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

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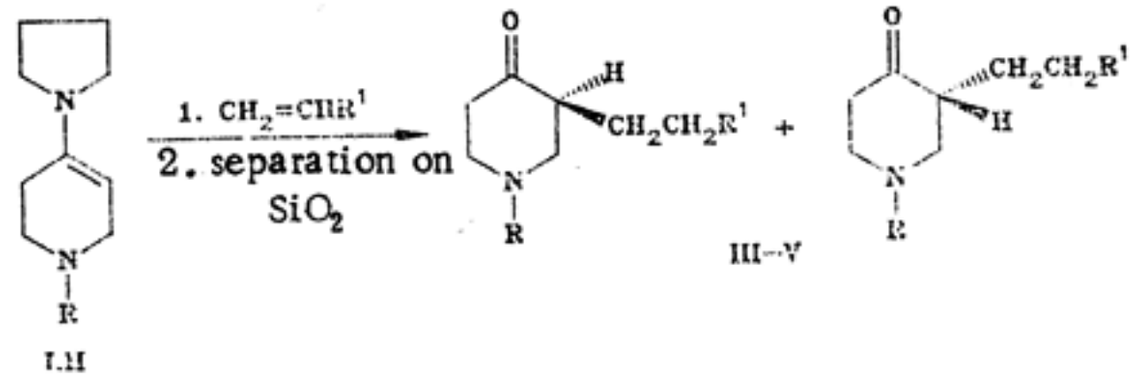
The Michael addition of acrylonitrile to the pyrrolidine enamine of 1-(S-α-phenylethyl)-4-piperidone proceeds with the formation of a 1:1 mixture of 1-(S-α-phenylethyl)-3-(2-cyanoethyl)-4-piperidone diastereomers. A diastereomer isolated in pure form was shown by x-ray diffraction structural analysis 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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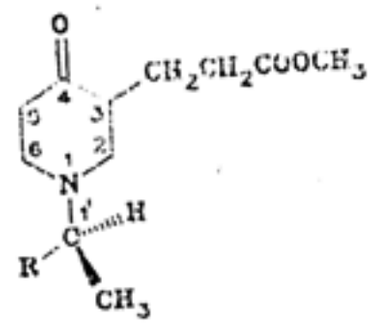
TABLE 1. ^{13}C NMR Chemical Shifts of Piperidones III and IV (δ, ppm, in C_6D_6)*



Compound	R	$C_{(2)}$	$C_{(3)}$	$C_{(5)}$	$C_{(6)}$	$NCH(CH_3)R$			$CH_2CH_2COOCH_3$		
						1'-CH_3	1'-CH_2	1'-CH	CH'_2	CH''_2	OCH_3
III	C_6H_5	56,13; 55,64	49,17 —	40,99 —	50,76; 50,03	19,26; 18,53	— —	63,21; 62,84	23,28 —	31,60 —	50,76 —
IV	C_2H_5	55,86; 52,81	50,12 —	41,48 —	49,87; 47,07	13,89; 13,69; 11.09	31,81; 27,05	60,27 —	26,69 —	41,82 —	50,85 —

*The signal assignment was carried out by incomplete proton decoupling and comparison with the data for 1-substituted 3-methyl-4-piperidones [4, 5].

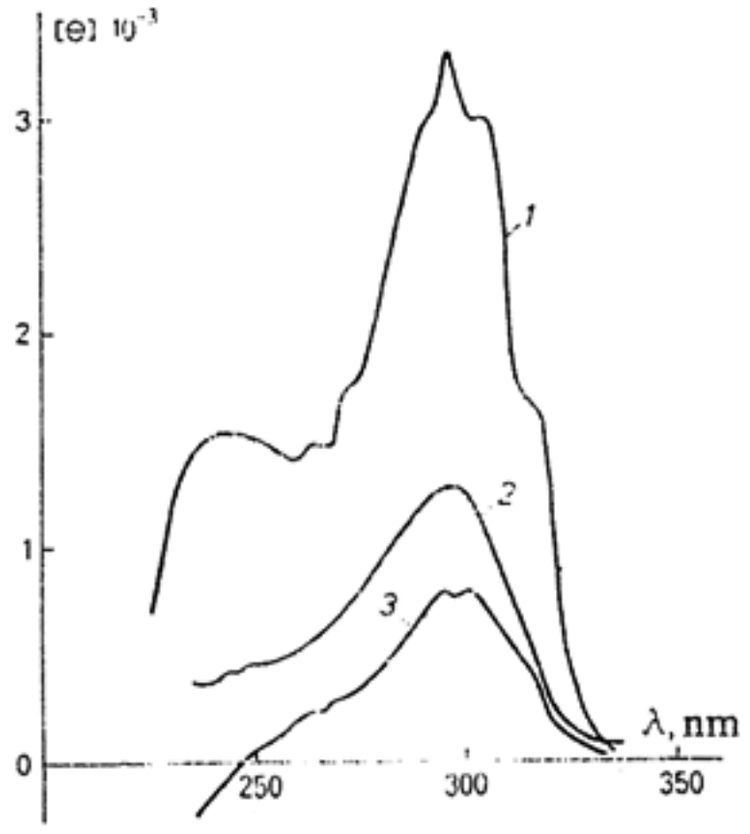


Fig. 1. Circular dichroism curves in heptane: 1) optically pure piperidone diastereomer Va, 2) 1:1 mixture of diastereomers V and Vb, 3) 28:72 mixture of diastereomers Va and Vb.

The addition of acrylonitrile to enamine I was carried out by analogy. Decomposition of the reaction on the silica gel column gave a 68% yield of chromatographically pure 1-α-phenylethyl-3-(2-cyanoethyl)-4-piperidone (V). The doubling of the signals of the methyl (1.34 and 2.41 ppm) and methine (3.64 and 3.67 ppm) groups of the α-phenylethyl substituent with 1:1 intensity ratio in the PMR spectrum of piperidone V indicates the formation of a 1:1 diastereomer mixture. After three-fold crystallization of the diastereomer mixture of Va and Vb from heptane, crystalline diastereomer Va was isolated with $[\alpha]_D^{20} = -45.9°$ with invariant specific rotation and melting point upon recrystallization. The mother liquor gave an oily mixture of diastereomers Va and Vb with $[\alpha]_D^{20} = -4.3°$ enriched in isomer Vb. The diastereomeric purity of the isomers isolated before and after recrystallization was monitored by PMR at 250 MHz and was found to be 100% for diastereomer Va and 44% for diastereomer Vb. The specific rotation of optically pure diastereomer Vb should be +12° taking account of the 1:2.6 diastereomer ratio for the fraction enriched in diastereomer Vb and the specific rotation of this fraction (-4.3°). Diastereomer Va shows a positive Cotton effect for the n—π* transition of the carbonyl chromophore with [θ] +3300° in heptane. A positive Cotton effect with [θ] +771° is also observed for diastereomer Vb having 44% diastereomeric purity. The molecular ellipticity for optically pure diastereomer Vb was calculated to be -210° (Fig. 1).

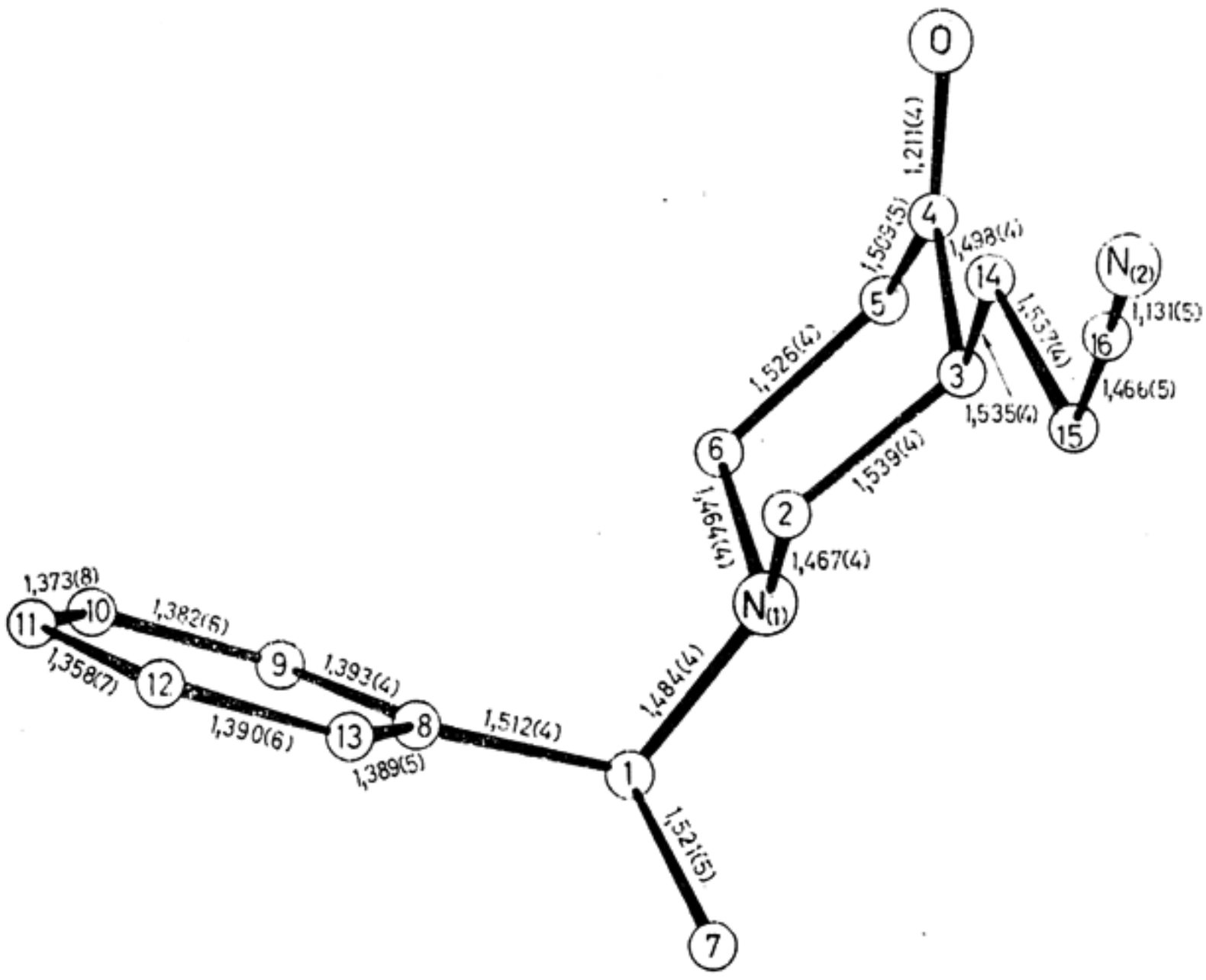


Fig. 2. X-ray diffraction structural data for optically pure 4-piperidone diastereomer Va

TABLE 2. Atomic Coordinates ($\times 10^4$) and Their Equivalent Isotropic Temperature Factors $B^{eq}_{iso} = \frac{1}{3}\sum_i\sum_j Bij\alpha^*i\alpha^*j(a_i a_j)$ Å^2

Atom	x	y	z	B^{eq}_{iso}, Å^2
O	−744 (5)	−2627 (2)	−5527 (0,9)	5,00 (7)
$N_{(1)}$	−4940 (4)	−153 (2)	−6225,7 (0,9)	3,48 (6)
$N_{(2)}$	4109 (7)	1360 (3)	4349 (2)	7,5 (1)
$C_{(1)}$	−5756 (6)	703 (3)	−6711 (1)	3,77 (8)
$C_{(2)}$	−2621 (6)	141 (3)	−6004 (1)	3,57 (8)
$C_{(3)}$	−2169 (6)	−634 (3)	−5467 (1)	3,54 (7)
$C_{(4)}$	−2289 (6)	−1911 (3)	−5640 (1)	3,62 (8)
$C_{(5)}$	−4494 (7)	−2239 (3)	−5982 (1)	4,35 (9)
$C_{(6)}$	−4889 (7)	−1372 (3)	−6479 (1)	4,14 (8)
$C_{(7)}$	−6416 (7)	1874 (3)	−6428 (2)	5,0 (1)
$C_{(8)}$	−4075 (6)	831 (3)	−7221 (1)	3,97 (8)
$C_{(9)}$	−4347 (8)	107 (3)	−7704 (1)	5,7 (1)
$C_{(10)}$	−2783 (12)	166 (4)	−8167 (2)	7,6 (2)
$C_{(11)}$	−944 (11)	973 (5)	−8160 (2)	8,0 (2)
$C_{(12)}$	−642 (8)	1695 (4)	−7695 (2)	7,2 (1)
$C_{(13)}$	−2205 (7)	1641 (3)	−7228 (1)	5,3 (1)
$C_{(14)}$	219 (6)	−333 (3)	−5174 (1)	3,86 (8)
$C_{(15)}$	91 (7)	866 (3)	−4860 (2)	5,0 (1)
$C_{(16)}$	2360 (3)	1128 (3)	−4568 (2)	5,0 (1)

An x-ray diffraction structural analysis of diastereomer Va was carried out to establish the absolute configuration of the new chiral center at $C_{(3)}$. The piperidone ring was found to have asymmetrical chair conformation with equatorial orientation of the cyanoethyl substituent at $C_{(3)}$ and of the α-phenylethyl substituent. $N_{(1)}$ extrudes by 0.708(2) Å for the $C_{(2)}$ $C_{(3)}$ $C_{(5)}$ $C_{(6)}$ plane (plane I) (the atoms are planar to within ± 0.012 (4) Å), while $C_{(4)}$ extrudes from this plane by 0.586 (3) Å [the dihedral angles of plane I and the $N_{(1)}$-$C_{(2)}C_{(6)}$ plane and of plane I and the $C_{(3)}C_{(4)}C_{(5)}$ plane are 56.8 and 46.5°, respectively]. Figure 2 shows the complete molecular geometry of Va and Table 2 gives the atomic coordinates and their isotropic temperature factors. The bond angles and some torsion angles in Va are given in Tables 3 and 4. The absolute S-configuration of $C_{(3)}$ of the piperidone ring was established unequivocally using the known S-configuration of the 1-α-phenylethyl substituent as a chiral label.

TABLE 3. Bond Angles ω (deg)

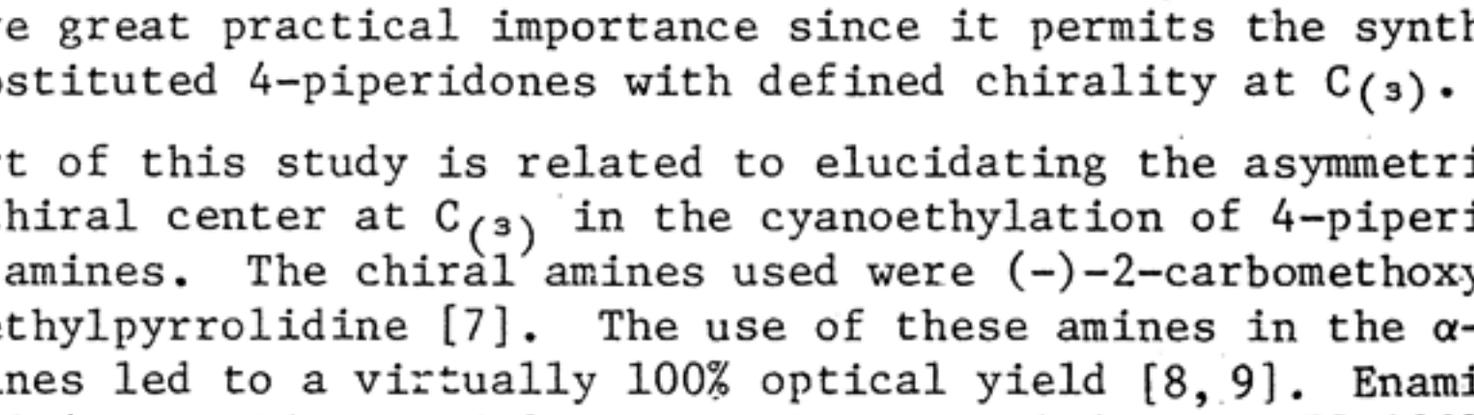
Bond angle	ω	Bond angle	ω
$C_{(1)}N_{(1)}C_{(2)}$	114,2 (2)	$C_{(4)}C_{(5)}C_{(6)}$	110,8 (3)
$C_{(1)}N_{(1)}C_{(6)}$	112,7 (2)	$N_{(1)}C_{(6)}C_{(5)}$	110,7 (3)
$C_{(2)}N_{(1)}C_{(6)}$	109,5 (2)	$C_{(1)}C_{(8)}C_{(9)}$	120,0 (3)
$N_{(1)}C_{(1)}C_{(7)}$	110,1 (3)	$C_{(1)}C_{(8)}C_{(13)}$	122,6 (3)
$N_{(1)}C_{(1)}C_{(8)}$	114,3 (2)	$C_{(9)}C_{(8)}C_{(13)}$	117,3 (3)
$C_{(7)}C_{(1)}C_{(8)}$	113,7 (3)	$C_{(8)}C_{(9)}C_{(10)}$	121,5 (4)
$N_{(1)}C_{(2)}C_{(3)}$	110,4 (2)	$C_{(9)}C_{(10)}C_{(11)}$	119,7 (5)
$C_{(2)}C_{(3)}C_{(4)}$	109,0 (2)	$C_{(10)}C_{(11)}C_{(12)}$	120,1 (15)
$C_{(2)}C_{(3)}C_{(14)}$	111,7 (3)	$C_{(8)}C_{(13)}C_{(12)}$	120,7 (3)
$OC_{(4)}C_{(3)}$	123,6 (3)	$C_{(3)}C_{(14)}C_{(15)}$	111,3 (3)
$OC_{(4)}C_{(5)}$	122,1 (3)	$C_{(14)}C_{(15)}C_{(16)}$	110,8 (3)
$C_{(3)}C_{(4)}C_{(5)}$	114,3 (3)	$N_{(2)}C_{(16)}C_{(15)}$	178,2 (4)

TABLE 4. Torsion Angles in Piperidone Va τ (deg)

Angle	τ	Angle	τ
$OC_{(4)}C_{(3)}C_{(2)}$	128,5 (4)	$C_{(7)}C_{(1)}C_{(8)}C_{(9)}$	−142,4 (5)
$OC_{(4)}C_{(3)}C_{(14)}$	4,4 (3)	$C_{(7)}C_{(1)}C_{(8)}C_{(13)}$	38,6 (4)
$C_{(4)}C_{(3)}C_{(2)}N_{(1)}$	57,2 (3)	$C_{(7)}C_{(1)}N_{(1)}C_{(6)}$	164,7 (4)
$C_{(4)}C_{(3)}C_{(14)}C_{(15)}$	165,3 (4)	$C_{(8)}C_{(1)}N_{(1)}C_{(6)}$	66,0 (4)
$C_{(3)}C_{(2)}N_{(1)}C_{(6)}$	−64,3 (3)	$C_{(1)}N_{(1)}C_{(6)}C_{(5)}$	164,5 (4)
$C_{(3)}C_{(2)}N_{(1)}C_{(1)}$	168,3 (4)	$N_{(1)}C_{(6)}C_{(5)}C_{(4)}$	−53,8 (3)
$C_{(2)}N_{(1)}C_{(6)}C_{(5)}$	62,2 (2)	$C_{(6)}C_{(5)}C_{(4)}C_{(3)}$	49,2 (3)
$C_{(2)}N_{(1)}C_{(1)}C_{(7)}$	−69,5 (4)	$C_{(6)}C_{(5)}C_{(4)}O$	129,7 (5)
$C_{(2)}N_{(1)}C_{(1)}C_{(8)}$	59,9 (4)	$C_{(5)}C_{(4)}C_{(3)}C_{(2)}$	−50,3 (3)
$N_{(1)}C_{(1)}C_{(8)}C_{(9)}$	90,1 (4)	$C_{(5)}C_{(4)}C_{(3)}C_{(14)}$	−174,5 (4)
$N_{(1)}C_{(1)}C_{(8)}C_{(13)}$	−88,9 (4)	$C_{(3)}C_{(14)}C_{(15)}C_{(16)}$	178,4 (5)

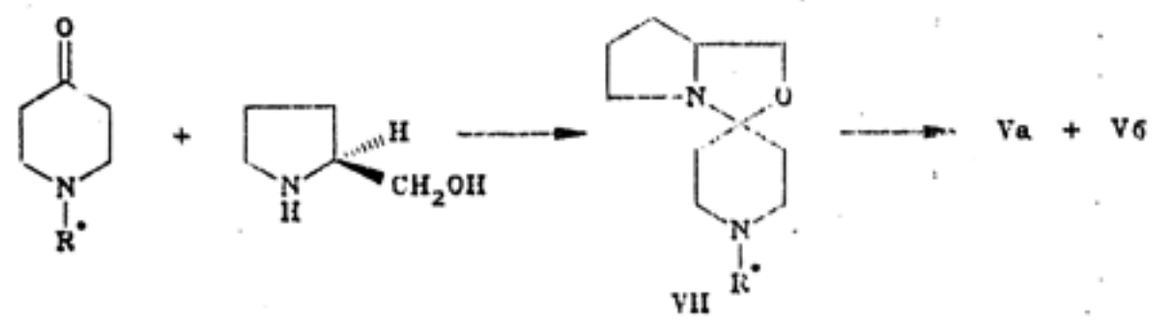
The proposed simple method for the preparation of optically active 3-substituted 4-piperidones may have great practical importance since it permits the synthesis of pure diastereomers of 3-substituted 4-piperidones with defined chirality at $C_{(3)}$.

The second part of this study is related to elucidating the asymmetric effect on the generation of the chiral center at $C_{(3)}$ in the cyanoethylation of 4-piperidone enamines obtained from chiral amines. The chiral amines used were (-)-2-carbomethoxypyrrolidine [6] and (+)-2-hydroxymethylpyrrolidine [7]. The use of these amines in the α-alkylation of cyclohexanone enamines led to a virtually 100% optical yield [8, 9]. Enamine VI obtained from 1-α-phenylethyl-4-piperidone and 2-carbomethoxypyrrolidine in 72-100% yield depending on the reaction conditions (maintenance at room temperature for 24 h or heating at reflux for 1 h) was shown by PMR spectroscopy to be a mixture of rotational isomers. Indeed, the PMR spectrum of enamine VI showed two vinyl proton triplets at 4.0 and 4.23 ppm with equal intensities. The doubling of the vinyl proton signal is actually related to hindered rotation of the 2-carbomethylpyrrolidine residue about the C—N bond, which was established by the observation of an analogous doubling of the vinyl proton triplet (4.0 and 4.29 ppm) in the PMR spectrum of 1-butyl-4-piperidone and 2-carbomethoxypyrrolidine.



The action of acrylonitrile on enamine VI in absolute benzene at room temperature gave a 40% yield of piperidone V, which was shown by PMR spectroscopy to be a 1:1 mixture of diastereomers Va and Vb. The reaction of 1-(α-phenylethyl)-4-piperidone with (-)-2-hydroxymethylpyrrolidine leads not to an enamine but to oxazolidine VII in 50% yield, as indicated

by the lack of the enamine group IR stretching band at 1660 cm^{-1} and the lack of the vinyl proton triplet in the PMR spectrum in the vicinity of 4 ppm. The cyanoethylation of oxazolidine VII upon heating for 8 h in benzene at reflux or maintenance at room temperature for one week gives a 1:1 mixture of piperidone diastereomers Va and Vb, as indicated by PMR spectroscopy, in 40 and 35% yield, respectively.



The formation of different ratios of the diastereomers of piperidones III-V obtained by Michael addition of electrophilic olefins to different chiral piperidone enamines I, II and VI and oxazolidine VII may be attributed to the high basicity of 4-piperidones [8], leading to the loss of diastereoselectivity in the alkylation of of 4-piperidone enamines.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer. The PMR spectra were taken on Varian T-60 and XL-100 and Bruker M-250 spectrometers at room temperature with TMS as the internal standard in $CDCl_3$ and CCl_4 solutions. The ^{13}C NMR spectra were taken on CFT-20 and FT-80 spectrometers in C_6D_6 and CCl_4 solutions and given relative to TMS. The mass spectra were taken on an MKh-1303 spectrometer with direct sample inlet into the ion source with 100-150°C injector temperature and 50-60 eV ionization energy. The gas-liquid chromatography was carried out on an LKhM-8MD chromatograph on a 30 m capillary column with SE-30 liquid phase. The circular dichroism curves were taken on a Jasco-20 spectropolarimeter. The unit cell parameters of orthorhombic crystals of 1-(S-α-phenylethyl)-3-(2-cyanoethyl)-4-piperidone at 20°C are as follows: a = 5.586(1), b = 11.296(2), c = 23.104(4) Å, d_{calc} = 1.174 g/cm^3, Z = 8, space group $P2_12_12_1$. The unit cell parameters and intensities of 1041 independent reflections with $F \geqslant 2\sigma$ were measured on a Hilger-Watts Y/290 automatic four-circle diffractometer using λCuK_α radiation, graphite monochromator, $\theta/2\theta$ scan, and $\theta \leqslant 66°$. The structure was solved by the direct method using the MULTAN program and refined by the full-matrix method of least squares, initially in the isotropic approximation and then in the anisotropic approxiamtion. All the hydrogen atoms were revealed in the difference map and included in the refinement with fixed positional and temperature parameters (B_{iso} = 6.0 Å^2). The final R factor was 0.0358 (R_w = 0.0421). The calculations were carried out on an Eclipse/200 computer using the INEXTL program [9].

The 4-piperidone enamines were prepared according to our previous procedure [3].

1-(S-α-Phenylethyl)-4-pyrrolidino-3-piperideine (I). A mixture of 0.85 g (4.1 mmoles) 1-α-phenylethyl-4-piperidone and 0.34 g (5 mmoles) pyrrolidine in 5 ml absolute benzene was heated at reflux in an argon stream with a Dean–Stark trap until water was no longer liberated. Benzene was removed in vacuum to yield 1.05 g (100%) enamine I. IR spectrum (neat): 1660 cm^{-1} (N–C=C). PMR spectrum in $CDCl_3$: 1.40 (d, J = 6.6 Hz, 3H, β-CH_3), 4.25 (t, J = 3 Hz, 1H, H–C=C), 7.40 ppm (s, 5H, C_6H_5).

1-(S-sec-Butyl)-4-pyrrolidino-3-piperideine (II). A mixture of 0.47 g (3 mmoles) 1-S-sec-butyl)-4-piperidone and 0.34 g (5 mmoles) pyrrolidine in 5 ml absolute benzene was heated at reflux in an argon stream. Benzene was removed in vacuum to yield 0.62 g (100%) enamine II. IR spectrum (neat): 1670 cm^{-1} (N–C=C). PMR spectrum in $CDCl_3$: 4.3 ppm (t, J = 3H, 1H, C=C–H).

1-(S-α-Phenylethyl)-4-(2-carbomethoxypyrrolidino)-3-piperideine (VI). A. An analogous procedure using 1.17 g (5.8 mmoles) piperidone and 0.75 g (5.8 mmoles) (–)-(2-carbomethoxy) pyrrolidine gave 1.3 g (72%) enamine VI, bp 110-112°C (1 mm), n_D^{25} 1.5335, $[\alpha]_D^{20}$ = -62° (c = 2, benzene). IR spectrum (neat): 1660 (N–C=C), 1745 cm^{-1} (ester C=O). PMR spectrum in C_6H_6: 1.28 (d, J = 6.5 Hz, 3H, β-CH_3), 3.35 (s, 3H, OCH_3), 4.00 (t, J = 3 Hz, 1H, C=C–H), 4.23 ppm (t, J = 3 Hz, 1H, =C–H).

B. A mixture of 5.8 mmoles 1-α-phenylethyl-4-piperidone, 5.8 mmoles (–)-2-carbomethoxypyrrolidine and 2 g anhydrous magnesium sulfate in absolute ether was left at room temperature for 10 h. The drying agent was filtered off and ether was removed in vacuum to give 5.8 mmoles enamine VI. The PMR spectrum of this sample was identical to that obtained for the sample obtained by procedure A.

1-Butyl-4-(2-carbomethoxypyrrolidino)-3-piperideine. A mixture of 5.1 mmoles 1-butyl-4-piperidone, 5.1 mmoles (–)-2-carbomethoxypyrrolidine and 2 g anhydrous magnesium sulfate at room temperature gave 1.3 g (95%) 1-butyl-4-(2-carbomethoxypyrrolidino)-3-piperideine, n_D^{20} 1.4878, $[\alpha]_D^{20} = -22.8°$ (c = 5, C_6H_6). IR spectrum (neat): 1660 cm^{-1} (N–C=C). PMR spectrum in C_6H_6: 3.23 (s, 3H, OCH_3), 4.00 (t, J = 3 Hz, C=C–H), 4.29 ppm (t, J = 3 Hz, C=C–H).

1,2-Trimethylene-1,8-diaza-4-oxaspiro[4,5]decane (VII). A mixture of 5.5 mmoles 1-α-phenylethyl-4-piperidone, 5.5 mmoles (+)-2-hydroxymethylpyrrolidine [5] [bp 65-60°C (1 mm), $[\alpha]_D^{20} = +39.4°$ (c = 1, benzene) and 2 g anhydrous magnesium sulfate in 10 ml absolute ether was stirred at room temperature for 5 h. Ether was removed and the residue was distilled in vacuum to yield 1.1 g (64%) oxazolidine VII, bp 90-95°C (1 mm), n_D^{20} I.5400, $[\alpha]_D^{20}$ +10.7° (c = 0.1, benzene). Found: C, 75.3; H, 9.2%. Calculated for $C_{18}H_{26}N_2O$: C, 75.5; H, 9.2%.

1-(S-α-Phenylethyl)-3-(2-carbomethyoxyethyl)-4-piperidone (IIIa and IIIb). A mixture of 4.1 mmoles enamine I and 4.1 mmoles methyl acrylate in 5 ml absolute benzene was heated at reflux in an argon stream for 4 h. Benzene was removed and the residue was placed on silica gel column and eluted with 10:1 benzene–acetone. The chromatographically uniform fractions were combined to give 0.48 g (40%) 4-piperidone (III), R_f 0.6 (Silufol, 3:1 benzene–acetone). IR spectrum (neat): 1730 (C=O), 1745 cm^{-1} (ester C=O). PMR spectrum in $CDCl_3$: 1.39 (d, J = 6.5 Hz, 3H, β-CH_3), 3.63 (s, 3H, OCH_3), 7.36 ppm (s, 5H, C_6H_5). Found: C, 70.3; H, 8.4%, M 289 (mass spectrometry). Calculated for $C_{17}H_{23}NO_3$: C, 70.6; H, 8.0%, M.289.

1-(S-sec-Butyl)-3-(2-carbomethyoxyethyl)-4-piperidone (IVa and IV b) was obtained analogously from a mixture of 5.8 mmoles enamine I and 5.8 mmoles acrylonitrile in 10 ml absolute benzene. Chromatography on a silica gel column with elution by 5:1 benzene–acetone gave 0.54 g (76%) product, R_f 0.45 (Silufol, 3:1 benzene–acetone). IR spectrum (neat): 1735 (C=O), 1750 cm^{-1} (ester C=O). PMR spectrum in $CDCl_3$: 0.91 (d, J = 7 Hz, 3H, β-CH_3), 0.95 (d, J = 7 Hz, 3H, β-CH_3), 3.60 ppm (s, OCH_3). Found: C, 64.4; H, 9.9%, M.241 (mass spectrometery). Calculated for $C_{13}H_{23}NO_3$: C, 64.7; H, 9.6%, M 241.

1-(S-α-Phenylethyl)-3-(2-cyanoethyl)-4-piperidone (Va and Vb). A. An analogous procedure using a mixture of 5.8 mmoles enamine I and 5.8 mmoles acrylonitrile in 10 ml absolute benzene with chromatographic separation on a silica gel column with elution by 15:1 benzene–acetone gave 0.94 g (68%) of a 1:1 mixture of diastereomers Va and Vb with identical chromatographic mobility, R_f 0.5 (Silufol, 3:1 benzene–acetone), mp 65-66°, $[\alpha]_D^{20} = -16.7°$ (c = 10, benzene). IR spectrum (neat): 1730 (C=O), 2245 cm^{-1} (C≡N). PMR spectrum in $CDCl_3$; 1.40, 1.42 (two d, J = 6.8 Hz, 3H, β-CH_3), 3.63, 3.67 (two q, J = 6.8 Hz, 1H, α-CH), 7.33 ppm (s, 5H, C_6H5). Found: C, 75.1; H, 8.3%. Calculated for $C_{16}H_{20}N_2O$: C, 75.0; H, 7.9%. Two crystallizations of the Va-Vb mixture from heptane gave diastereomer Va, mp 88-89°C, $[\alpha]_D^{20} = -45.9°$ (c = 3.3, benzene). PMR spectrum in $CDCl_3$: 1.42 (d, J = 6.8 Hz, 3H, β-CH_3), 3.63 (q, J = 6.8 Hz, 1H, α-CH), 7.33 ppm (s, 5H, C_6H_5). The mother liquor gave a 28:72 mixture of diastereomers Va and Vb with $[\alpha]_D^{20} = -4.3°$ (c = 4.2, benzene).

B. A mixture of 5.8 mmoles enamine II and 5.8 mmoles acrylonitrile in 5 ml absolute benzene was maintained at room temperature for one week and subjected to chromatography as described above to yield 0.59 g (40%) of a 1:1 mixture of piperidone diastereomers Va and Vb.

C. A mixture of 2.4 mmoles oxazolidine VII and 2.4 mmoles acrylonitrile in 5 ml absolute benzene was heated at reflux for 8 h in an argon stream. Ordinary chromatographic separation of the reaction mixture on a silica gel column with elution by 10:1 benzene–acetone gave 0.24 g (40%) of a 1:1 mixture of diastereomers Va and Vb.

D. Maintenance of a mixture of 2.4 mmoles oxazolidine VII and 2.4 mmoles acrylonitrile in 5 ml absolute benzene at room temperature for one week and subsequent separation by the ordinary technique gave 0.22 g (35%) of a 1:1 mixture of isomers Va and Vb.

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