41,57	41,57	47,84
Calculated for 2e-CH_3	50,87	49,77	41,86	47,73
Calculated for 2a-CH_3	49,84	47,77	40,87	40,64
$\Delta(\delta_{exp} - \delta_{calc})$ for isomer Ia (2e-CH_3)	2,95	0,19	0,35	−4,31
Same for isomer Ia (2a-CH_3)	3,92	2,19	1,34	2,78
Same for isomer Ib (2e-CH_3)	3,35	0,27	0,20	−4,94
Same for isomer Ib (2a-CH_3)	4,38	2,27	1,19	2,30

TABLE 3. Increments for Axial and Equatorial Methyl Groups in 1,2-Dimethyl-4-piperidone and 2-Methyl-4-piperidone [2, 3]

Group	α	β	γ	δ
e-CH_3	3,03	8,2	−0,11	0,29
a-CH_3	2,0	6,2	−7,2	−0,7

The diastereomeric purity of isomers Ia and Ib was at least 95% as shown by thin-layer and gas-liquid chromatography. The nature of the fragmentation of both isomers upon electron impact was identical involving formation of ions with m/z 91 and 140 corresponding to the loss of the benzyl group; there is no molecular ion peak.



^{13}C NMR spectroscopy was used to determine the structure of piperidone I (Table 1). The signal assignment was carried out using incomplete proton decoupling and comparison with the data for 1,2-dimethyl-, 1,3-dimethyl- and 1-benzyl-3-methyl-4-piperidones given by Hirsch [2] and Jones [3]. In this case, a rigorous assignment of the signals for the 2-CH_2 and 1-methyl-2-phenylethyl methyl groups for isomers Ia and Ib proved impossible. Thus, we synthesized a deuterated analog of 4-piperidone I (II). The D_6-isotopomer II was obtained by transamination of the iodomethylate of 1,2-dimethyl-4-piperidone by 1-methyl-2-phenylethylamine-d_6 and was separated by preparative thin-layer chromatography on silica gel into pure

TABLE 4. Experimental and Calculated ^{13}C CS of 1-sec-Butyl-2-methyl-4-piperidone Diastereomers IIIa and IIIb and 1-sec-Butyl-4-piperidone (δ, ppm, in C_6D_6)

Spectrum	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	1′-CH_3	1′-CH	1′-CH_2	1-CH_2CH_3	2-CH_3
Experimental for 1-sec-butyl-4-piperidone	48,22	42,23	42,22	48,23	14,01	60,75	27,07	11,60	—
Experimental for isomer IIIa	53,58	50,01	41,92	42,86	11,46	53,64	28,03	11,27	19,85
Calculated for III with 2e-CH_3	51,80	50,26	42,43	42,77					
$\Delta(\delta_{exp} - \delta_{calc})$	1,78	−0,25	−0,51	0,09					
Calculated for III with 2a-CH_3	50,30	48,71	34,90	41,21					
$\Delta(\delta_{exp} - \delta_{calc})$	3,28	1,30	7,02	1,65					
Experimental for IIIb	54,27	50,12	42,19	42,68	18,63	55,37	23,51	11,43	18,26
$\Delta(\delta_{exp} - \delta_{calc})$ for IIIb (2e-CH_3)	2,97	−0,14	−0,24	−0,18					
$\Delta(\delta_{exp} - \delta_{calc})$ for IIIb (2a-CH_3)	−3,97	1,41	7,29	1,47					

TABLE 5. Chromatographic Monitoring of the Isomerization and Equilibrium State of Diastereomers Ia and Ib

Isomer	Solvent	Ia : Ib diastereomer ratio	
		20°C (6 days)	reflux (4 h)
Ia	Hexane	1,2 : 1	1 : 1
	Absolute C_6H_6	1,2 : 1	3 : 1
	$CHCl_3$	1 : 1	—
	Absolute CH_3OH	1 : 1	1 : 1
	96% C_2H_5OH	1 : 1	1 : 1
	CH_3CN	—	1 : 1
Ib	Hexane—SiO_2	1,5 : 1	—
	$CHCl_3$	1,1 : 1	—
	$(CH_3)_2CO$—SiO_2	1,2 : 1	—
	CH_3OH	1 : 1	—
	CH_3OH—SiO_2	1 : 1	—
	Hexane	—	1 : 1
	Absolute C_6H_6	—	1,3 : 1
	CH_3CN	—	1 : 1

*Relative to spot area on Alufolien Kieselgel plates after twofold elution using 3:1 benzene-acetone.

isomers IIa and IIb. The PMR spectra of these isomers did not show proton signals for the aliphatic part of the 1-methyl-2-pheylethyl substituent. The signal at 19.7 ppm remains unchanged in the ^{13}C NMR spectrum of isotopomer IIa, which thus should be assigned to the 2-CH_3 group, while the absent signal at 11.6 ppm should be assigned to the methyl group of the 1-methyl-2-phenylethyl substituent. In a similar comparison of the spectra of isomer Ib and its isotopomer IIb, the signal at 18.4 ppm is assigned to the CH_3 group of the 1-methyl-2-phenylethyl substituent while the signal at 19.3 ppm is assigned to the 2-CH_3 group (Table 1). Comparison of the experimental chemical shifts (CS) of the carbon atoms of the piperidone ring of diastereomers Ia and Ib with the values calculated using additive schemes for the chair conformation with equatorial or axial orientation of the 2-CH_3 group (Tables 2 and 3) showed that good agreement of the experimental and calculation chemical shifts is observed using the equatorial methyl group increments. The additive schemes were calculated using the formula: $\delta_{Cj} = \delta_{Cjstart} + \text{increment } (C_j)$. The starting point for the calculation was the ^{13}C NMR spectrum of 1-(1-methyl-2-phenylethyl)-4-piperidone obtained by transamination of the iodomethylate of 1-methyl-4-piperidone by 1-methyl-2-phenylethylamine in 40% yield. Parameters obtained by averaging of the increments of the methyl groups for 1,2-dimethyl-, 1,3-dimethyl- and 1-benzyl-3-methyl-4-piperidones [2, 3] were used as the

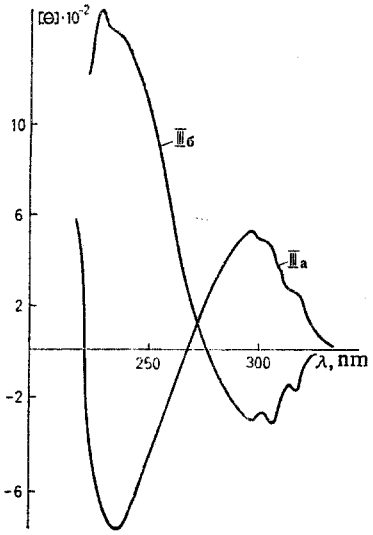
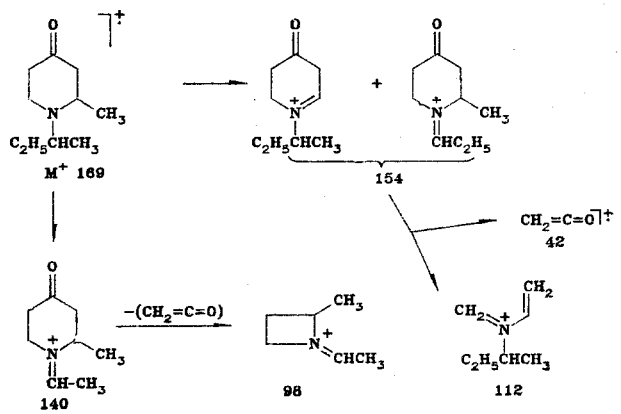


Fig. 1. Circular dichroism curves for 1-sec-butyl-2-methyl-4-piperidones IIIa and IIIb in heptane.

contributions of the equatorial methyl group. Parameters derived for the diastereomers of 1-α-phenylethyl-2-methyl-4-piperidone (IV) having predominantly axial orientation of the 2-CH_3 group were used as increments of the axial methyl group. The observed chemical shift of the methyl group at $C_{(2)}$ in both diastereomers Ia and Ib lie at 19-20 ppm, which is in good accord with the chemical shifts of equatorial methyl groups given by Hirsch [2] and Booth [4]. Thus, both diastereomers Ia and Ib exist predominantly as the conformer with an equatorial 2-CH_3 group. The observed significant differences of the calculated CS for $C_{(2)}$ and $C_{(6)}$ with the experimental values is attributed to hindered rotation of the substituent at the nitrogen atom about the C–N bond. A consequence of the existence of different preferred N-rotamers is strong shielding of $C_{(6)}$ ($\Delta = -4.3$ for Ia and -4.9 ppm for Ib) and deshielding of $C_{(2)}$ (Δ = 2.96 for Ia and 3.65 ppm for Ib).*

The transamination of the iodomethylate of 1,2-dimethyl-4-piperidone by (+)-sec-butylamine was studied under analogous conditions. This reaction gave a 39% yield of 1-sec-butyl-2-methyl-4-piperidone (III) which was shown by thin-layer chromatography to be a mixture of two diastereomers. The pure diastereomers IIIa and IIIb were separated in 2:1 ratio by preparative chromatography on silica gel plates. The diasteromeric purity of isomers IIIa and IIIb was shown by ^{13}C NMR spectroscopy and thin-layer chromatography to be at least 95%. A mass spectral study confirmed the structures of isomers IIIa and IIIb and identical fragmentation of the molecular ion was observed for both isomers:

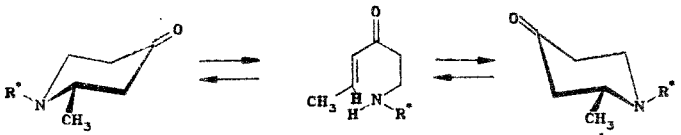


^{13}C NMR spectroscopy was also used to determine the three-dimensional structure of diastereomers IIIa and IIIb. Comparison of the experimental chemical shifts of the carbon atoms of the piperidone ring for isomers IIIa and IIIb with those calculated using the

*A detailed NMR study of the structure of the piperidones obtained in this work will be described in a separate work.

additive schemes for axial and equatorial 2-CH_3 groups showed good accord for use of the increments for the equatorial methyl group (Table 4). The starting point was the ^{13}C NMR spectrum of 1-sec-butyl-4-piperidone, obtained in 80% yield by the transamination of the iodomethylate of 1-methyl-4-piperidone using sec-butylamine. The observed CS of the 2-CH_3 group in both diastereomers IIIa and IIIb is in good accord with the chemical shifts characteristic for equatorial methyl groups. Thus, the conformational equilibrium in both isomers IIIa and IIIb is strongly shifted toward the conformer with equatorial orientation of the methyl group at $C_{(2)}$.

Thus, a change in the nature of the chiral amine in the transamination of the iodomethylate of 1,2-dimethyl-4-piperidone showed that the greatest optical yield (50%) is found upon transamination with α-phenylethylamine [1]. The use of sec-butylamine lowers the optical yield to 33% and transamination with 1-methyl-2-phenylethylamine is accompanied by complete loss of diastereoselectivity. We attempted to explain the reason for this dependence of the optical yield on the nature of the chiral amine and found that a mixture of diastereomers I and Ib is formed upon maintaining the pure diastereomers I and Ib in solvents of different polarity at room temperature for 16 h or at reflux for 9 h (Table 5). In other words, these isomers interconvert and the final result of the isomerization of pure diastereomers Ia and Ib is their presence in 1:1 ratio. The isomerization process is significantly accelerated in the presence of silica gel and under conditions of acid and basic catalysis. Such isomerization presumably may occur only through opening of the piperidone ring at the $C_{(2)}$—N bond with subsequent recyclization.

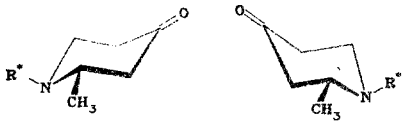


Ia Ib

R*=CH(CH$_3$)CH$_2$C$_6$H$_5$

Transamination of the iodomethylate of 1,2-dimethyl-4-piperidone occurs in aqueous medium in the presence of amine, i.e., under conditions which strongly accelerate the opening of the piperidone ring at the C—N bond. Thus, the 4-piperidone diastereomer ratio obtained in the transamination process is not the true result of the asymmetric synthesis but rather is altered due to interconversion of diastereomers Ia and Ib. An analogous but slower isomerization was observed for 1-α-phenylethyl-2-methyl-4-piperidone (IVa and IVb) upon heating in methanol at reflux for 2 h [1]. In this case, the pure isomers IVa and IVb form their equilibrium mixture, which was separated by preparative chromatography on Silufol. The diastereomers obtained in pure form in 1.3:1 ratio were identical to starting isomers IVa and IVb in their specific rotation and IR and PMR spectral characteristics.

Knowledge of the absolute configuration of the asymmetric sites of the chiral 4-piperidones obtained (Ia, Ib, IIIa and IIIb) is required to explain the steric control of the asymmetric transamination. For this purpose, we compared the circular dichroism (CD) data for the pure isomers of 4-piperidone I, IIIa, IIIb, and (+)-(3R)-methylcyclohexanone [5], since CD data are are lacking in the literature. The signs of the Cotton effect of the n—π* transition of the carbonyl conformer are opposite for the diastereomer pair of 4-piperidone I and IIIa and IIIb in heptane (Fig. 1). With an increase in solvent polarity, the curves remain virtually unaltered which indicates the absence of significant conformational changes in these compounds. Thus, in the case of the same S-chirality of the substituent at the nitrogen atom, the sign of the Cotton effect of the n—π* transition of the carbonyl group reflects the different chirality of $C_{(2)}$ within the diastereomer pair of I and of IIIa and IIIb. The S-configuration of the $C_{(2)}$ chiral centers in diastereomers Ia and IIIa was established on the basis of the agreement of the sign of the Cotton effect of the n—π* transition of the carbonyl chromophore of diastereomers Ia and IIIa as well as of (+)-(3R)-methylcyclohexanone. Diastereomers Ib and IIIb which display a negative Cotton effect correspondingly have 2R configuration.



(2S)-Ia,IIIa (2R)-Ib, IIIb

These results indicate the possibility of extending the octant rule to chiral 4-piperidones.

EXPERIMENTAL

The IR spectra were obtained neat or in vaseline mull on a UR-20 spectrometer. The IR spectra were taken on Varian T-60 and XL-100 spectrometers in $CDCl_3$ or CCl_4 at room temperature with TMS as the internal standard. The ^{13}C NMR spectra were taken on Varian CFT-20 and XL-100 spectrometers in $CDCl_3$ and C_6D_6. The mass spectra were taken on a Varian MAT-44 mass spectrometer with chromatographic inlet. The UV spectra were taken on a Varian Cary-15 spectrometer. The CD spectra were taken on a Jasco J-20 spectropolarimeter at room temerature.

1-(1-Methyl-2-phenylethyl)-2-methyl-4-piperidone Diastereomers Ia and Ib. A mixture of 1.35 g (5 mmoles) iodomethylate of 1,2-dimethyl-4-piperidone, 0.75 ml (5 mmoles) (+)-1-methyl-2-phenylethylamine [6] with $[\alpha]_D^{20}$ + 35.8° (without solvent) and 1 ml (60 mmoles) water was stirred for 2 h at room temperature and then saturated with potassium carbonate and extracted with ether. The combined extracts were dried over anhydrous K_2CO_3 and extracted with ether. Ether was distilled off to give 1.1 g residue, which was subjected to chromatography on a silica gel colum with 1:1 petroleum ether–ether as the eluent to yield 0.56 g (48%) of a mixture of isomers Ia and Ib. The picture of the mixture of isomers Ia and Ib was 148-149°C (from benzene–ethanol). Found: C, 54.5; H, 5.4; N, 11.9%. Calculated for $C_{15}H_{21}NO \cdot C_6H_3N_3O_7$: C, 54.8; H, 5,3; N, 12.2%. Diastereomers Ia and Ib were separated by thin-layer chromatography on (15 × 15) Silufol plates using an 8:2:1 mixture of benzene, acetone and chloroform saturated with ammonia as the eluent. A sample of 0.95 g isomer mixture gave 0.34 g isomer Ia, mp 42-43°C (from pentane), 0.17 g isomer Ib, mp 54-55°C (from pentane) and 0.12 g mixture of isomers Ia and Ib enriched in isomer Ib.

Isomer Ia: R_f 0.6 on Silufol with 3:1 benzene–acetone as the eluent (triple elution); M^+ 231. IR spectrum in vaseline oil: 1730 cm^{-1} (carbonyl group). UV spectrum in heptane (λ_{max}, nm (ε)): 290 (sh, 56) 268, 264, 258, (230, 249, 364). PMR spectrum in CCl_4: 0.89(3H, d, J = 6.6 Hz, 2-CH_3), 1.05(3H, d, J = 6.2 Hz, α-CH_3), 7.15 ppm (5H, c, C_6H_5).

Isomer Ib: R_f 0.5 on Silufol with 3:1 benzene-acetone as the eluent (triple elution); M^+231.IR spectrum in vaseline oil: 1730 cm^{-1}(carbonyl group). UV spectrum in heptan, (λ_{max}, nm(ε)):290 (sh, 51) 270 (333), 263 (441), 253 (551). PMR spectrum in $CDCl_3$: 1.13 (3H, d, J = 6.7 Hz, 2-CH_3), 1.25 (3H, d, J = 6.2 Hz, α-CH_3) 7.35 ppm (5H, m, C_6H_5).

1-(1-Methyl-2-phenylethyl)-4-piperidone. An analogous procedure using 1.83 g (7.2 mmoles) iodomethylate of 1-methyl-4-piperidone, 2g (14.4 mmoles) (+)-1-methyl-2-phenylethylamine and 0.8 g (43 mmoles) water gave 0.6 g (38%) 1-(1-methyl-2-phenylethyl)-4-piperidone, R_f 0.4 (Silufol, 6:1 benzene–acetone). Mass spectrum: m/z 123 (M^+ -91), 91 ($C_9H_{11}^+$). IR spectrum (neat): 1730 cm^{-1} (carbonyl group). UV spectrum in heptane (λ_{max}, nm (ε): 304 (96), 268 (234), 258 (372), 253 (390). PMR spectrum (CCl_4): 0.98 (3H, d, J = 6 Hz, α-CH_3), 2.33-3.13 (11H, m, CH and CH_2 group protons), 7.17 ppm (5H, s, C_6H_5). Picrate, mp 59-60°C (from ethanol). Found: C, 53.2; H, 4.6; N, 12.1%. Calculated for $C_{14}H_{19}NO \cdot C_6H_3N_3O_7$: C, 53.8; H, 5.0; N, 12.6%.

1-(1-Methyl-2-phenylethyl)-2-methyl-4-piperidone Isotopomers IIa and IIb. A mixture of 9.5 g (70 mmoles) 1-phenyl-2-propanone [7], 27 g (750 mmoles) CD_3OD and 5.5 g (36 mmoles) $POCl_3$ was maintained at room temperature for 96 h and the solvent was distilled off. The residue was distilled in vacuum to yield 6.6 g (70%) 75%-deuterated 1-phenyl-2-propanone. Repeated deuteration was carried out by maintaining 6.6 g partially deuterated ketone in a mixture of 20 g CD_3OD and 5 ml absolute dioxane in the presence of NaOD obtained from 0.2 g (8.70 mmoles) sodium and 16 ml D_2O. The solvent was removed in vacuum and the residue was extracted with absolute benzene and dried over $MgSO_4$. Benzene was removed and the residue was distilled in vacuum to yield 4.6 g (70%) 1-phenyl-2-propanone-d_5, bp 98-99°C (15 mm). PMR spectrum (without solvent): 7.17 ppm (5H, s, C_6H_5). The signals for the methyl and methylene groups at 2.0 and 3.55 ppm were completely absent. Mass spectrum: M^+ 139.

A solution of 4.6 g (33 mmoles) of the deuteroketone obtained, 2.3 g (33 mmoles) hydroxylamine hydrochloride, and 2.71 (33 mmoles) anhydrous sodium acetate in 25 ml CD_3OD and 18 ml D_2O was stirred at room temperature for six days. After solvent removal, the residue was extracted with absolute benzene and dried over $MgSO_4$. Benzene was distilled off and distillation in vacuum gave 4.1 g (81%) 1-phenyl-2-propanone-D_5 oxime, bp 147-148°C (18 mm), n_D^{20} 1.5478. PMR spectrum in $CDCl_3$: 7.27 ppm (5H, s, C_6H_5). Mass spectrum: m/z 154 (M^+), 136 ($M^+ - CD_3$), 135 ($C_6H_5CD_2C{=}N{=}O^+$).

A sample of 6 g (260 mmoles) sodium was added with rapid stirring over 60 min to a solution of 4 g (26 mmoles) 1-phenyl-2-propanone-d_5 oxime in 66 g (1.8 mole) CD_3OD heated at reflux. After the complete dissolution of the sodium added, a sample of 15 ml D_2O was added and the reaction mixture was steam distilled into a flask containing 2.4 ml concentrated hydrochloric acid. Water was evaporated in vacuum. The residue was made basic by the addition of saturated aq. NaOH to pH 11 and extracted with benzene and dried over fused NaOH. Distillation of the benzene at atmospheric pressure and distillation of the residue in vacuum gave 0.84 g (23%) 1-methyl-2-phenylethylamine-d_6, bp 91-92°C (18 mm), n_D^{20} 1.5292. PMR spectrum (without solvent): 0.90 (2H, s, NH_2), 7.13 ppm (5H, s, C_6H_5). Mass spectrum: M^+ 141.

The transamination of 1.53 g (5.7 mmoles) iodomethylate of 1,2-dimethyl-4-piperidone by 0.8 g (5.7 mmoles) 1-methyl-2-phenylethylamine-d_6 in the presence of 1.2 ml (60 mmoles) water under ordinary conditions and separation on seven 24 × 18-cm 2-mm-thick silica gel plates with acetone as the eluent gave 0.26 g IIa, R_f 0.6 (Silufol, 4:1:2 benzene–acetone–chloroform saturated with ammonia), 0.165 g IIb, R_f 0.5 with 28% total yield. The mass spectrum of the isomer mixture: m/z 237 (M^+), 144 ($M^+ - CD_2C_6H_5$), 93 ($C_7H_5D_2^+$).

1-sec-Butyl-2-methyl-4-piperidone Diastereomers IIIa and IIIb. The transamination of 5.7 g (20 mmoles) iodomethylate of 1,2-dimethyl-4-piperidone by 3 g (30 mmoles) (+)-sec-butylamine with $[\alpha]_D^{20}$ + 7.9° (without solvent) in the presence of 1 ml (60 mmoles) water gave 2.9 g of a reaction mixture which was subjected to chromatography on a silica gel column with elution by 3:1 benzene-acetone to yield 0.6 g diastereomer IIIa, R_f 0.4 (Silufol, triple elution with 3:1 benzene–acetone), 0.1 g of a mixture of IIIa and IIIb and 0.4 g IIIb, R_f 0.3 (Silufol, triple elution with 3:1 benzene–acetone). The total yield of IIIa and IIIb was 1.2 g (40%). Picrate of this mixture of isomers IIIa and IIIb, mp 150-151°C (from ethanol). Found: C, 48.5; H, 5.6%. Calculated for $C_{10}H_{19}NO \cdot C_6H_3N_3O_7$: C, 48.2; H, 5.6%.

Isomer IIIa. Mass spectrum: M^+ 169. IR spectrum (neat): 1735 cm^{-1} (C=O). UV spectrum in heptane (λ_{max}, nm [ε]): 308 (100, sh). PMR spectrum in $CDCl_3$: 0.85 (3H, d, J = 6 Hz, 2-CH_3), 1.08 ppm (3H, d, J = 6 Hz, αCH_3). Hydrochloride, mp 150-152°C (dec., from ether).

Isomer IIIb. Mass spectrum: M^+, 169. IR spectrum (neat): 1735 cm^{-1} (C=O). UV spectrum in heptane (λ_{max}, nm [ε]): 290 (122, sh). PMR spectrum in $CDCl_3$: 1.11 (3H, d, J = 6 Hz, 2-CH_3), 1.14 ppm (3H, d, J = 6 Hz, α-CH_3).

1-(S)-sec-Butyl-4-piperidone. An analogous procedure with 2.6 g (10 mmoles) iodomethylate of 1-methyl-4-piperidone, 1.1 g (15 mmoles) (+)-sec-butylamine [8] with $[\alpha]_D^{20}$ + 7.9° (without solvent) and 1.1 g (60 mmoles) water and separation of the product on a silica gel column using ether as the eluent gave 0.4 g (26%) 1-sec-butyl-4-piperidone, R_f 0.3 (Silufol, 3:1 benzene–acetone), $[\alpha]_D^{20}$ + 5.1° (c = 4.3, benzene). Mass spectrum: m/z 155 (M^+), 140 ($M^+ - CH_3$), 129 ($M^+ - C_2H_5$). IR spectrum (neat): 1730 cm^{-1} (C=O). PMR spectrum in $CDCl_3$: 0.87-1.67 (8H, m), 2.27-293 ppm (9H, m). Picrate, mp 84-85°C (from ethanol). Found: C, 46.5; H, 5.8%. Calculated for $C_9H_{17}NO \cdot C_6H_3N_3O_7$: C, 46.9; H, 5.2%.

1-(1-Methyl-2-phenylethyl)-4-piperidone was obtained analogously from 5.1 g (20 mmoles) iodomethylate of 1-methyl-4-piperidone, 3.6 g (30 mmoles) α-phenylethylamine, and 2.2g (0.12 mole) water. Chromatographic separation on a silica gel column with 7:1 benzene–acetone as the eluent gave 1.7 g (43%) 1-α-phenylethyl-4-piperidone, R_f (Silufol, 5:1 benzene–acetone). n_D^{18} 1.5400, $[\alpha]_D^{20}$ = -25.3° (c = 4.6, benzene). Mass spectrum: m/z 203 (M^+), 188 ($M^+ - CH_3$) 105 ($C_6H_5CHCH_3^+$). IR spectrum (neat): 1730 cm^{-1} (C=O). UV spectrum in heptane (λ_{max}, nm [ε]): 295 (45), 264 (159), 258 (168), 251 (178). PMR spectrum in $CDCl_3$: 1.35 (3H, d, J = 6.6 Hz, CH_3), 3.58 (1H, q, J = 6.6 Hz, CH), 7.16 ppm (5H, s, C_6H_5). Picrate, mp 157-158°C (from benzene–ether). Found: C, 52.8; H, 4.5; N, 12.9%. Calculated for $C_{13}H_{17}NO \cdot C_6H_3N_3O_7$: C, 52.8; H, 4.6; N, 12.9%.

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SYNTHESIS, MOLECULAR STRUCTURE, AND ABSOLUTE CONFIGURATION OF 1-α-PHENYLETHYL-3-(2-CYANOETHYL)-4-PIPERIDONE

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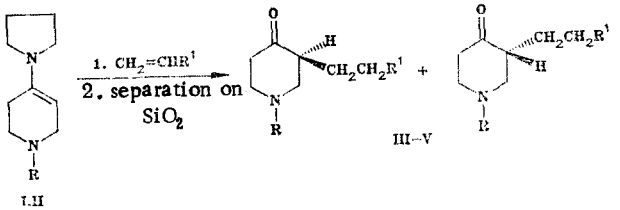
UDC 547.824.541.65.548.737

The Michael addition of acrylonitrile to the pyrrolidine enamine of 1-(S-α-phenylethyl)-4-piperidone proceeds with the formation of a 1:1 mixture of 1-(S-α-phenylethyl)-3-(2-cyanoethyl)-4-piperidone diastereomers. A diastereomer isolated in pure form was shown by x-ray diffraction structural analysis to have S-configuration of the new chiral center at $C_{(3)}$ of the piperidone ring.

The great practical importance of 3-alkyl-4-piperidone derivatives due to their much enhanced biological activity relative to their 2-alkyl analogs [1] and the great difficulty in preparing and separating the enantiomeric derivatives of 4-piperidones [2] led us to seek convenient pathways for the preparation of chiral 3-substituted 4-piperidones. No information on such pathways was found in the literature.

In order to solve this problem, we studied the addition of electrophilic olefins to enamines I and II obtained from 1-(S-α-phenylethyl)- and 1-(S-sec-butyl)-4-piperidones. We attempted to elucidate whether the addition of these olefins leads to chirality at $C_{(3)}$ in the 3-substituted 4-piperidone formed and the nature of the stereoselectivity of this reaction. The addition of methyl acrylate to enamines I and II was carried out by heating these reagents in equimolar amounts at reflux with subsequent separation of 1-α-phenylethyl- (III) and 2-sec-butyl-3-(2-carboethoxyethyl)-4-piperidones using chromatography on a silica gel column in 40 and 76% yield, respectively [3]. The separation of the products of the alkylation of 4-piperidone enamines does not require carrying out the hydrolysis usual for such cases and the decomposition of the reaction mixture occurs on the silica gel column. The structures of piperidones III and IV were confirmed by elemental analysis, chromato-mass spectrometry and IR spectroscopy. Analysis of the PMR spectra of piperidones III and IV also supports their assigned structures but does not lead to a solution of the stereochemical problem of the diastereomeric composition of each of the piperidones since the PMR spectra did not show signal doubling which is characteristic for a diastereomeric pair. However, the ^{13}C NMR spectra show doubling of the signals for $C_{(2)}$, $C_{(6)}$ and the α- and β-carbon atoms of the α-phenylethyl substituent for 4-piperidone III and the carbon atoms of the methyl and methylene groups of the 1-sec-butyl substituent for piperidone IV with equal ratio of integral intensities, indicating the formation of both piperidones III and IV as a 1:1 diastereomer mixture (Table 1).



I, III, V R=CH(CH$_3$)C$_6$H$_5$, II, IV R=*s*-C$_4$H$_9$; III, IV R^1=COOCH$_3$, V R^1=CN

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 0009-3122/85/2112-1362$09.50