ASYMMETRIC SYNTHESIS, STEREOCHEMISTRY, AND ABSOLUTE CONFIGURATION OF 1,2-5-TRIMETHYL-5-(2-CYANOETHYL)- AND 1,2,5-TRIMETHYL-4-PIPERIDINONES

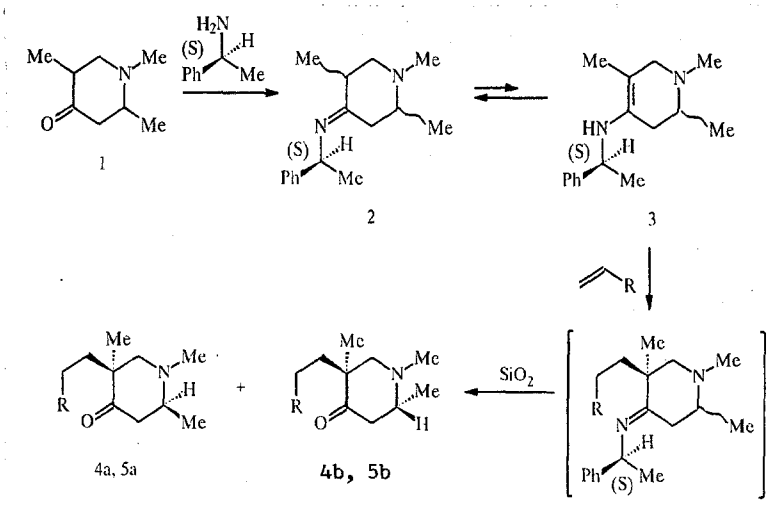
G. V. Grishina, E. L. Gaidarova, and A. É. Aliev

The asymmetric Michael alkylation of (−)-1,2,5-trimethyl-4-(1S-phenylethylimino)piperidine by electron-deficient alkenes proceeds with the formation of (+)-cis-(2S,5S)- and (−)-trans-(2R,5S) diastereomers of 1,2,5-trimethyl-5-(2-cyanoethyl)- and 1,2,5-trimethyl-5-(2-methoxycarbonylethyl)-4-piperidinones containing a chiral quaternary center $C_{(5)}$. The spatial structure of these new chiral 4-piperidinones has been established on the basis of ^1H and ^{13}C NMR spectroscopic data. The absolute configuration of the $C_{(2)}$ and $C_{(5)}$ chiral centers in the diastereomers has been determined by stereochemical correlation on the basis of circular dichroism data.

The asymmetric synthesis of piperidine derivatives is a promising method for obtaining natural and synthetic biologically active substances and pharmaceutical preparations of this class with a high level of optical purity and the required stereochemistry. Here we are reporting on a study of the stereochemistry of asymmetric synthesis of (+)-*cis* and (−)-*trans* diastereomers of 1,2,5-trimethyl-5-(2-cyanoethyl)- and 1,2,5-trimethyl-5-(2-methoxycarbonylethyl)-4-piperidinones, compounds **4a,b** and **5a,b**, respectively. In this work we used a method that we had developed previously for the highly enantioselective synthesis of 3,3-disubstituted 4-piperidinones, based on asymmetric alkylation of the chiral imines of 1,3-dimethyl-4-piperidone by electron-deficient alkenes [1].

The key compound, (−)-1,2,5-trimethyl-4-(1*S*-phenylethylimino)piperidine (**2**) was obtained with a yield of 85% by refluxing, in absolute benzene, equimolar quantities of racemic 1,2,5-trimethyl-4-piperidinone (a 95:5 mixture of *trans* and *cis* isomers) and (−)-(1*S*)-phenylethylamine, in the presence of catalytic quantities of *p*-toluenesulfonic acid (Scheme 1).

Scheme 1



(4a,b) R = CN; (5a,b) R = COOMe.

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TABLE 1. Optical Purity of 4-Piperidinones **4a,b** and **5a,b**

Compound	$[\alpha]_D^{24}$ (and concentration in benzene)	Enantiomeric purity, %*
4a	+132,9 (1,0)	80
4b	-62,6 (1,8)	66
5a	+121,3 (3,8)	86
5b	-65,6 (3,9)	70

*Accuracy of integration of proton signals was ±1%.

The addition of acrylonitrile to the chiral (−)-imine **2** was accomplished by refluxing equimolar quantities of the substances in absolute tetrahydrofuran for 72 h in a flow of argon. Upon decomposition of the reaction mixture in a column packed with silica gel, upon elution with a 7:1 benzene—acetone system, two new optically active 4-piperidinones, the (+) isomer **4a** and the (−) isomer **4b** were recovered in a 3:1 ratio, with a total yield of 71%. The addition of methyl acrylate to the (−)-imine **2** was performed under analogous conditions. By means of column chromatography on silica gel, the 4-piperidinones (+)-**5a** and (−)-**5b** were recovered in a 3:1 ratio with a total yield of 72%.

Thus, the addition of acrylonitrile or methyl acrylate to the chiral (−)-imine **2** proceeds as an asymmetric Michael alkylation, in each case leading to the formation of a pair of optically active 4-piperidinone isomers, **4a,b** and **5a,b**, respectively.

The optical purity of the diastereomers **4a,b** and **5a,b** was established on the basis of ^{1}H NMR spectra in the presence of a chiral LSR (lanthanide shift reagent). Proton spectra were registered for 0.1 M solutions of the samples in $CDCl_3$ with the addition of Eu(facam)$_3$ in the form of a 0.25 M solution in $CDCl_3$, at room temperature. The LSR/substrate mole ratio varied from 0.17 to 0.7. For the enantiomeric analysis, we used as the reference point the signal of the 5-methyl group. The results of these studies are presented in Table 1.

The spatial structure of the 4-piperidinones **4a,b** and **5a,b**, containing a new chiral quaternary center $C_{(5)}$, was established from an analysis of parameters of the ^{1}H and ^{13}C NMR spectra, using 2M NOESY spectroscopy and the INADEQUATE method (^{13}C—^{13}C SSCC). For comparison, we examined ^{1}H and ^{13}C NMR data for 1,2,5-trimethyl-4-piperidinone (**1**), (1*S*,3*S*)-(1-phenylethyl)-3-(2-cyanoethyl)-4-piperidinone (**7**), and 1,3-dimethyl-4-piperidinone (**6**), the steric structure of which had been established reliably in previous work [2, 3, 4, 5].

The equatorial orientation of the 2-CH_3 group in the molecules of the 4-piperidinones **4a,b** and **5a,b** was established on the basis of the following data. The observed ^{13}C chemical shift of the 2-CH_3 group in all four of these compounds **4a,b** and **5a,b** (19-20 ppm, Table 4) is in good agreement with the values reported for the chemical shifts of equatorially oriented 2-CH_3 groups in 4-piperidinones [6, 7] and in 2-methylpiperidine [8]. When the experimental values of the chemical shifts of the $C_{(2)}$ and $C_{(3)}$ atoms of the piperidine ring in the isomers **4a,b** and **5a,b** are compared with the values calculated from an additive scheme using increments given in [6] for equatorial 2-CH_3 groups in 4-piperidinones, we find that the two sets of values are in good agreement (Table 4). As a starting point in these calculations we used the ^{13}C NMR spectra of 1,3-dimethyl-3-(2-cyanoethyl)- (**8**) and 1,3-dimethyl-3-(2-methoxycarbonylethyl)-4-piperidinones (**9**), respectively. The presence of large *trans*-vicinal constants $^3J_{2a3a}$ 10.60 and 10.03 Hz in the ^{1}H NMR spectra of compounds **4a,b**, and $^3J_{2a3a}$ 11.23 and 8.46 Hz for compounds **5a** and **5b**, respectively (Table 3), also provides evidence in favor of the equatorial orientation of the 2-methyl groups in these compounds. Thus, each of the isomers of the chiral 4-piperidinones **4a,b** and **5a,b** exists in the form of a conformer in which the 2-CH_3 group is oriented equatorially.

In determining the spatial orientation of the 5-CH_3 group at the chiral quaternary carbon atom in compounds **4a,b** and **5a,b**, it was found that the ^{13}C chemical shift of the 5-CH_3 group (18-22 ppm) falls between the values that are characteristic for equatorially oriented (11-12 ppm) and axially oriented (23 ppm) 5-methyl groups in 4-piperidinones [6] (Table 4). However, evidence in favor of the axial orientation of the 5-CH_3 group in the 4-piperidinone isomer **4a,b** may be found in the existence of long-range SSCC for this isomer in the ^{1}H NMR spectra, $^4J_{(5\text{-}CH_3,6a)} = 0.57$ Hz (Table 3). In order to establish unambiguously the orientation of the 5-methyl group, we carried out an analysis of direct SSCCs $^1J_{(C,C)}$. A comparison of the magnitudes of the direct SSCCs $^1J_{C(5),C(5\text{-}CH_3)}$ for the 4-piperidinones **4a,b** and **5a,b** (Table 5), with allowance for the stereospecificity of these constants in relation to the carbonyl group ($^1J_{(C,Cax)} < {}^1J_{(C,Ceq)}$ provides evidence for the axial position of the 5-CH_3 group in the isomers **4a,b** and **5a,b**. In the isomers **4a,b** and **5a,b**, the 5-methyl group, consequently,

TABLE 2. ^1H Chemical Shifts (δ, ppm, TMS internal standard) in 4-Piperidinones **4a,b** and **5a,b**

Compound	Solvent	2a	3a	3e	6a	6e	2-CH_3	5-CH_3, eq	5-CH_3, ax	N—CH_3	5-CH_3	CH_2R	R
4 a	C_6D_6	1,74	1,85	1,98	1,63	2,08	0,65	0,64	—	1,85	1,28; 1,94	1,42; 1,55	—
	$CHCl_3$	—	—	—	2,22	2,73	1,12	1,00	—	2,30	—	—	—
4 b	C_6D_6	1,81	2,02	1,95	1,65	2,00	0,67	—	0,83	1,88	1,27; 1,51	1,69; 1,83	—
	$CHCl_3$	—	—	—	2,26	2,65	1,10	—	1,28	2,30	—	—	—
5 a	C_6D_6	1,83	2,20	2,04	1,80	2,33	0,74	0,85	—	1,93	1,68	2,00	3,33 (OCH_3)
5 b	C_6D_6	1,96	2,08	2,13	1,90	2,20	0,70	—	1,02	1,93	1,76; 2,02	2,24; 2,32	3,36 (OCH_3)

TABLE 3. SSCCs $^1J_{HH}$ (Hz) in 4-Piperidinones **4a,b** and **5a,b**

Compound	Solvent	Geminal		Vicinal		Distant	
		6a6e	3a3e	2a3e	2a3a	2a2e-CH_3	6a5a-CH_3
4 a	C_6D_6	-12,03	-14,94	3,74	10,60	6,05	—
4 b	C_6D_6	-11,68	-14,54	4,17	10,03	6,17	0,57
5 a	C_6D_6	-11,94	-14,58	3,50	11,23	6,10	—

TABLE 4. ^{13}C Chemical Shifts (δ, ppm, C_6D_6) in 4-Piperidinones **4a,b** and **5a,b**

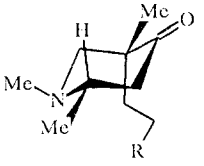
Compound	Spectrum	$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(5)}$	$C_{(6)}$	N—CH_3	2-CH_3	5-CH_3	$C_{(7)}$	$C_{(8)}$	$C_{(9)}$	$C_{(10)}$
4 a	Experimental	59,54	46,29	210,13	48,78	66,17	41,79	19,75	18,61	33,05	12,09	119,73	—
	Calculated for 2-CH_3, eq (Δδ)	59,42 (0,12)	46,45 (0,16)										
	Calculated for 2-CH_3, ax (Δδ)	57,75 (1,79)	44,59 (1,70)										
4 b	Experimental	59,26	46,15	210,62	48,13	65,10	41,90	18,95	21,76	31,85	12,26	120,00	—
	Calculated for 2-CH_3, eq (Δδ)	59,42 (0,16)	46,45 (0,30)										
	Calculated for 2-CH_3, ax (Δδ)	57,75 (1,51)	44,59 (1,56)										
5 a	Experimental	59,91	46,62	210,57	48,98	67,56	41,89	20,19	18,80	32,84	29,03	173,10	51,11
	Calculated for 2-CH_3, eq (Δδ)	58,83 (1,08)	46,60 (0,02)										
	Calculated for 2-CH_3, ax (Δδ)	58,06 (1,85)	44,74 (1,88)										
5 b	Experimental	59,19	46,25	211,21	48,30	65,26	42,15	18,48	22,22	31,22	29,12	173,46	51,19
	Calculated for 2-CH_3, eq (Δδ)	58,83 (0,36)	46,60 (0,35)										
	Calculated for 2-CH_3, ax (Δδ)	58,06 (1,13)	44,74 (1,51)										

TABLE 5. Direct SSCCs $^1J_{CC}$ (Hz) in 4-Piperidinones **4a,b** and **5a,b** (C_6H_6)

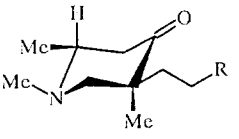
Compound	$C_{(2)}$–$C_{(3)}$	$C_{(3)}$–$C_{(4)}$	$C_{(4)}$–$C_{(5)}$	$C_{(5)}$–$C_{(6)}$	$C_{(6)}$–$C_{5\text{-Me}}$	$C_{(2)}$–$C_{2\text{-Me}}$
4 a	34,5	37,6	37,7	34,9	37,6	38,7
4 b	34,4	34,5	37,8	38,0	34,2	38,5
5 a	34,8	38,2	38,0	34,8	38,2	38,6
5 b	34,5	38,0	38,0	34,9	34,7	38,3

is oriented equatorially. Additional proof of the equatorial orientation of the methyl group at the quaternary $C_{(5)}$ atom in the 4-piperidinone isomers **4a,b** and **5a,b** is the downfield shift of the signal of the 5-CH_3 group protons in comparison with the shift of this group in the isomers **4a,b** and **5a,b** (0.64 and 0.85 ppm; 0.83 and 1.02 ppm, respectively, Table 2). This is the result of stereoselective influence of the magnetic anisotropy of the carbonyl group, manifested in shielding of the equatorial protons and the groups at the neighboring carbon atom [9].

From an examination of these data it follows that the preferentially formed diastereomers 1,2,5-trimethyl-5-(2-cyanoethyl)- (**4a,b**) and 1,2,5-trimethyl-3-(2-methoxycarbonylethyl)-4-piperidinone (**5a,b**) are *cis* isomers, for which the conformational equilibrium is completely (98%) shifted toward the conformer with equatorially oriented 2- and 5-methyl groups. The minor 4-piperidinones **4b** and **5b** are *trans* isomers, and they exist primarily in the (1*e*2*e*5*e*) conformation.



cis-(1ele5a): 4a, 5a



trans-(1e2e5e): 4b, 5b

Thus, asymmetric Michael alkylation of the chiral (−)-imine **2** by electron-deficient alkenes leads to the formation of a mixture of optically active *cis* and *trans* isomers of the 4-piperidinones **4a,b**, in which the *cis* isomer is predominant.

TOPOLOGY OF ASYMMETRIC MICHAEL ALKYLATION

In order to elucidate the stereochemical directions of the asymmetric synthesis, we analyzed in detail the isomeric and conformational compositions of (−)-1,2,5-trimethyl-4-(1*S*-phenylethylimino)piperidine (**2**) obtained from racemic 1,2,5-trimethyl-4-piperidinone (**1**) and (1*S*)-phenylethylamine. An analysis of ^1H and high-resolution ^{13}C NMR spectra, using the INADEQUATE method and ^1H,^{13}C two-dimensional heteronuclear spectroscopy (COSY) demonstrated for the (−)-imine **2** the existence of a complex conformational and tautomeric equilibrium (Scheme 2, and Table 6).

Scheme 2

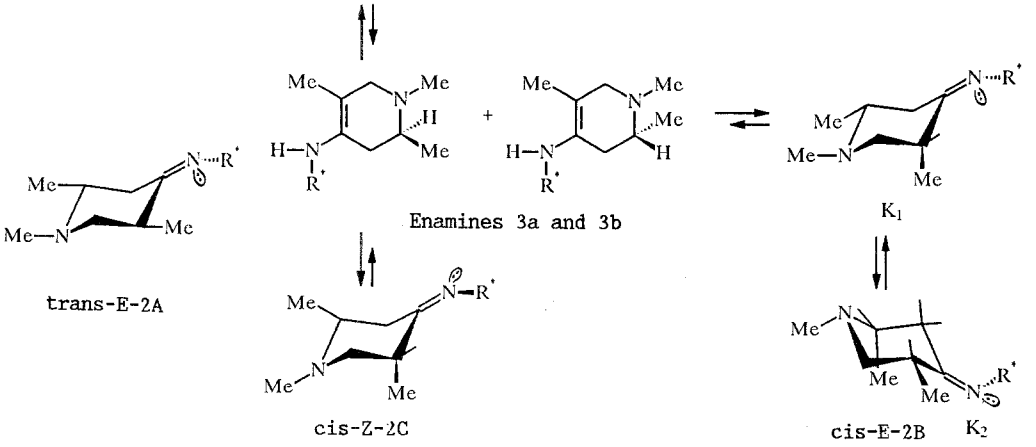


TABLE 6. Conformational and Tautomeric Composition of (−)-1,2,5-Trimethyl-4-(1*S*-phenylethylimino)piperidine (**2**)

Isomer	Content, %	Conformaiton	Diastereomeric Composition, %
trans-E-2A	57	1*e*2*e*5*e*	26 : 31
cis-E-2B	27	1*e*2*a*5*e* ⇄ 1*e*2*e*5*a*	12 : 15
cis-Z-2C	14	1*e*2*e*5*a*	6 : 8
Enamine 3	2	1*e*2*e*	—

In the ^{13}C NMR spectrum of the chiral (−)-imine **2** in the 170 ppm region, we found three doubled signals corresponding to the quaternary imine carbon atom $C_{(4)}$ in each of the three isomeric imine forms 2A, 2B, and 2C, which are *E* and *Z* isomers with respect to the C=N bond; the ratio of the three imine isomers was 4.1:1.9:1. According to the ^{13}C NMR data, the original 1,2,5-trimethyl-4-piperidinone (**1**) exists in the form of *trans* and *cis* epimers with respect to $C_{(5)}$ in a 95:5 ratio; at higher temperatures, and under conditions of basic catalysis, the process of epimerization at the $C_{(5)}$ atom is accelerated. As a consequence, the chiral (−)-imine **2** is also formed as a mixture of optically active *trans* and *cis* isomers. The *E* isomer 2A is a *trans* isomer, the conformational equilibrium for which is completely shifted toward the conformer with diequatorial orientation of the 2- and 5-methyl groups. The *Z* isomer 2C is a conformationally homogeneous *cis* isomer in which the 2- and 5-methyl groups are oriented equatorially and axially, respectively. For the imine 2B that we found in the mixed *cis-E* isomer of the imine, we established the existence of a conformational equilibrium chair (2*e*5*a*) ⇄ chair (2*a*5*e*) with approximately identical populations of the conformers. Since the molecule of the chiral (−)-imine **2** contains three asymmetric atoms — $C_{(2)}$, $C_{(5)}$, and the carbon atom of the (1*S*)-phenylethyl substituent in the amine part — each of the isomers 2A, 2B, and 2C is formed as a mixture of two diastereomers, the ratio of which is 1:1 according to the NMR data. The diastereomers of the *trans-E* isomer 2A have (2*S*,4′*S*,5*R*) and (2*R*,4′*S*,5*S*) configurations, and the diastereomers of both the *cis-Z* and *cis-E* isomers 2C and 2B have the (2*S*,4′*S*,5*S*) and (2*R*4′*S*,5*R*) configurations.

In the ^1H NMR spectrum we also found signals pertaining to protons of the tautomeric enamine form **3**, in which the $C_{(4)}$=$C_{(5)}$ double bond is tetrasubstituted, and the 2-CH_3 group is oriented equatorially. In the molecule of the chiral secondary enamine **3** there are asymmetric atoms $C_{(2)}$ and (*S*)-$C_{(4')}$. This means that the enamine **3** exists in the form of a mixture of two diastereomers **3a** and **3b** that differ only in the configuration of the $C_{(2)}$ atom and thus have the (2*S*,4′*S*) and (2*R*,4′*S*) configurations, respectively. We have not been able to establish the exact diastereomeric composition of the secondary enamine **3**, owing to the small content of this substance in the mixture. However, since the $C_{(2)}$ center is not involved when the original racemic 1,2,5-trimethyl-4-piperidinone interacts with (1*S*)-phenylethylamine, the ratio of diastereomers of the enamine **3a** and **3b** should be 1:1.

The reaction form in which the chiral (−)-1,2,5-trimethyl-4-(1*S*-phenylethylimino)piperidine (**2**) enters into interaction with electron-deficient alkenes is actually the chiral secondary enamines **3a** and **3b**, as was shown previously in the case of derivatives of α-substituted cycloalkanones [10, 11] and 3-substituted 4-piperidinones [1]. Each of the diastereomeric enamines **3a** and **3b** subsequently enters into interaction with electron-deficient alkenes as an individual compound.

Attack by electron-deficient alkenes on the $C_{(4)}$=$C_{(5)}$ double bond of the enamine (2*S*,4′*S*)-**3a** takes place from the pro-*S* side, opposite to the position of the phenyl group of the (*S*)-phenylethyl substituent in the imine part of the molecule, with synclinal approach of the reactants (Fig. 1). In the cyclic transition state, the proton bonded to the nitrogen atom of the enamine fragment is transferred to the β-carbon atom of the alkene, in a process that is synchronous with the formation of the new bond $C_{(5)}$—$C_{(7)}$. As a result of such stereocontrol in the process of asymmetric alkylation of the (2*S*,4′*S*) diastereomer of the enamine **3a**, the reaction should form predominantly the *cis* isomer of 5,5-disubstituted 4-piperidinones with diequatorial orientation of the 2- and 5-methyl groups. This is precisely the spatial structure that was established on the basis of NMR spectroscopic data for the predominant isomers of the 5,5-disubstituted 4-piperidinones **4a** and **5a**. In accordance with such a topology, a new quaternary center $C_{(5)}$ of the *S*-configuration appears in the process of alkylation. Here the asymmetric $C_{(2)}$ center retains the *S*-configuration, the same as in the original chiral enamine **3a**.

Attack by electron-deficient alkenes from the pro-*S* side of the $C_{(4)}$=$C_{(5)}$ double bond of the second enamine (2*R*,4′*S*)-**3b** leads to the formation of *trans*-(1*e*2*e*5*e*) isomers of alkylated 4-piperidinones (Fig. 2). This is exactly the spatial structure that was established on the basis of NMR data for the minor isomers of the 5,5-disubstituted 4-piperidinone **4b** and **5b**. According to our prediction, the new asymmetric $C_{(5)}$ center that appears in this case as a result of alkylation will also have the *S*-configuration, and the $C_{(2)}$ chiral center will retain the *R*-configuration of the original diastereomeric enamine **3b**.

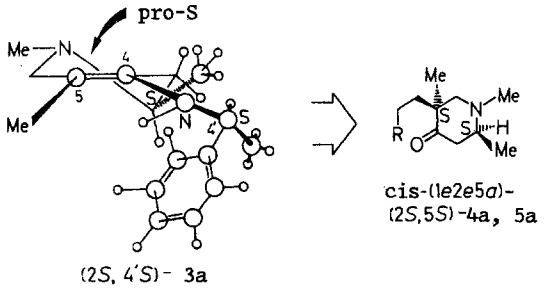


Fig. 1

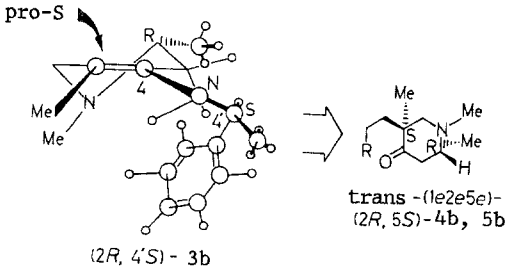


Fig. 2

On the basis of the results of a conformational analysis of the *cis* and *trans* isomers of the 5,5-disubstituted 4-piperidinones **4** and **5** and an analysis of the topology of asymmetric Michael alkylation of the chiral (−)-imine **2** by electron-deficient alkenes, we have predicted the absolute configuration of the resulting diastereomers of 5,5-disubstituted 4-piperidinones: (2*S*,5*S*) as the configuration for the predominant *cis* isomers 4-piperidinones **4a** and **5a**, and (2*R*,5*S*) as the configuration for the minor *trans* isomers of the 4-piperidinones **4b** and **5b**.†

The correctness of this hypothesis is supported by results obtained from circular dichroism (CD) data. For a correct determination of the absolute configuration of asymmetric centers in the (+)-*cis* and (−)-*trans* isomers of the 5,5-disubstituted 4-piperidinones **4a, 5a**, and **4b**, **5b** respectively, we carried out a comparison of the chiroptical properties of these compounds and the following compounds that were selected for stereochemical correlation: (1*S*,3*S*)-1-phenylethyl-3-(2-cyanoethyl)-4-piperidinone (**7**); (2*R*,5*S*)-1,2,5-trimethyl-4-piperidinone (**10**); (3*S*)-1,3-dimethyl-3-(2-cyanoethyl)-4-piperidinone (**8**), and (1*S*,2*S*)-1-*tert*-butyl-2-methyl-4-piperidinone (**11**), with a known absolute configuration.

For the (+)-*cis*-diastereomer **4a**, on the CD curve in heptane at 300 nm, we observe an intense positive CE (Cotton effect) of the $n \rightarrow \pi^*$ transition of the carbonyl chromophore, with molecular ellipticity [Θ] +3851°; then, at 260 nm, the curve intersects the zero line; and at 234 nm, we observe a second, negative CE, probably related to the $n \rightarrow \sigma^*$ transition of the nitrogen atom (Fig. 3). With increasing polarity of the solvent, we observe a hypsochromic shift of the maxima of both CEs, characteristic for $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transitions. When a methanol solution of the (+)-*cis* diastereomer of the 4-piperidinone **4a** is protonated by trifluoroacetic acid, the short-wave negative CE disappears, thus confirming the correctness of its assignment to the $n \rightarrow \sigma^*$ transition of the nitrogen atom.

An analogous course of the CD curves in solvents with differing polarities is also observed for the (+)-*cis*-diastereomer of the 4-piperidinone (**5a**) (Fig. 3). However, the intensity of the band corresponding to the $n \rightarrow \pi^*$ transition of the carbonyl chromophore increases to [Θ] +4742°.

For the (−)-*trans* disastereomers of the 5,5-disubstituted 4-piperidinones **4b** and **5b** in these same solvents, the signs of the observed CEs of the $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transitions are reversed in comparison with the (+)-*cis*-diastereomers; also, both CEs are lower in intensity (Figs. 3 and 4).

For determination of the absolute configuration of the (+)-*cis* and (−)-*trans* isomers of the 4-piperidinones **4** and **5**, we carried out a comparison of the course of the CD curves and the signs of the CEs of the $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transitions for the compounds **4** and **5** that are the subject of our investigation, and also the model compounds **7**, **8**, **10**, and **11**.

For the (+)-*cis* isomers of the 4-piperidinones **4a** and **5a**, and for the 4-piperidinones **7** and **8**, which have the (3*S*) and (5*S*) configurations, respectively, we observe identical positive CEs of the $n \rightarrow \pi^*$ transitions of the carbonyl chromophore in the 300-nm region (Fig. 4). This means that the (+)-*cis*-disastereomers of the 5,5-disubstituted 4-piperidinones **4a** and **5a**

†Probable absolute configurations.

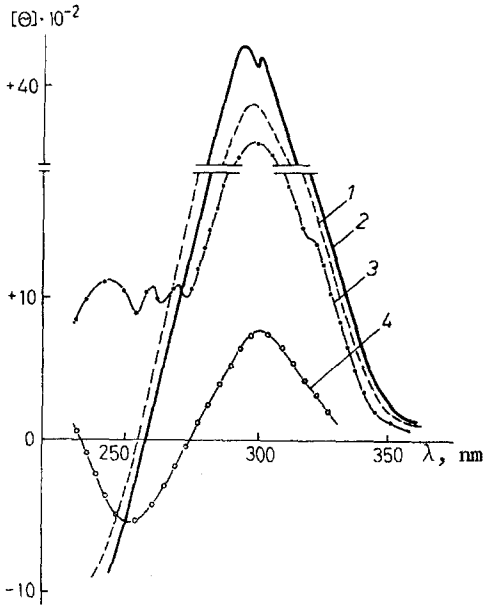


Fig. 3. CD curves in heptane: 1) (+)-*cis*-**4a**; 2) (+)-*cis*-**5a**; 3) (1*S*,3*S*)-4-piperidinone (**8**); 4) (1*S*,2*S*)-4-piperidinone (**11**).

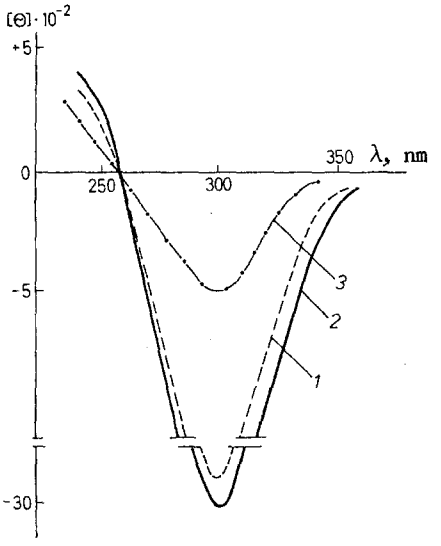


Fig. 4. CD curves in heptane: 1) (−)-*trans*-**4b**; 2) (−)-*trans*-**5b**; 3) (−)-*trans*-(2*R*,5*S*)-4-piperidinone (**10**).

and the 4-piperidinones **7** and **8** have an identical (*S*) configuration of the asymmetric carbon center in the α position relative to the carbonyl group. The coincidence of the signs of the CEs of the $n \rightarrow \sigma^*$ transition of the nitrogen atom in the (+)-*cis* isomers of the 4-piperidinones **4a** and **5a** and in the 4-piperidinone **11** indicates an identical (*S*) configuration of the $C_{(2)}$ chiral center in these compounds (Fig. 5). On the basis of the rule of octants, for the predominant conformers (+)-*cis*-(1*e*,2*e*,5*e*)trimethyl-5*A*-(2-cyanoethyl)- (**4a**) and (+)-*cis*-(1*e*2*e*5*e*)-trimethyl-5*A*-(2-methoxycarbonylethyl)-4-piperidinone (**5a**), we also predict the (2*S*,5*S*) configuration.

For the determination of the absolute configuration of the $C_{(2)}$ and $C_{(5)}$ asymmetric centers in the minor (−)-*trans* isomers of the 4-piperidinones **4b** and **5b**, which are characterized by a negative sign of the CE of the $n \rightarrow \pi^*$ transition of the carbonyl chromophore and a positive sign of the CE of the $n \rightarrow \sigma^*$ transition of the nitrogen atom, we selected as the reference point the (−)-*trans*-(2*R*,5*S*)-1,2,5-trimethyl-4-piperidinone (**10**). The coincidence of the signs of the CEs of these transitions in the (−)-*trans* isomers of the 5,5-disubstituted 4-piperidinones **4b** and **5b** and in the (2*R*,5*S*)-4-piperidinone **10** is evidence of an identical (2*R*,5*S*) configuration of the asymmetric centers in these compounds. For the (−)-*trans*-(2*R*,5*S*)-(1*e*2*e*5*a*)-trimethyl-5*e*-(2-cyanoethyl)- and (−)-*trans*-(2*R*,5*S*)-(1*e*2*e*5*a*)-5*e*-(2-methyoxycarbonylethyl)-4-piperidinone, on the basis of the rule of octants, we also predict a negative sign of the EC of the $n \rightarrow \pi^*$ transition of the carbonyl chromophore.

Thus, the absolute configurations of the $C_{(2)}$ and $C_{(5)}$ chiral centers in the molecules of the (+)-*cis* and (−)-*trans* diastereomers of the 5,5-disubstituted 4-piperidinones **4a,b**, as predicted from an analysis of the topology of asymmetric Michael alkylation of the chiral (−)-imine **2** by electron-deficient alkenes, are in complete agreement with the absolute configurations established by stereochemical correlation. Consequently, the stereochemical relationships that we have found in the topological scheme proposed on the basis of these relationships are correct.

EXPERIMENTAL

The IR spectra were recorded in a UR-20 spectrometer. The UV spectra were taken in a Varian Cary-15 spectrophotomer. The ^1H NMR spectra were measured in Tesla-260 and Bruker-400 spectrometers at room temperature, with TMS internal standard, in solutions in $CDCl_3$, C_6D_6, and $(CD_3)_2CO$. The ^{13}C NMR spectra were taken in a Bruker WP-400 spectrometer in solutions in $CDCl_3$ and C_6D_6; the chemical shifts are given relative to TMS. The mass spectra were obtained in an MKh-1321 spectrometer with direct introduction of the sample into the ion source, with a vaporizer temperature of 150-200°C and an ionization energy of 70 eV. The circular dichroism curves were taken in a Jobin-Yvon Dichrographe III Roussel-Jouan spectropolarimeter at room temperature, in a 0.1-cm cuvette.

The elemental analyses for C, H, and N matched the calculated data.

(−)-1,2,5-Trimethyl-4-(1*S*-phenylethylimino)piperidine (2) ($C_{16}H_{24}N_2$). A mixture of 3.00 g (21.3 mmoles) of 1,2,5-trimethyl-4-piperidinone (**1**) and 2.57 g (21.3 mmoles) of (−)-1*S*-phenylethylamine with $[\alpha]_D^{24}$ −39.7° (without solvent) in 30 ml of absolute benzene was refluxed with a Dean and Stark head until the theoretical quantity of water was collected. The benzene was evaporated, and the residue was vacuum-distilled. Obtained 4.42 g (85%) of (−)-1,2,5-trimethyl-4-(1*S*-phenylethylimino)piperidine (**2**), bp 110-111°C (0.5 mm), n_D^{24} 1.5240. $[\alpha]_D^{24}$ −41.3° (*c* 10.0 in benzene). IR spectrum (in thin layer): 1670 cm^{-1} (C=N). ^1H NMR spectrum ($CDCl_3$): 0.98 (3H, d, J = 7 Hz, 5-C$\underline{H}_3$); 1.05 (3H, d, J = 7 Hz, 2-C$\underline{H}_3$); 1.32 (3H, d, J = 7 Hz, CH(C$\underline{H}_3$)C_6H_5); 2.25 (3H, s, N—CH_3); 4.62 (1H, q, J = 7 Hz, C$\underline{H}$(CH_3)C_6H_5); 7.25 ppm (5H, m, CH(CH_3)C_6H_5). UV spectrum (heptane), λ_{max} (log ε): 320 (1.8); 250 nm (2.8, shoulder). Mass spectrum: found M^+ 244, calculated M 244.

Diastereomers of 1,2,5-Trimethyl-5-(2-cyanoethyl)4-piperidinone (4a,b) (C_{11},H_{18},N_2O). A mixture of 1.74 g (7.1 mmoles) of (−)-1,2,5-trimethyl-4-(1*S*-phenylethylimino)piperidine (**2**) and 0.38 g (7.1 mmoles) of freshly distilled, hydroquinone-stabilized acrylonitrile in 20 ml of absolute tetrahydrofuran was refluxed in a flow of argon for 72 h. The tetrahydrofuran was evaporated, and the residue (2.15 g) was applied to a column packed with silica gel in accordance with the HPFC principle, and eluted with a 5:1 benzene—acetone system. The chromatographically homogeneous fractions were combined. Obtained 0.73 g (53%) of (+)-1,2,5-trimethyl-5-(2-cyanoethyl)-4-piperidinone (**4a**), R_f 0.53 (Silufol, 2:1 benzene—acetone), mp 37-38°C (from hexane), and also 0.25 g (18%) of the (−)-isomer **4b**, R_f 0.47 (Silufol, 2:1 benzene—acetone) in the form of an oil. The total yield of the isomers **4a** and **4b** was 71%, with a ratio **4a**:**4b** = 3:1.

(2*S*,5*S*)-4a: $[\alpha]_D^{24}$ +132.9° (*c* 1.0 in benzene). IR spectrum (in white mineral oil): 2230 (C≡N), 1720 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$): 1.01 (3H, s, 5-C$\underline{H}_3$); 1.12 (3H, d, J = 6 Hz, 2-C$\underline{H}_3$); 2.31 ppm (3H, S, N—C$\underline{H}_3$). Mass spectrum: found M^+ 194, calculated M 194.

(2*R*,5*S*)-4b: $[\alpha]_D^{24}$ −62.6° (*c* 1.8 in benzene). IR spectrum (in thin layer): 2230 (C≡N), 1720 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$): 1.10 (3H, d, J = 6 Hz, 2-C$\underline{H}_3$); 1.30 (3H, s, 5-C$\underline{H}_3$); 2.29 ppm (3H, s, N—C$\underline{H}_3$). Mass spectrum: found M^+ 194, calculated M 194. Picrate, $C_{17}H_{21}N_5O_8$, mp 175-176°C (from ethanol).

Diastereomers of 1,2,5-Trimethyl-5-(2-methoxycarbonylethyl)-4-piperidinone (5a,b). Analogously, from a mixture of 3.72 g (15.2 mmoles) of (−)-1,2,5-trimethyl-4-(1*S*-phenylethylimino)piperidine (**2**) and 1,31 g (15.2 mmoles) of freshly distilled, hydroquinone-stabilized methyl acrylate, obtained 1.60 g (54%) of (+)-1,2,5-trimethyl-5-(2-methoxycarbonylethyl)-4

-piperidinone (**5a**), R_f 0.62 (Silufol, 2:1 benzene—acetone) in the form of an oil, and also 0.53 g (18%) of the (−)-isomer **5b**, R_f 0.56 (Silufol, 2:1 benzene—acetone) in the form of an oil. The total yield of the isomers **5a** and **5b** was 72%, and the isomer ratio **5a**:**5b** = 3:1.

(2*S*,5*S*)-5a: $[\alpha]_D^{24}$ +121.3° (*c* 3.8 in benzene). IR spectrum (in white mineral oil): 1740 (C=O), 1720 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$): 0.90 (3H, s, 5-C$\underline{H}_3$); 1.10 (3H, d, J = 7 Hz, 2-C$\underline{H}_3$); 2.30 (3H, s, N—CH_3); 3.70 ppm (3H, s, COOC$\underline{H}_3$). Mass spectrum: found M^+ 227, calculated M 227. Picrate $C_{18}H_{24}N_4O_{10}$, mp 180-181°C (from ethanol).

(2*R*,5*S*)-5b: $[\alpha]_D^{24}$ −65.6° (*c* 3.9 in benzene). IR spectrum (in thin layer): 1740 (C=O), 1720 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$): 1.10 (3H, d, J = 7 Hz, 2-C$\underline{H}_3$); 1.30 (3H, s, 5-C$\underline{H}_3$); 2.32 (3H, s, N—C$\underline{H}_3$); 3.70 ppm (3H, s, COOC$\underline{H}_3$). Mass spectrum: found, M^+ 227, calculated M 227. Picrate $C_{18}H_{24}N_4O_{10}$, mp 176-177°C (from ethanol).

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