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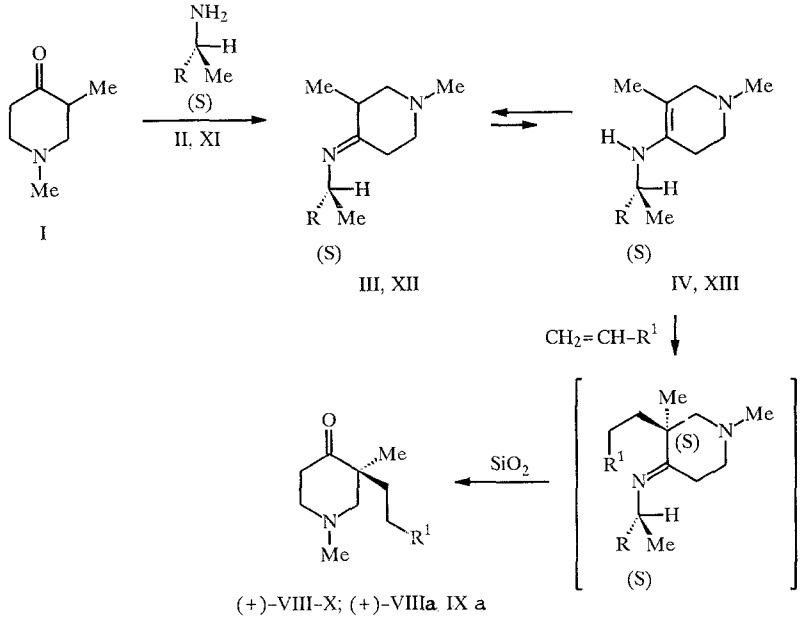
HIGHLY ENANTIOSELECTIVE SYNTHESIS OF 3,3-DISUBSTITUTED 4-PIPERIDONES BY MICHAEL ALKYLATION OF CHIRAL PIPERIDONE IMINES

G. V. Grishina and E. L. Gaidarova

A method for the highly enantioselective synthesis of (3S)- and (3R)-3,3-disubstituted 4-piperidones with an optical purity of 98% based on the "deracemizing" alkylation of 3-substituted 4-piperidones during Michael addition of their chiral imines to electrophilic alkenes was developed.

The great practical value of 3,3-disubstituted 4-piperidones, which are chiral synthones for obtaining natural and synthetic biologically active compounds, has determined the direction of our research in the area of the asymmetric synthesis of chiral derivatives of piperidine that have high optical purity.

A quaternary carbon atom is the key fragment of many alkaloids, aza steroids, and other natural compounds [1]; however, up until now there have been only a few methods that lead to the formation of a quaternary carbon center with high enantioselectivity [2-4]. One of the most elegant methods for the enantioselective formation of a C—C bond consists in the creation of a quaternary carbon center during the "deracemizing" alkylation of α-substituted cycloalkanones by Michael addition of their chiral imines to electrophilic olefins [5].



II—VIII R=Ph; XI—XIII R=CH_2Ph; V, VIII, VIIIa R^1=CN; VI, IX, IXa R^1=COOMe; VII, X R^1=COMe

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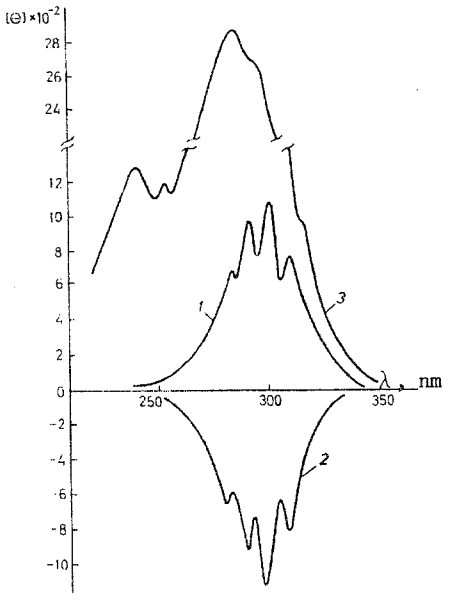


Fig. 1. Circular dichroism (CD) curves measured in heptane: 1) (+)-1,3-dimethyl-(3S)-(2-cyanoethyl)-4-piperidone (VIII); 2) (−)-1,3-dimethyl-(3R)-(2-cyanoethyl)-4-piperidone(VIII);3)(1S)-phenylethyl-(3S)-(2-cyanoethyl)-4-piperidone (XVI).

The goal of the present research was to develop selective approaches to chiral 3,3-disubstituted 4-piperidones during asymmetric Michael alkylation. It must be noted that no information regarding attempts to accomplish asymmetric transformations of this sort in piperidine derivatives is available in the literature.

Regioselective "deracemizing" alkylation of 1,3-dimethyl-4-piperidone is realized during Michael addition of its chiral imines to electrophilic alkenes.

Chiral 1,3-dimethyl-4-[(1S)-phenylethyl]iminopiperidine (III) was obtained in 85% yield by refluxing equimolar amounts of 1,3-dimethyl-4-piperidone (I) and (−)-(S)-α-phenylethylamine (II) in absolute benzene (Table 1).

The reaction of equimolar amounts of imine III and acrylonitrile, methyl acrylate (tetrahydrofuran, refluxing, 72 h), or methyl vinyl ketone (tetrahydrofuran, 10°C, 72 h) leads to only one diastereomer of alkylated imines V-VII, respectively. The isolation of the (+) enantiomers of 3,3-disubstituted 4-piperidones VIII-X from adducts V-VII without the usual (for such cases) acidic hydrolysis occurs in a column packed with silica gel by elution with benzene—acetone (see Table 1).

The (−) enantiomers of VIII-X (see Table 1) were similarly obtained from 1,3-dimethyl-4-piperidone (I), (+)-(R)-α-phenylethylamine (II), and electrophilic olefins.

According to the ^1H NMR data obtained in the presence of chiral shift reagents — tris[(heptafluoropropyloxymethylene)-D-camphorato]europium(XIV)andTris[3-trifluoroacetyl-(1R)-camphorato]europium(XV) — the enantiomeric purity of the isolated (+) and (−) enantiomers of 4-piperidones VIII-X was 98 ± 2%.

The signal of the methyl group of the ester fragment (the singlet at 3.7 ppm) in the proton spectrum of (+)-1,3-dimethyl-3-(2-carbomethoxyethyl)-4-piperidone (VIII) is the most suitable for enantiomeric analysis. In the spectrum of a racemic sample of 1,3-dimethyl-3-(2-carbomethoxyethyl)-4-piperidone (VIII) the signal of the ester methyl group is split at a chiral reagent XV:substrate ratio of 0.1. The recorded enantiomeric shift is small; this can be explained by the great distance between the methyl group and the asymmetric center of the molecule. The spectrum of a sample of (+)-VIII at room temperature in the presence of chiral shift reagent XV at the same reagent:substrate ratio demonstrates the presence of a lone signal of the ester methyl group without visible distortions of the symmetrical character of the line from the possible presence of a second low-intensity signal. Consequently, the enantiomeric purity of the (+) isomer of 4-piperidone VIII is 98 ± 2%.

The enantiomeric purity of the (+) enantiomers of 3,3-disubstituted 4-piperidones IX and X was similarly determined and also is 98 ± 2%. The absolute configurations of the enantiomers of the 3,3-disubstituted 4-piperidones were established by comparison of the data on the circular dichroism (CD) of piperidones VIII-X and (1S)-phenylethyl-(3S)-(2-cyanoethyl)-4-piperidone (XVI), the absolute configuration of which was previously established by x-ray diffraction analysis (XDA) [6]. The (+) and (−) enantiomers of 1,3-dimethyl-3-(2-cyanoethyl)-4-piperidone (VIII) are characterized in the CD spectra, respectively,

TABLE 1. Physicochemical Properties of the Synthesized Compounds

Compound	R_f*	n_D^{24}, bp, °C (mm)	$[\alpha]_D^{24}$ (c, C_6H_6)	Optical purity, %	IR spectrum (film), cm^{-1}	PMR spectrum, ppm	Yield, %
(−)-III		1,5337; 120...121 (1)	−32,8° (10,4)	—	1670 (C=N)	1,05 (d, 3H, 3-CH_3, J = 6 Hz); 1,30 (d, 3H, $CH(CH_3)C_6H_5$, J = 7 Hz); 2,25 (s, 3H, N−CH_3); 4,55 (q, 1H, $CH(CH_3)C_6H_5$, J = 7 Hz); 7,15 m, 5H, $CH(CH_3)C_6H_5$)	84
(+)-III		1,5340; 120...121 (1)	+32,4° (6,7)	—	1670 (C=N)	1,08 (d, 3H, 3-CH_3, J = 6Hz); 1,32 (d, 3H, $CH(CH_3)C_6H_5$, J = 7 Hz); 2,25 (s, 3H, N−CH_3); 4,55 (q, 1H, $CH(CH_3)C_6H_5$, J = 7Hz); 7,20 (m, 5H, $CH(CH_3)C_6H_5$)	85
(+)-XII		1,5300; 104...105 (0,5)	+59,8° (4,1)	—	1665 (C=N)	1,02 (d, 3H, 3-CH_3, J = 6 Hz); 1,10 (d, 3H, $C_6H_5CH_2CH_3$, J = 6 Hz); 2,30 (s, 3H, N-CH_3); 2,75 (m, 2H, $C_6H_5CH_2$); 3,76 (m, 1H, $C_6H_5CH_2CHCH_3$); 7,35 (m, 5H, $C_6H_5CH_2$)	75
(+)-VIII	0,45	1,4718	+25,0° (12,5)	98±2	2230(C≡N), 1720 (C=O)	1,15 (s, 3H, 3-CH_3); 2,30 (s, 3H, N−CH_3)	41
(−)-VIII	0,45	1,4760	−24,5° (10,3)	98±2	2230(C≡N), 1720 (C=O)	1,10 (s, 3H, 3-CH_3); 2,30 (s, 3H, N−CH_3)	54
(+)-VIIIa	0,45	1,4720	+7,5° (4,4)	30±2	2230(C≡N), 1715 (C=O)	1,15 (s, 3H, 3-CH_3); 2,30 (s, 3H, N−CH_3)	60
(+)-IX	0,56	1,4770	+55,6° (10,7)	98±2	1740 (COOCH3), 1720 (C=O)	1,00 (s, 3H, 3-CH_3); 2,30 (s, 3H, N−CH_3); 3,58 (s, 3H, $COOCH_3$)	79
(−)-IX	0,56	1,4761	−56,8° (10,8)	98±2	1740 (COOCH3), 1715 (C=O)	0,95 (s, 3H, 3-CH_3); 2,28 (s, 3H, N-CH_3); 3,56 (s, 3H, $COOCH_3$)	57
(+)-IXa	0,56	1,4768	+25,0° (4,0)	45±2	1740 (COOCH3), 1720 (C=O)	1,00 (s, 3H, 3-CH_3); 2,30 (s, 3H, N−CH_3); 3,62 (s, 3H, $COOCH_3$)	55
(+)-X	0,26	1,4680	+55,6° (11,7)	98±2	1720 (C=O) (br)	1,01 (s, 3H, 3-CH_3); 2,15 (s, 3H, $COCH_3$); 2,32 (s, 3H, N−CH_3)	40
(−)-X	0,26	1,4700	−56,1° (6,3)	98±2	1720 (C=O) (br)	1,00 (s, 3H, 3-CH_3); 2,15 (s, 3H, $COCH_3$); 2,30 (s, 3H, N−CH_3)	36

*Silufol, benzene—acetone (2:1).

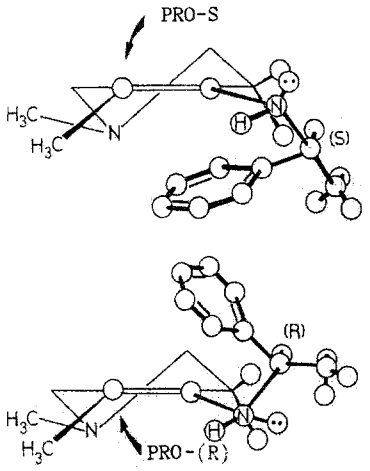


Fig. 2. Molecular model of enamine IV.

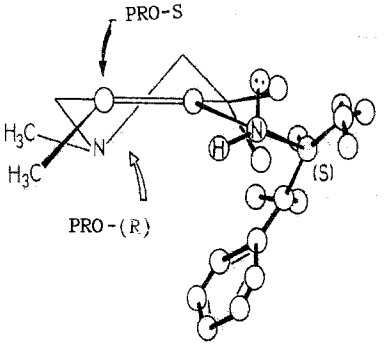
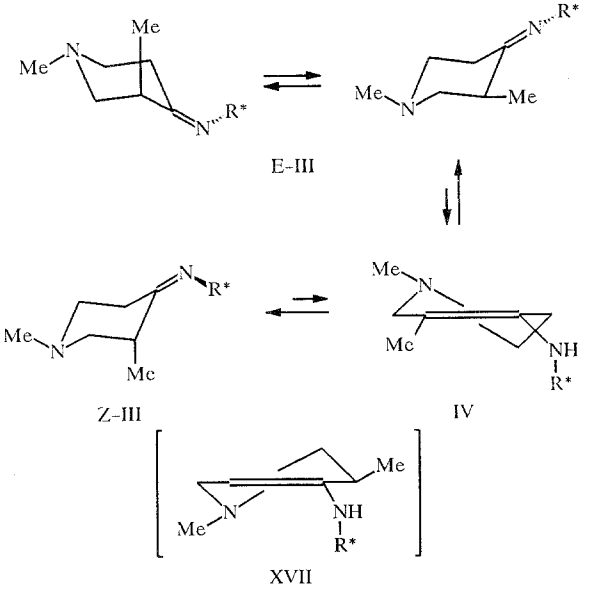


Fig. 3. Molecular model of enamine XIII.

by positive and negative signs of the Cotton effect (CE) of the $n \rightarrow \pi^*$ transition of the carbonyl chromophore (Fig. 1). On the basis of the same trend of the curves and the same sign of the CE of the (+) enantiomer of piperidone VIII and piperidone XVI, one can assign a (3S) configuration to the (+) enantiomers of VIII-X. A (3R) configuration of the quaternary carbon center was assigned to the (−) enantiomers of 4-piperidones VIII-X.

TOPOLOGY OF ASYMMETRIC MICHAEL ALKYLATION

It is known [5, 7-9] that the reaction form in which the chiral imines of cycloalkanones react with electrophilic alkenes is the tautomeric secondary enamine.

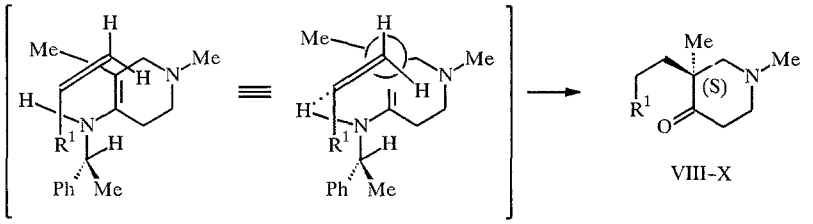


Our analysis of the imine-enamine equilibrium for chiral imine (−)-III by means of ^1H NMR spectroscopy showed that the preponderant form at room temperature is the conformationally nonhomogeneous E isomer of III (75%), which exists in the form of a mixture of two diastereomers. We also detected the presence of 22.5% of the Z isomer of III in the form of one diastereomer with an axially oriented 3-methyl group and 2.5% of the more substituted tautomeric enamine IV. Trisubstituted enamine XVII was not detected in the conformational equilibrium.

Thus the existence of an imine-enamine equilibrium was established for chiral 1,3-dimethyl-4-piperidone imine III; the reactive form in Michael alkylation is tautomeric secondary enamine IV.

It follows from an examination of molecular models of secondary enamine IV that the hydrogen atoms attached to the $C_{(5)}$ atom and the hydrogen atom of the (1S)-phenylethyl substituent are drawn together in the reaction conformation (Fig. 2); the orientation of the phenyl ring turns out to be such that the pro-R side of the double bond of the enamine, which is syn-oriented with respect to the N—H bond of the enamine fragment, is completely shielded. Owing to this molecular geometry, one might expect easy transfer of this proton in the transition state.

The reaction occurs with syn-wedge drawing together of the reactants and proceeds through quasi-cyclic transition state A, in which the proton bonded to the nitrogen atom in the enamine fragment is transferred, evidently concertedly, to the β-carbon atom of the alkene to give a new $C_{(3)}—C_{(\beta)}$ bond.



A

Thus the high enantioselectivity in the development of the new quaternary carbon center with a C_3(S) configuration is explained by the fact that the presence of an α-phenylethyl substituent with an (S) configuration in the amine part of secondary enamine IV creates a situation in which attack by the electrophilic olefin can be realized only from the pro-(S) side of the enamine. An α-phenylethyl substituent with an (R) configuration gives rise only to approach only from the pro-(R) side.

The legitimacy of our reasoning is confirmed by the dramatic change in the stereochemical result observed in the reaction of acrylonitrile and methyl acrylate with chiral imine XII, obtained from 1,3-dimethyl-4-piperidone (I) and (+)-S-α-benzylethylamine (XI). The optical purity of (+)-1,3-dimethyl-(3S)-(2-carbomethoxyethyl)-4-piperidone (IXa) in this case is only 45%, while for (+)-1,3-dimethyl-(3S)-(2-cyanoethyl)-4-piperidone (VIIIa) it decreases to 30%. In fact, it is apparent from an examination of molecular models (Fig. 3) that separation of the phenyl group from the asymmetric carbon atom by one methylene link in the reaction conformation of tautomeric secondary enamine XIII leads to a pronounced decrease in the degree of shielding of the pro-(S) side of the double bond of the enamine and, as a consequence of this, to a significant decrease in the stereoselectivity of Michael alkylation.

EXPERIMENTAL

The IR spectra of thin layers of the compounds were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in $CDCl_3$ were obtained with Varian XL-100 and Bruker WM-400 spectrometers at room temperature with tetramethylsilane as the internal standard. The circular dichroism (CD) curves were recorded with JASCO-20 spectropolarimeter at room temperature in 0.1 and 0.5 mm cuvettes.

1,3-Dimethyl-4-piperidone (I) was obtained in 71% yield by the method in [10]. (−)-(S)-α-Phenylethylamine (II) was obtained by the method in [11] and had $[\alpha]_D^{24}$ −39.7° (without a solvent) and an optical purity > 99%. (+)-(R)-α-Phenylethylamine was synthesized by the method in [11] and had $[\alpha]_D^{24}$ +39.8° (without a solvent) and an optical purity > 99%. (+)-(S)-α-Benzylethylamine (XI) was obtained by the method in [12] and had $[\alpha]_D^{24}$ +37.1° (without a solvent) and an optical purity > 99%.

(−)-1,3-Dimethyl-4-[(1S)-phenylethylimino]piperidine (III). A mixture of 2.55 g (20.1 mmole) of 1,3-dimethyl-4-piperidone (I) and 2.43 g (20.1 mmole) of (−)-(S)-α-phenylethylamine (II) in 30 ml of absolute benzene was refluxed with a

Dean—Stark adapter until the theoretical amount of water had separated. The benzene was removed in vacuo, and the residue was fractionally distilled to give 3.88 g (84%) of (−)-imine III.

(+)-1,3-Dimethyl-4-[(1R)-phenylethylimino]piperidine (III) was similarly obtained from 1,3-dimethyl-4-piperidone (I) and (+)-(R)-α-phenylethylamine.

(+)-1,3-Dimethyl-4-[(1S)-benzylethylimino]piperidine (XII) was similarly obtained from 1,3-dimethyl-4-piperidone (I) and (+)-(S)-α-benzylethylamine (XI).

The properties of chiral imines (−)-III, (+)-III, and (+)-XII are presented in Table 1.

(+)-1,3-Dimethyl-(3S)-(2-cyanoethyl)-4-piperidone (VIII, $C_{10}H_{16}N_2O$). A mixture of 2.52 g (10.9 mmole) of (−)-imine III and 0.58 g (10.9 mmole) of freshly distilled stabilized (by hydroquinone) acrylonitrile in 20 ml of absolute tetrahydrofuran was refluxed for 72 h, during which the progress of the reaction was monitored by chromatography. The tetrahydrofuran was evaporated in vacuo, and the residue (2.42 g) was applied to a column packed with silica gel in benzene and eluted with benzene—acetone (5:1). The chromatographically homogeneous fractions were combined to give 0.61 g of the (+) enantiomer of VIII.

(−)-1,3-Dimethyl-(3R)-(2-cyanoethyl)-4-piperidone (VIII, $C_{10}H_{16}N_2O$) was similarly obtained by refluxing a mixture of 2.37 g (10.3 mmole) of imine (+)-III and 0.55 g (10.3 mmole) of acrylonitrile in 20 ml of absolute tetrahydrofuran. Chromatographic isolation with a column packed with silica gel by elution with benzene—acetone (5:1) gave 1.0 g of the (−) enantiomer of VIII.

(+)-1,3-Dimethyl-3-(2-cyanoethyl)-4-piperidone (VIIIa) was similarly obtained from a mixture of 1.56 g (6.8 mmole) of imine (+)-XII and 0.36 g (6.8 mmole) of acrylonitrile by refluxing in 20 ml of absolute tetrahydrofuran. Chromatographic isolation with a column packed with silica gel by elution with benzene—acetone (5:1) gave 0.73 g of the (+) enantiomer of VIIIa.

(+)-1,3-Dimethyl-(3S)-(2-carbomethoxyethyl)-4-piperidone (IX, $C_{11}H_{19}NO_3$) was obtained from a mixture of 2.49 g (10.8 mmole) of imine (−)-III and 0.93 g (10.8 mmole) of freshly distilled stabilized (by hydroquinone) methyl acrylate in 20 ml of absolute tetrahydrofuran by refluxing for 72 h. Chromatographic separation with a column packed with silica gel in benzene by elution with benzene—acetone (5:1) gave 1.82 g of the (+) enantiomer of IX.

(−)-1,3-Dimethyl-(3R)-(2-carbomethoxyethyl)-4-piperidone (IX, $C_{11}H_{19}NO_3$) was similarly obtained from a mixture of 3.21 g (14.0 mmole of imine (+)-III and 1.20 g (14.0 mmole) of methyl acrylate by refluxing for 72 h in 20 ml of absolute tetrahydrofuran. Chromatographic isolation with a column packed with silica gel by elution with benzene—acetone (5:1) gave 1.69 g of the (−) enantiomer of IX.

(+)-1,3-Dimethyl-3-(2-carbomethoxyethyl)-4-piperidone (IXa) was obtained by refluxing a mixture of 1.50 g (6.5 mmole) of imine (+)-XII and 0.56 g (6.5 mmole) of methyl acrylate in 20 ml of absolute tetrahydrofuran. Chromatographic isolation with a column packed with silica gel by elution with benzene—acetone (5:1) gave 0.43 g of the (+) enantiomer of IXa.

(+)-1,3-Dimethyl-(3S)-(2-acetylethyl)-4-piperidone (X, $C_{11}H_{19}NO_2$) was obtained by maintaining a mixture of 1.24 g (5.4 mmole) of imine (−)-III and 0.38 g (5.4 mmole) of freshly distilled stabilized (by hydroquinone) methyl vinyl ketone in 20 ml of absolute tetrahydroquinone at 10°C for 72 h. Chromatographic isolation with a column packed with silica gel by elution with benzene—acetone (5:1) gave 0.43 g of the (+) enantiomer of X.

(−)-1,3-Dimethyl-(3R)-(2-acetylethyl)-4-piperidone (X) was similarly obtained from a mixture of 1.50 g (6.5 mmole) of imine (+)-III and 0.46 g (6.5 mmole) of methyl vinyl ketone. Chromatographic isolation with a column packed with silica gel by elution with benzene—acetone (5:1) gave 0.46 g of the (−) enantiomer of X.

The properties of the (+) and (−) enantiomers of the 3,3-disubstituted 4-piperidones are presented in Table 1.

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