Chemistry of Heterocyclic Compounds, Vol. 30, Nos. 11-12, 1994

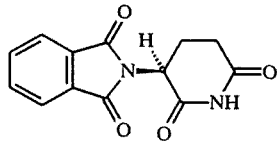
CHIRAL 4-PIPERIDONES AND THEIR BICYCLIC ANALOGS. STRATEGY OF STEREOSELECTIVE SYNTHESIS (REVIEW)*

G. V. Grishina, E. L. Gaidarova, and N. S. Zefirov

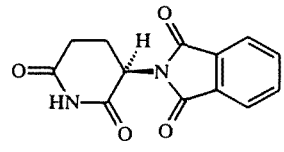
The principal stereoselective paths of synthesis and the stereochemistry of chiral 4-piperidones and their bicyclic analogs are examined critically in this article.

INTRODUCTION

The rather limited data thus far accumulated have furnished unambiguous evidence of a close relationship between the biological activity of chiral substances and their conformation, absolute configuration, and optical purity. Up to the present time, however, most synthetic pharmaceuticals are used in the racemic form. Human intake of these substances may have tragic consequences. When taken by pregnant women, the mild sedative and sopoforic preparation thalidomide, which was produced in the 1960s in racemic form, was responsible for serious deformities in newborn infants. It was shown that only the (−)-(S)-enantiomer I had a strong teratogenic effect, whereas the (+)-(R)-thalidomide II was actually a very good sedative and sopoforic [1].



(−)-(*S*)-I



(+)-(*R*)-II

This deplorable example demonstrates the need for studying "structure−activity" and "chirality−activity" relationships for all stereoisomers of any organic compound under consideration for drug use. Naturally, this requires the availability of convenient and efficient methods of synthesis by which the required substances can be obtained in chirally pure form, with a known steric structure and with the required absolute configuration. These ends can be achieved specifically by means of enantioselective and diastereoselective synthesis.

The search for paths of efficient enantioselective and diastereoselective synthesis becomes particularly important for chiral derivatives of piperidine, which constitute the base of a broad group of alkaloids, azasteroids, neurotoxins, and numerous synthetic pharmaceuticals and natural biologically active substances [2]. We should remember that piperidine derivatives have a broad spectrum of pharmacological properties. For example, 2,2-dimethyl-4-aryl-4-piperidols have a mixed stimulating and depressing effect on the central nervous system [3]. Among the derivatives of 4-piperidones we find compounds with antidepressant and antiarrhythmic [4, 5], antithrombogenic [6], and spasmolytic activity [7], as well as tranquilizers and agents lowering the blood cholesterol content [8]. Also found among these derivatives are antidotes for Thiophos [parathion] poisoning [9].

*We dedicate this review to the 30th anniversary of the journal *Khimiya Geterotsiklicheskikh Soedinenii* (Chemistry of Heterocyclic Compounds), which was founded at the same time we embarked on careers in chemistry.

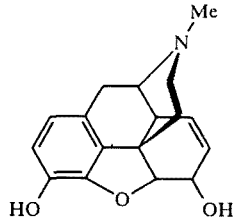
M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, Nos. 11-12, pp. 1619-1648, November-December, 1994. Original article submitted November 11, 1994.

0009-3122/94/1112-1401$12.50

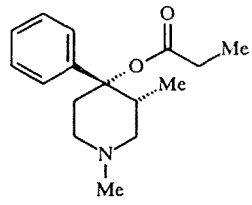
Significant advances in conformational analysis of saturated nitrogen-containing heterocycles have now created a base for detailed studies of specific features of the interaction of different stereoisomers of chiral derivatives of piperidine with receptors [10].

CHIRALITY–ACTIVITY RELATIONSHIP IN A SERIES OF PIPERIDINE DERIVATIVES

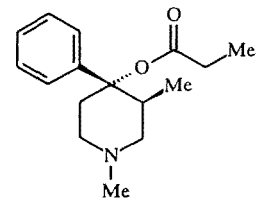
It has been established that the physiological action of chiral derivatives of piperidine depends not only on the nature of the substituents and their positions on the ring, but also on their steric orientation and the absolute configuration of the chiral centers. For example, in a series of esters of 2-phenyl- (or benzyl-) and 4-phenyl-4-piperidols, the propionate of 1,3-dimethyl-4-phenyl4-piperidol (prodine) has the strongest analgesic effect, with an activity several times that of morphine III. The α-isomer of prodine IV is 4-5 times as active as morphine, whereas its β-isomer V is only 2-3 times as active [11-14].



III

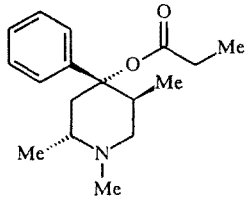


α–IV

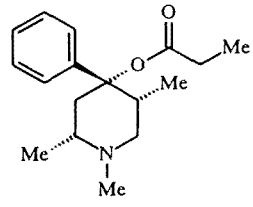


β–V

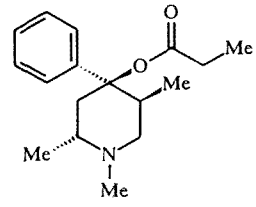
Differences are also noted in the analgesic activities of stereoisomers of promedol, which is used in this country as a pharmaceutical preparation in the form of the racemate, a mixture of stereoisomers of the propionate of 1,2,5-trimethyl-4-phenyl-4-piperidol: The activity of the α-isomer VI is 8-10 times that of morphine, that of the β-isomer VII 4-5 times, whereas the γ-isomer VIII is only 2-3 times as active as morphine, while the toxicity remains the same [15, 16].



α–VI



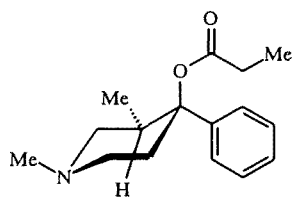
β–VII



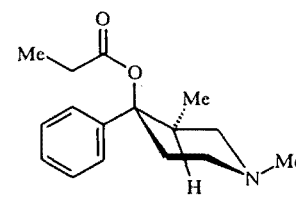
γ–VIII

Only very limited comparisons have been made of the chiral discrimination of enantiomers in physiological processes.

Relevant data have been reported by Portoghese [17, 18], who analyzed the relationship between the activity of stereoisomers of the morphine-like analgesics prodine and promedol and the configuration of the asymmetric centers. It was found that the analgesic receptors are capable of discriminating the enantiotropic sides of the piperidine ring. Also, it was established that the (+)-(3R,4S) enantiomer or α-prodine IX is 25 times as active as the (−)-(3S,4R) enantiomer X, and only twice as active the racemate [17].

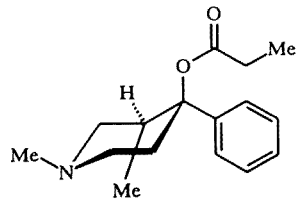


α–(+)–(3*R*, 4*S*)–IX

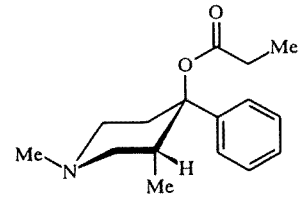


α–(−)–(3*S*, 4*R*)–X

A similar relationship is observed for the enantiomers of the β-isomer of prodine: The (+)-(3S,4S) enantiomer XI is 1.3 times as active as the racemate and 13 times as active as the (−)-(3R,4R) enantiomer XII [17].

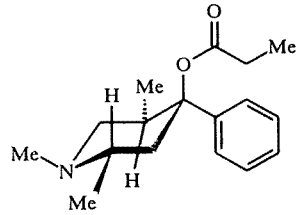


β-(+)-(3*S*, 4*S*)-XI

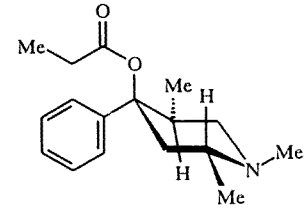


β-(−)-(3*R*, 4*R*)-XII

In a study of the analgesic activities of enantiomers of γ-promedol [18], it was shown that the (+)-(2S,4S,5R) enantiomer XIII is 9 times as active as the (−)-(2R,4R,5S) enantiomer XIV, but very nearly equal in activity to the racemate and to morphine.



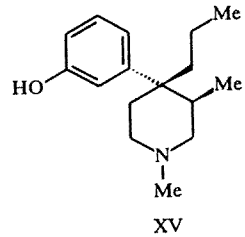
γ-(+)-(2*S*, 4*S*, 5*R*)-XIII



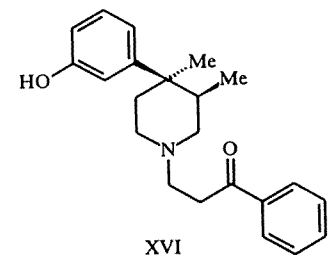
γ-(−)-(2*R*, 4*R*, 5*S*)-XIV

In the opinion of these investigators, the main factor determining the strength of analgesic activity in the series of morphine-like analgesics is the absolute configuration of the centers $C_{(4)}$ and $C_{(3)}$ or $C_{(5)}$, whereas the role of the 2-CH_3 group in interactions with the receptor proves to be insignificant [19]. Apparently, the best contact of a piperidine analgesic with opiate receptors of the brain is achieved with an equatorial orientation of the phenyl group and an axial orientation of the propionyl group, which is realized in (+)-(3R,4S)-α-prodine IX and in (+)-(2S,4S,5R)-γ-promedol XIII [20-23].

The strong analgesic picenadol, trans-1,3-dimethyl-4-(3-hydroxyphenyl)-4-n-propylpiperidine XV, in racemic form manifests mixed opioid properties. It was found that the unusual resultant activity of the racemate is made up of agonistic activity of the (+) enantiomer and antagonistic activity of the (−) enantiomer [24, 25].



XV

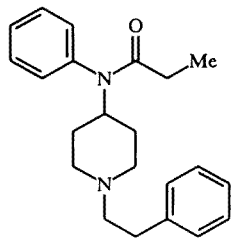


XVI

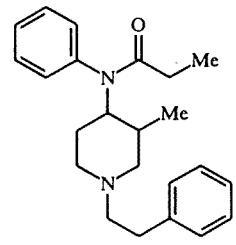
cis-1-(2-Benzoylethyl)-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine (XVI), which, the same as picenadol, contains a quaternary center $C_{(4)}$, manifests the properties of an extremely strong antagonist of morphine. In the triad of its stereoisomers, the (+) enantiomer manifests antagonistic activity 6 times as strong as that of the (−) enantiomer and 2 times as strong as that of the racemate [26].

A systematic search for effective analgesics in a series of piperidine derivatives has led to the discovery of a new class of analgesics that differ from morphine, prodine, and promedol in blocking a different section of the opiate receptor of the brain. This new class of analgesics is based on 4-anilido derivatives of piperidine. The ancestor of this class of extremely strong analgesic preparations is a compound that has found broad applications in medical practice, fentanyl XVII [1-(2-phenylethyl)-4-(N-phenyl-N-propionylamido)piperidine] [27], which has an analgesic activity 350 times that of morphine [28].

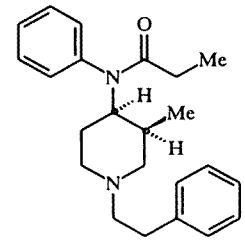
Upon introducing a methyl group into position 3 of the piperidine ring, the analgesic activity of the 4-anilidopiperidines is reinforced: the analgesic activity of the 3-methyl analog of fentanyl XVIII is 19 times that of fentanyl [29, 30], and the cis-(+)-(3S,4R) isomer of 3-methylfentanyl nitrate XIX is 6684 times more active than morphine [31].



XVII



XVIII



cis-(+)-(3*S*, 4*R*)-XIX

The most important key compounds for obtaining various chiral derivatives of piperidine are optically active 4-piperidones. However, 4-piperidones cannot be separated into optical isomers by classical splitting methods. Esentially the sole method for obtaining these compounds is asymmetric synthesis. In this review, therefore, we will analyze the basic paths of stereoselective synthesis of chiral 4-piperidones and their bicyclic analogs, which are versatile chiral synthons (chirons).

PRINCIPLES OF STEREOSELECTIVE SYNTHESIS

Let us remember that the efficiency of a stereoselective process, i.e., the ratio of the stereoisomers that are formed, is controlled either kinetically (by the relative rates of formation of the stereoisomers) or thermodynamically (by the equilibrium constant of the stereoisomers that are formed), or by simultaneous competitive effects from these two factors [32].

The relative rates of formation of stereoisomers in a kinetically controlled process (1) are determined by the difference between the corresponding activation energies $\Delta\Delta G_{BC}^{\neq}$.

$$B \longleftarrow A \longrightarrow C$$

$$-RT \ln([B]/[C]) = {}'\Delta G_B^{\neq} - \Delta G_C^{\neq} = \Delta\Delta G_{BC}^{\neq} \quad (1)$$

The equilibrium constant of the stereoisomers formed in a thermodynamically controlled process (2) is determined solely by the difference of their free energies in the standard state ΔG_{BC}^{0}:

$$A \longrightarrow B \rightleftharpoons C$$

$$-RT\ln K = G_C^0 - G_B^0 = \Delta G_{BC}^0 \quad (2)$$

Whence it becomes obvious that enantioselective and diastereoselective synthesis, in the first place, must be specifically a kinetically controlled process; and in the second place such syntheses must embody conversions of only conformationally fixed substrates. This will take place only if the substrate and the reagent, one of which is chiral, form diastereomeric transition states differing in free energy of the activated complexes ($\Delta\Delta G^{\neq}$). In order for such diastereomeric transition states to be formed, the approach of the reagent and substrate must be controlled either by specific stereoelectronic effects or by purely steric factors. Thus, the magnitude of $\Delta\Delta G^{\neq}$ is the criterion of efficiency of a stereoselective synthesis. However, according to calculated data, in order to obtain a chiral compound with an optical purity of 98%, it is sufficient for $\Delta\Delta G^{\neq}$ at 25°C to have a value of 2.7 kcal/mole [32].

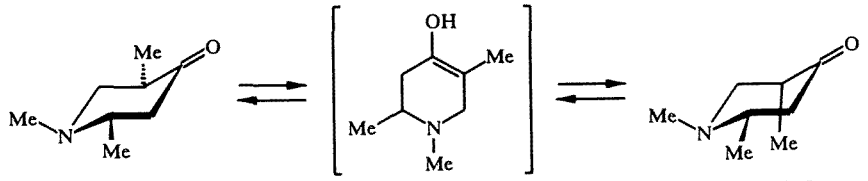
The excess of one of the enantiomers (or diastereomers) corresponds to the enantiomeric purity (or diastereomeric excess) of the compound that is formed, and it is termed the "optical yield" of the stereoselective synthesis.

Consequently, the development of a strategy of stereoselective synthesis must consist in selecting those particular chemical processes in which a maximum value of $\Delta\Delta G^{\neq}$ is achieved. However, such a synthesis presupposes a thorough analysis of the reaction mechanism and the structures of the substrate and reagent.

4-PIPERIDONES AS SUBSTRATES IN STEREOSELECTIVE SYNTHESIS

4-Piperidones are distinguished by a number of specific chemical properties that may be serious hindrances to their use in stereocontrolled processes.

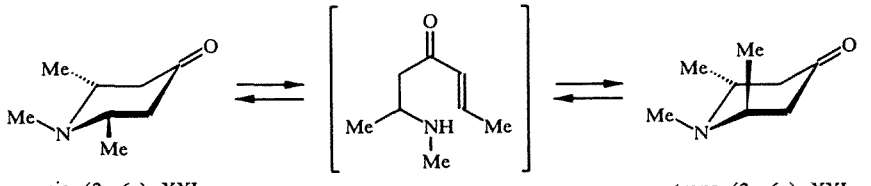
For 2,3-, 3,5-, and 2,5-disubstituted 4-piperidones in alkaline media, a facile process of cis-trans isomerization is observed. For example, the ratio of trans-(2e,5e) to cis(2e,5a) epimers of 1,2,5-trimethyl-4-piperidone (XX) is 95:5 at 20°C, whereas after 20 h of heating in a 2:1 mixture of tert-butylamine and water, the ratio of epimers has already reached 31:69 [33].



trans- (2*e*, 5*e*)–XX cis- (2*e*, 5*a*)–XX

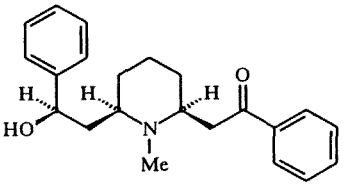
Epimerization at the $C_{(5)}$ atom proceeds as a consequence of enolization of the carbonyl group, accelerated to a considerable degree by the high basicity of these compounds (pK_a 9) [34].

For 2,6-disubstituted 4-piperidones in aqueous caustic media, still another type of cis-trans isomerism has been discovered. According to GLC data, when cis-(2e,6e)-1,2,5-trimethyl-4-piperidone (XXI) is held for 2 h at 50°C in a 2:1 mixture of tert-butylamine and water, an epimeric mixture cis-(2e,6e)/trans-(2a,6e) is formed, with a 51:49 composition [33].



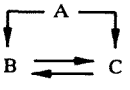
cis- (2*e*, 6*e*)–XXI A trans- (2*a*, 6*e*)–XXI

In this case, epimerization at the $C_{(2)}$ atom is the result of facile opening of the piperidone ring at the $C_{(2)}$–N bond with the formation of the intermediate enolamine A and its subsequent recyclization. An analogous process has been observed for an alcoholic solution of the alkaloid lobeline XXII [35].



XXII

For stereochemically labile 4-piperidones, this feature of their chemical properties means that stereoselective synthesis in this series will be controlled by competitive effects of the kinetic and thermodynamic factors. In other words, a stereoselective synthesis will be described by the scheme



(3)

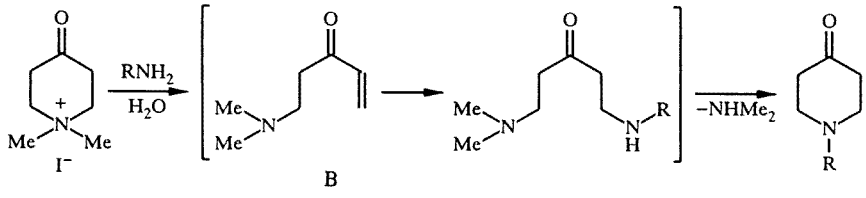
In turn, this may lead to loss of selectivity. Consequently, in order to accomplish asymmetric conversions in the 4-piperidone series, model reactions must be selected with particular care. Such behavior of the 4-piperidones is undoubtedly the reason why hardly any information has been available on asymmetric synthesis in this series for many years.

Now let us examine a group of stereoselective conversions in a series of 4-piperidones and their bicyclic analogs.

PRINCIPLE OF "DERACEMIZATION" IN ASYMMETRIC TRANSANIMATION

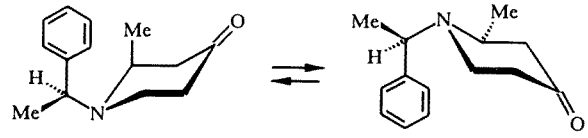
N-Substituted 2-Methyl-4-piperidones

A method has been reported for obtaining N-substituted 4-piperidones, based on the interaction of the iodomethylate of N-methyl-4-piperidone with various primary amines [36].



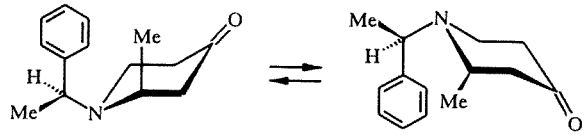
The key intermediate – the enolamine B that is formed upon opening the piperidine ring at the $C_{(2)}-N$ bond – is elegantly used in the diastereoselective synthesis of N-substituted 4-piperidones in [37-40].

And in fact, upon transamination of the iodomethylate of 1,2-dimethyl-4-piperidone (XXIII) with (S)-1-phenylethylamine, 1-(1-phenylethyl)-2-methyl-4-piperidone is formed as two diastereomers (1'S,2S)-XXIV and (1'S,2R)-XXV (Scheme 1) [37-39]. The individual diastereomers of the 4-piperidones XXIV and XXV were recovered by chromatographic methods in a 3:1 ratio. Their diastereomeric purity, according to NMR data, is 95% or higher. The steric structure and absolute configuration of the 2-methyl-4-piperidones XXIV and XXV were established by means of ^{13}C NMR and circular dichroism [38, 39, 41].



(1'*S*, 2*S*)–XXIV

50 : 50

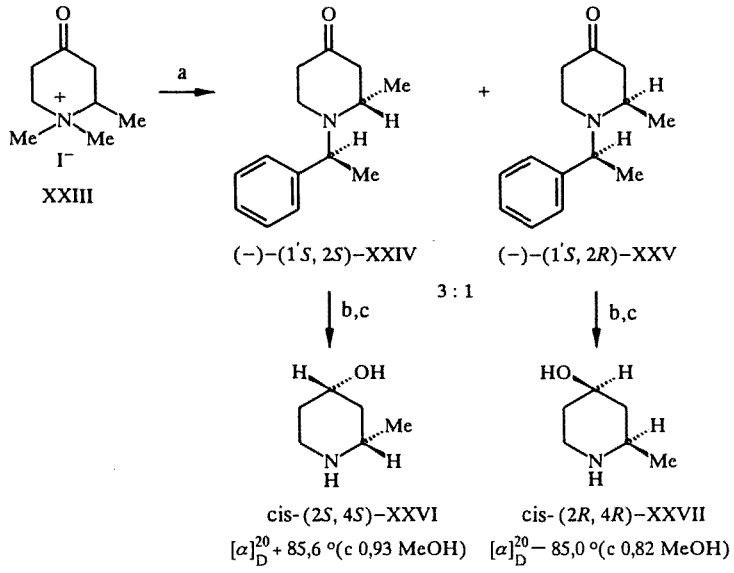


(1'*S*, 2*R*)–XXV

80 : 20

The fact that diastereoselective transanimation had taken place was confirmed by synthesis of the enantiomeric 2-methyl-4-piperidols XXVI and XXVII from the individual diasteromers XXIV and XXV (Scheme 1).

Scheme 1

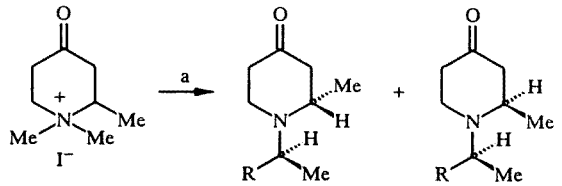


Reagents and conditions: a) (−)-(S)-$H_2NCHMePh$, H_20, 25°C, 2 h; b) $NaBH_4$, C_2H_5OH—H_2O 1:1, 25°C, 2 h; *c*) H_2, Pd—C, C_2H_5OH, 25°C, 3 h.

Thus, the stereochemical result of transamination of the iodomethylate of 1,2-dimethyl-4-piperidone (XXIII) is the preferential formation of (1'S,2S)-1-(1-phenylethyl)-2-methyl-4-piperidone (XXIV) with an optical yield of 50%.

Upon transamination of the iodomethylate XXIII by (+)-(S)-sec-butylamine and (+)-(S)-1-benzylethylamine under analogous conditions, the corresponding optically active N-substituted 2-methyl-4-piperidones are also formed as the diastereomeric pairs XXVIII-XXIX and XXX-XXXI (Scheme 2) [38]. In the diastereomeric pair of 1-sec-butyl-2-methyl-4-piperidone, again prominent is the (1'S,2S) diastereomer XXVIII, but the optical yield is only 30%. The diastereomers of 1-(1-benzylethyl)-2-methyl-4-piperidone (1'S,2S)-XXX and (1'S,2R)-XXXI were recovered in a 1:1 ratio; i.e., in this case, the diastereoselectivity dropped to zero.

Scheme 2

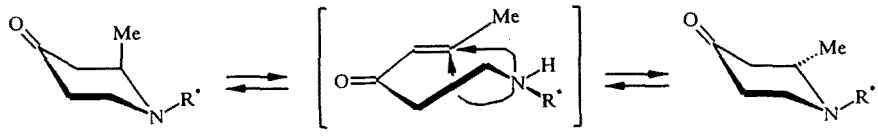


Reagents and conditions: a) (+)-(*S*)-$H_2NCH(CH_3)CH_2CH_3$ or (+)-(*S*)-$H_2NCH(CH_3)CH_2C_6H_5$ H_2O, 25 °C, 2 h

Thus, the maximum optical yield (50%) is achieved in the transamination of the iodomethylate of the 1,2-dimethyl-4-piperidone (XXIII) by (S)-1-phenylethylamine.

The decrease of diastereoselectivity in the transamination reaction, in the opinion of the authors, is a consequence of the differing thermodynamic stabilities of the N-substituted 2-methyl-4-piperidones that are formed [39]. It has been established that under conditions of thermodynamic control (upon holding and boiling in solvents with various polarities), the individual diastereomers of 1-(1-phenylethyl)-2-methyl-4-piperidone (XXIV) and (XXV) are converted to mixtures of diastereomers XXIV and XXV with a different composition; i.e., they undergo mutual isomerization as a result of epimerization at the $C_{(2)}$ center [38]. The isomerization process is considerably accelerated by the presence of silica gel under conditions of acidic and basic catalysis. An analogous but faster isomerization is observed for the pair of diastereomers of 1-(1-benzylethyl)-2-methyl-4-piperidone (XXX and XXXI). An unexpected and important result is the spontaneous epimerization that is found for the diastereomeric pair of 1-(1-benzylethyl)-2-methyl-4-piperidone (XXX, XXXI), which proceeds in

nonpolar aprotic solvents at 20°C. We should assume that for 2-methyl-4-piperidones, epimerization at the $C_{(2)}$ center can be accomplished by opening the piperidine ring at the $C_{(2)}-N$ bond, with subsequent recyclization. The phenomenon of spontaneous epimerization reflects a characteristic and specific property of the 2-methyl-4-piperidones that is determined by their structure and the character of the N-substituent.



(1'*S*, 2*R*) (1'*S*, 2*S*)

R*=(*S*)-CHMePh; (*S*)-CHMeCH$_2$Ph

Transamination of the iodomethylate of 1,2-dimethyl-4-piperidone (XXIII) proceeds in a basic medium, i.e., as shown previously [33], under conditions that strongly accelerate the process of opening the piperidine ring at the $C_{(2)}-N$ bond. Consequently, the ratio of diastereomers of 2-methyl-4-piperidones obtained as a result of transamination is determined by the resultant effect of kinetically controlled asymmetric synthesis and the thermodynamic stability of the N-substituted 2-methyl-4-piperidones that are formed.

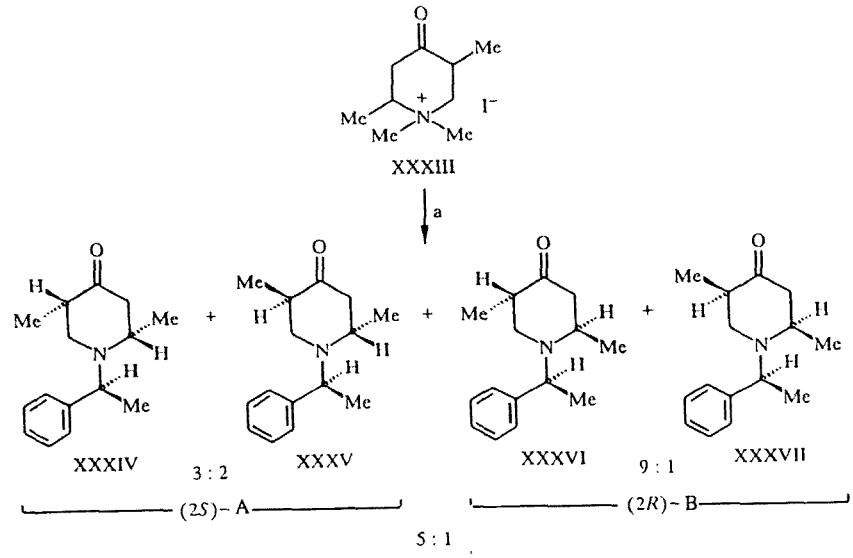
This type of asymmetric conversion in the 4-piperidone series can be formally termed "deracemizing" transamination, since it leads to the formation, from a racemic 1,2-dimethyl-4-piperidone, optically active diastereomers of N-substituted 2-methyl-4-piperidones.

N-Substituted 1,2,5-Trimethyl-4-piperidones

The stereochemistry of the diastereoselective transamination of the iodomethylate of trans-1,2,5-trimethyl-4-piperidone (XXXIII) has proved to be quite interesting [40]. The original 1,2,5-trimethyl-4-piperidone (XXXII) is a complex stereochemical model. According to ^{13}C NMR data, it exists in the form of a mixture of cis-(2e,5a) and trans-(2e,5e) epimers with respect to the $C_{(5)}$ atom, in a 5:95 ratio. Also possible is cis-trans isomerization with opening of the ring at the $C_{(2)}-N$ bond.

Interaction of the iodomethylate of trans-1,2,5-trimethyl-4-piperidone (XXXIII) with (S)-1-phenylethylamine leads to the formation of 1-(1-phenylethyl)-2,5-dimethyl-4-piperidone in the form of two cis-trans diasteromeric pairs A and B in a 5:1 ratio (Scheme 3). The optical yield of the reaction is 66%.

Scheme 3



XXXIII

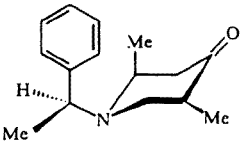
XXXIV 3 : 2 XXXV — (2*S*)-A

XXXVI 9 : 1 XXXVII — (2*R*)-B

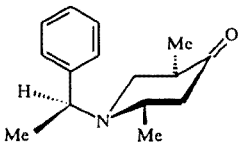
5 : 1

Reagents and conditions: a) (-)-(*S*)-H$_2$NCHMePh, H$_2$O, 25 °C, 2 h.

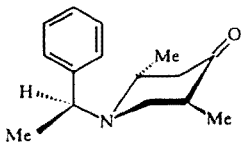
According to ^{13}C NMR data, the diastereomeric pair A is an inseparable thermodynamic mixture of the cis-(2a,5e) and trans-(2e,5e) isomers XXXIV and XXXV with a 3:2 composition. From the diastereomeric pair B, only the trans-(2e,5e) isomer XXXVI has been segregated. Manifestation of the corresponding cis-isomer XXXVII is observed upon chromatographing diastereomerically pure trans-XXXVI on Silufol. Conversion of trans-(XXXVI) to a mixture of cis-trans isomers (XXXVI, XXXVII) was also registered chromatographically after holding a benzene solution of diastereomerically pure trans-XXXVI for 3 h in the presence of aluminum oxide. The steric structure of the isomers XXXIV-XXXVII was established by means of ^{13}C NMR spectroscopy [41, 42]. By means of x-ray structure analysis [40], the (1'S,2R,5S) configuration of the trans-isomer XXXVI was established; the absolute configurations of the 4-piperidones XXXIV and XXXV were assigned by means of stereochemical correlation.



cis-(1'*S*, 2*S*, 5*S*)-XXXIV



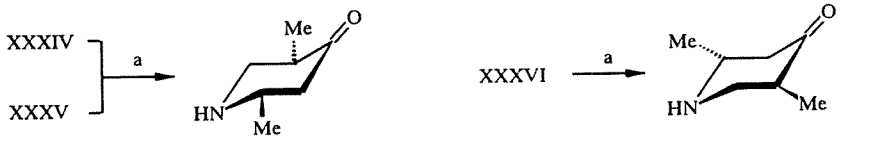
trans-(1'*S*, 2*S*, 5*R*)-XXXV



(−) trans-(1'*S*, 2*R*, 5*S*)-XXXVI

The enantiomers of trans-2,5-dimethyl-4-piperidone XXXVIII and XXXIX were obtained upon removal (by hydrogenolysis in the presence of palladium black) of the (S)-phenylethyl substituent from the nitrogen atom in the diastereomeric pair A and in the trans-isomer of XXXVI; this confirms the occurrence of asymmetric synthesis in transamination of the iodomethylate of 1,2,5-trimethyl-4-piperidone XXXIII by optically active α-phenylethylamine (Scheme 4).

Scheme 4



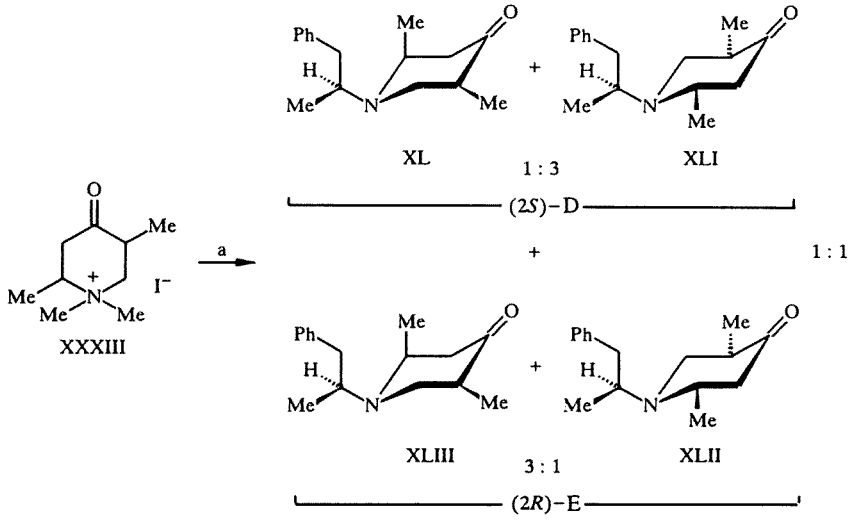
trans-(2*S*, 5*R*)-XXXVIII
$[\theta]_{292}$ + 730 ° (heptane)

trans-(2*R*, 5*S*)-XXXIX
$[\theta]_{292}$ −1660 ° (heptane)

Reagents and conditions: a) H_2, Pd, CH_3COOH, 25 °C

Transamination of the iodomethylate XXXIII by (+)-(S)-1-benzylethylamine under analogous conditions leads to the formation of 1-(1-benzylethyl)-2,5-dimethyl-4-piperidone in the form of two cis-trans diastereomeric pairs D and E in a 1:1 ratio (Scheme 5). According to ^{13}C NMR data, each of the D pairs (XL, XLI) and E pairs (XLII, XLIII) is a mixture of cis-(2a,5e) and trans-(2e,5e) isomers in a 1:3 ratio, with predominance of the trans iosmers XLI and XLIII.

Scheme 5



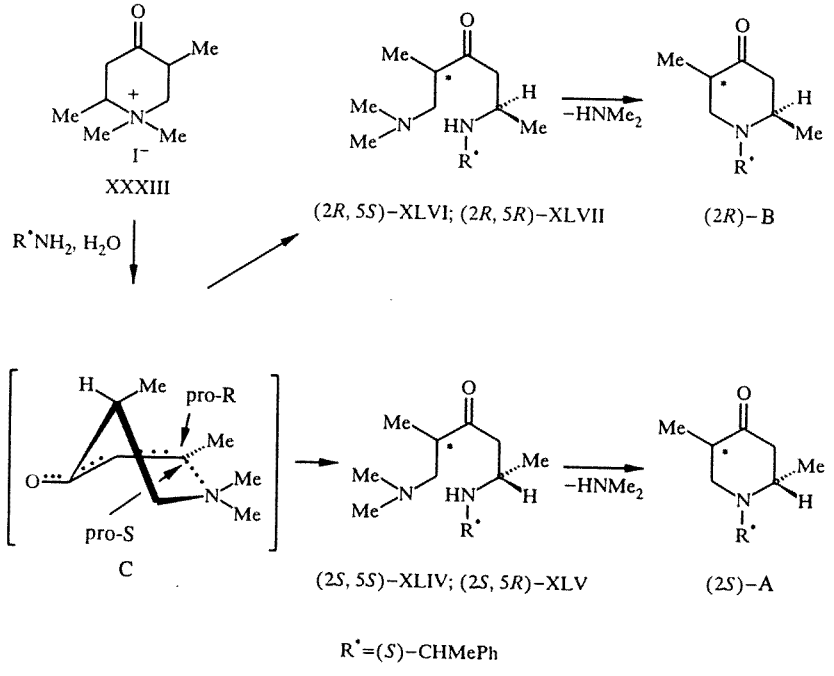
Reagents and conditions: a) (+)-(*S*)-$H_2NCHMeCH_2C_6H_5$, H_2O, 25 °C, 2 h

In this case, we will turn our attention only to the fact that, the same as in transamination of the iodomethylate of 1,2-dimethyl-4-piperidone (XXIII), the use of (S)-1-benzylethylamine as the chiralizing agent leads to complete loss of the diastereoselectivity of transamination. Apparently, the thermodynamic stability of the stereoisomers of substituted 4-piperidones containing an N-1-benzylethyl substituent proves to be considerably lower than that of their N-1-phenylethyl analogs.

Now we can draw certain general conclusions. Transamination of iodomethylates of racemic 2-substituted and 2,5-disubstituted 4-piperidones by chiral primary amines proceeds as a deracemizing conversion and leads to the formation of optically active 2- and 2,5-substituted 4-piperidones, with various degrees of stereoselectivity. Preferential formation of diastereomers of 2- and 2,5-substituted 4-piperidones having the (S)-configuration of the chiral center $C_{(2)}$ is observed when using α-phenylethylamine with the (S) configuration. The highest optical yield is obtained upon forming stereoisomers of 4-piperidones containing an α-phenylethyl substituent on the nitrogen atom – stereoisomers that are more thermodynamically stable. Consequently, asymmetric transamination of the iodomethylates of substitutes 4-piperidones is controlled by the competitive influence of kinetic and thermodynamic control, and thus is described by Eq. (3), in which the final state of the reaction products is determined by their thermodynamic stability.

On the basis of the stereochemistry of the series of optically active N-substituted 4-piperidones that have been obtained, a scheme of asymmetric transamination has been proposed (Scheme 6) [40]. The opinion has been expressed that transamination of the iodomethylate XXXIII proceeds not through the open form of the α,β-unsaturated aminoketone B, as was suggested previously [33], but rather through a quasicyclic transition state C. The key stage, in which the new chiral center $C_{(2)}$ is formed, is the kinetically controlled nucleophilic addition of (S)-1-phenylethylamine to the prochiral double bond $C_{(2)}=C_{(3)}$ of the intermediate C. Here, the *Re* and *Si* approaches of the amine prove to be nonequivalent: The approach is sterically hindered by the presence of the 5-CH_3 group on the pro-(R) side, and hence attack by the (S)-phenylethylamine is accomplished primarily on the pro-(S) side, leading to preferential formation of the diastereomeric pair of diaminoketones XLIV and XLV, which have the (S) configuration of the new asymmetric center $C_{(2)}$. Intramolecular cyclization of the diaminoketones XLIV-XLVII, with the ejection of a dimethylamine molecule, leads to preferential formation of 1-(1-phenylethyl)-2,5-dimethyl-4-piperidone in the form of the stereochemically labile cis-trans diastereomeric pair (2S)-A.

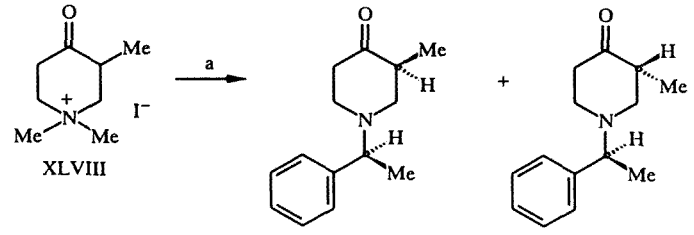
Scheme 6



N-Substituted 3-Methyl-4-piperidones

Here, the use of the "deracemization" methodology for obtaining chiral N-substituted 3-methyl-4-piperidones does not lead to the desired result: Upon transamination of the iodomethylate of 1,3-dimethyl-4-piperidone (XLVIII) with (S)-1-phenylethylamine, the 1-(1-phenylethyl)-3-methyl-4-piperidone, according to ^{1}H and ^{13}C NMR data, is formed as an inseparable mixture of the (1'S,3S) and (1'S,3R) diastereomers XLIX and L in a 1:1 ratio, as a consequence of the extremely facile epimerization at the $C_{(3)}$ atom, caused by enolization of the carbonyl group (Scheme 7).

Scheme 7



Reagents and conditions: a) (*S*)-$H_2NCHMePh$, H_2O, 25 °C, 2 h

ALKYLATION OF CHIRAL ENAMINES AND METALATED IMINES OF 4-PIPERIDONES

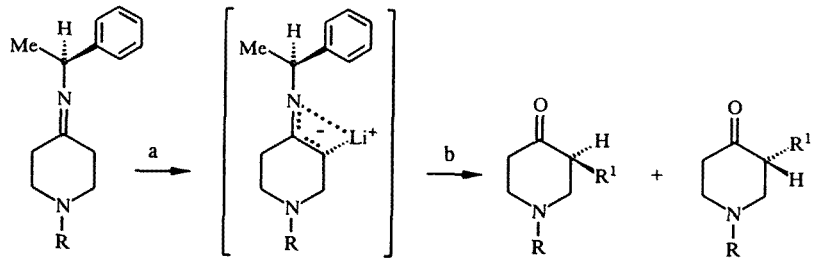
3-Substituted 4-Piperidones

The great practical importance of piperidine derivatives containing a methyl group in position 3 has been responsible for an intensive search for effective methods to obtain chiral 3-substituted 4-piperidones.

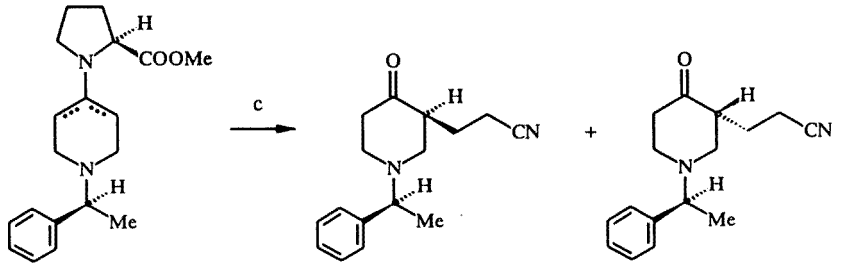
It is known that the alkylation of chiral enamines [43-47] and chiral metalated imines of cyclohexanone [48-51] results in the formation of α-substituted cyclohexanes with a very nearly 100% optical yield.

Extension of this strategy to the stereoselective introduction of a substituent into position 3 of the piperidine ring, i.e., the creation of a tertiary chiral center $C_{(3)}$, according to [52-55], was always accompanied by the formation of equal quantities of the diastereomers of 3-substituted 4-piperidones (Scheme 8).

Scheme 8



R=Me, C_4H_9, (*S*)–CHMePh; R^1=Me, CH_2Ph



Reagents and conditions: a) LDA, −20°C, THF, 1.5 h; b) R^1X, −78°C, 3 h;
c) CH_2=CH−CN, benzene, Δ, 4 h

The absence of any diastereoselectivity in creating a tertiary chiral center in the α-position relative to the carbonyl group is due to the extremely facile epimerization at $C_{(3)}$.

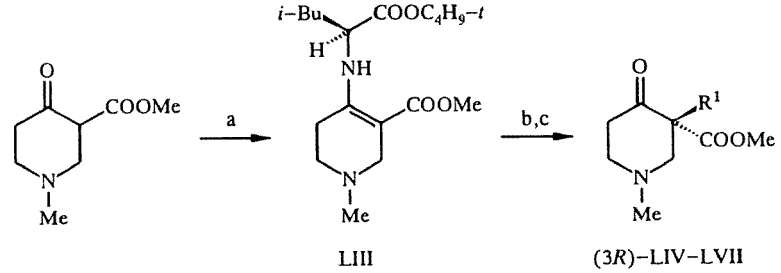
Nonetheless, a simple and preparatively convenient method has been found for segregating the (1'S, 3S)-1-(1-phenylethyl)-3-(2-cyanoethyl)-4-piperidone (LI). The isomer LI can easily be obtained in nearly 100% diastereomeric purity by three recrystallizations of a mixture of the diastereomers LI and LII with the 1:1 composition. Its absolute configuration was determined by means of x-ray structure analysis [55].

3-Methoxycarbonyl-3-alkyl-4-piperidones

All of the foregoing discussion indicates that the strategy of effective enantioselective synthesis of 3-substituted 4-piperidones comes down to the creation of a quaternary carbon center in the α-position relative to the carbonyl group; naturally, this eliminates the possibility of processes of epimerization and racemization.

The first example of the development of this strategy was the successful enantioselective synthesis of a series of (3R)-3-methoxycarbonyl-3-alkyl-4-piperidones (LIV-LVII) [56]. Optically active 4-piperidones LIV-LVII are formed by the alkylbromide alkylation of the key lithium derivative − the chiral enaminoester LIII (Scheme 9).

Scheme 9



LIV R^1=CH_2Ph (*ee* 85%); LV R^1= CH_2CH=CH_2; LVI R^1= CH_2−C≡CH; LVII R^1=CH_2COOEt

Reagents and conditions: a) (S)-$H_2NCH(i\text{-}C_3H_7)COO\text{-}t\text{-}C_4H_9$, benzene, Δ, 5 h; b) lithium diisopropylamide, −80°C, toluene, 1 h; c) R^1Br, −80°C, 1.5 h, then 10 h at 25°C

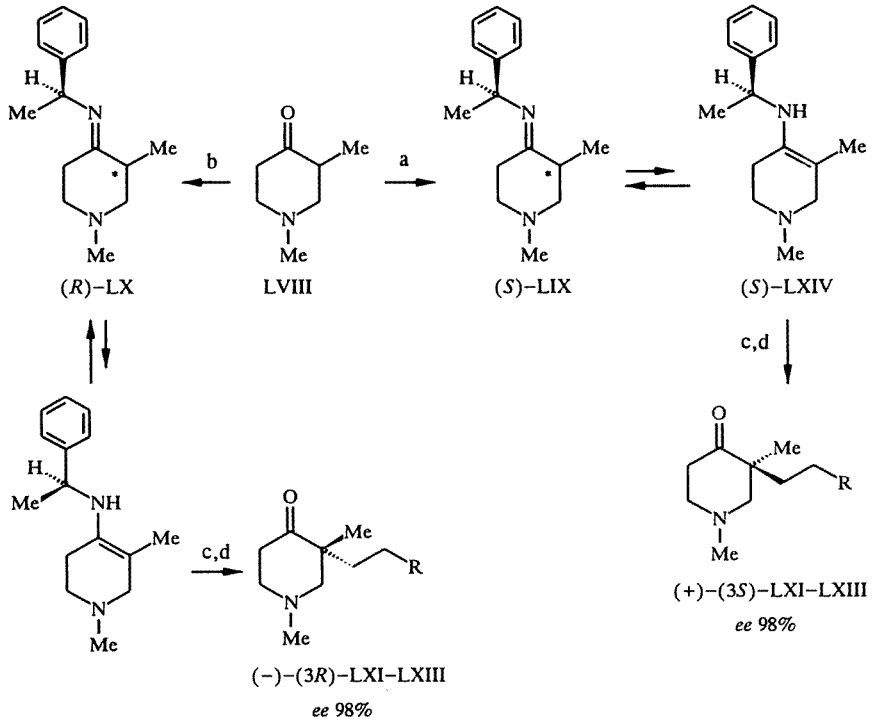
DERACEMIZING ALKYLATION

3,3-Disubstituted 4-Piperidones

Effective enantioselective synthesis of 3,3-disubstituted 4-piperidones with a high optical purity was described in [57, 58]. This path of asymmetric synthesis is based on the use of one of the elegant methods for creating a chiral quaternary center that had been developed previously in a series of cyclic ketones [59]. The essence of the method is a regioselective

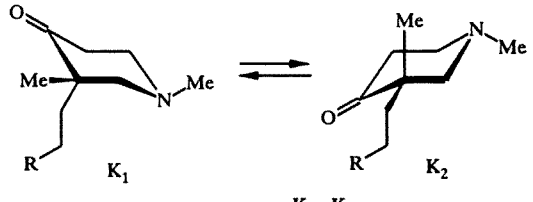
deracemizing alkylation of racemic 1,3-dimethyl-4-piperidone (LVIII), which is accomplished in the course of conjugate Michael addition of electrophilic olefins to its chiral imines (S)-LIX and (R)-LX, and which leads to the formation of (+) and (−) enantiomers of the 3,3-disubstituted 4-piperidones LXI-LXIII (Scheme 10).

Scheme 10



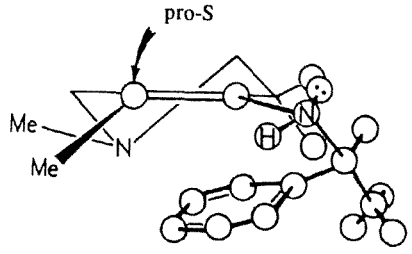
Reagents and conditions: a) (s)-$H_2NCHMePh$, benzene, Δ, 5 h; b) (R)-$H_2NCHMePh$, benzene, Δ; c) $CH_2=CH-R$, THF, Δ, 72 h; d) SiO_2

The enantiomeric purity of the 3,3-disubstituted 4-piperidones LXI-LXIII was determined by means of ^1H and ^{13}C NMR spectroscopy, using the chiral shift reagents tris[(heptafluoropropyloxymethylene)-D-camphorato]europium and tris[3-trifluoroacetyl-(1R)-camphorato]europium; the enantiomeric purity was 98%. The absolute configurations of the (+) and (−) enantiomers of the 3,3-disubstituted 4-piperidone LXI-LXIII were established by stereochemical correlation with (1'S,3S)-1-(1-phenylethyl)-3-(2-cyanoethyl)-4-piperidone (LI). Their steric structures were established by means of ^1H and ^{13}C NMR spectroscopy [58].



	$K_1 : K_2$
LXI R=CN	55 : 45
LXII R=COOMe	71 : 29
LXIII R=COMe	70 : 30

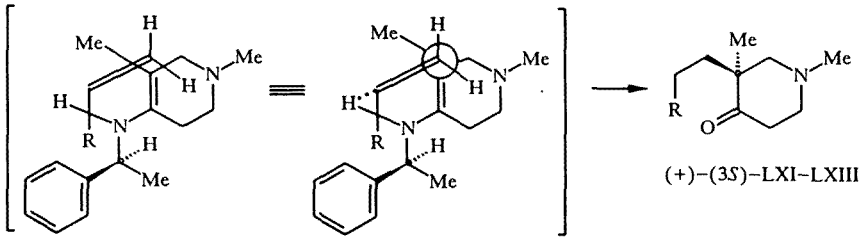
The key substrate of the reaction – the chiral imine LIX, obtained from racemic 1,3-dimethyl-4-piperidone (LVIII) and (S)-1-phenylethylamine – exists in the form of two diastereomers with the (1'S,3S) and (1'S,3R) configurations in a 1:1 ratio [57]. However, the reaction form in which the chiral imine LIX interacts with electron-deficient alkenes is the secondary tetrasubstituted enamine LXIV, in the molecule of which there is only one chiral center with the (S) configuration of the N-1-phenylethyl group. The preferred reaction conformation of the secondary enamine LXIV is conformation D, in which the basic steric interactions are minimized. In this configuration, the hydrogen atoms on the $C_{(5)}$ atom of the piperidine ring and the hydrogen atom of the N-phenylethyl substituent are close to each other. As a consequence, the hydrogen atom of the N–H bond proves to be in a plane formed by the triad atoms $C_{(3)}=C_{(4)}-N$, and this bond itself has the syn-position relative to the double bond of the enamine. With such a molecular geometry of the enamine LXIV, the pro-(R) side of the prochiral double bond $C_{(3)}=C_{(4)}$ proves to be completely shielded by the phenyl ring, and hence attack of electron-deficient alkenes is accomplished only from the noneclipsed pro-(S) side.



D

The reaction proceeds through a quasicyclic transition state E with synclinal approach of the reagents. Here the N–H hydrogen bond approaches the α-carbon atom of the electron-deficient alkene and is readily transferred to the alkene in a six-membered chairlike transition state, apparently in concert with the formation of a new carbon bond $C_{(3)}-C\beta$ (Scheme 11).

Scheme 11



(+)-(3*S*)-LXI–LXIII

E

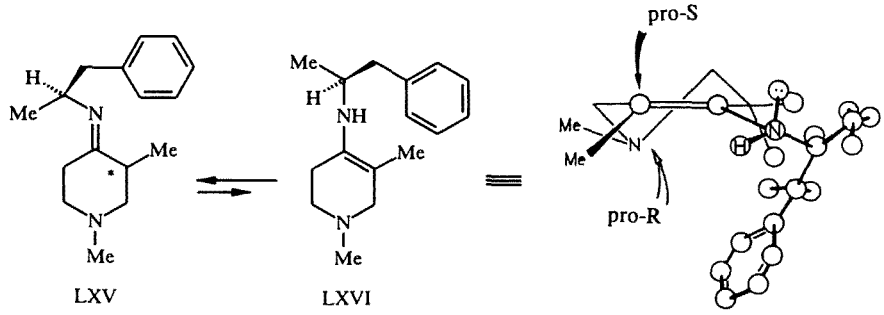
The end result of such interaction is the formation of a new quaternary center $C_{(3)}$, specifically with the (S) configuration.

The high enantioselectivity in the formation of the new quaternary center $C_{(3)}$, specifically with the (S) configuration, is controlled by the presence of the N-(S)-1-phenylethyl substituent, which is responsible for approach of the electrophilic olefin to the prochiral double bond $C_{(3)}=C_{(4)}$ of the enamine LXIV only from the pro-(S) side. Naturally, an α-phenylethyl substituent with the (R) configuration will promote approach from the pro-(R) side only.

The enantioselectivity of the reaction depends on many factors. Changes in the structure of the original 4-piperidone, the nature of the asymmetrizing amine, and the position of the chiral marker in the imine molecule will lead to a considerable decrease of enantioselectivity. This fact is completely explainable within the framework of the topological Scheme 11. Thus, for example, in the interaction of acrylonitrile and methyl acrylate with the chiral imine LXV, obtained from 1,3-dimethyl-4-piperidone (LVIII) and (+)-(S)-1-benzylethylamine, the optical purity of the product, (+)-(1S,3S)-1,3-dimethyl-3-(2-carbomethoxyethyl)-4-piperidone (LXII) is only 45%; and for (+)-(1S,3S)-1,3-dimethyl-3-(2-cyanoethyl)-4-piperidone (LXI), it drops to 30%. The decrease of enantioselectivity becomes understandable through examination of molecular models of the enamine LXVI. In the molecule of the tautomeric secondary enamine LXVI, the appearance of a benzyl group in the asymmetrizing N-substituent, i.e., removal of the phenyl group from the asymmetric carbon atom by a distance of one

methylene unit, results in a very marked decrease in the degree of shielding of the pro-(S) side of the double bond of the enamine, and, as a consequence, allows pro-(R) attack. For this reason there is also a decrease in stereoselectivity of alkylation of chiral imines of 4-piperidones in the Michael reaction.

A great success was the enantioselective solid-phase synthesis of (+) and (−) enantiomers of the 3,3-disubstituted 4-piperidones LXI-LXIII, in which the key stereoselective stage − the addition of electron-deficient alkenes to the chiral imine LIX − takes place on the surface of activated aluminum oxide or a modified cellulose DÉAÉ without the use of any organic solvent [58]. This was the first example of an enantioselective synthesis performed on the surface of a solid phase.

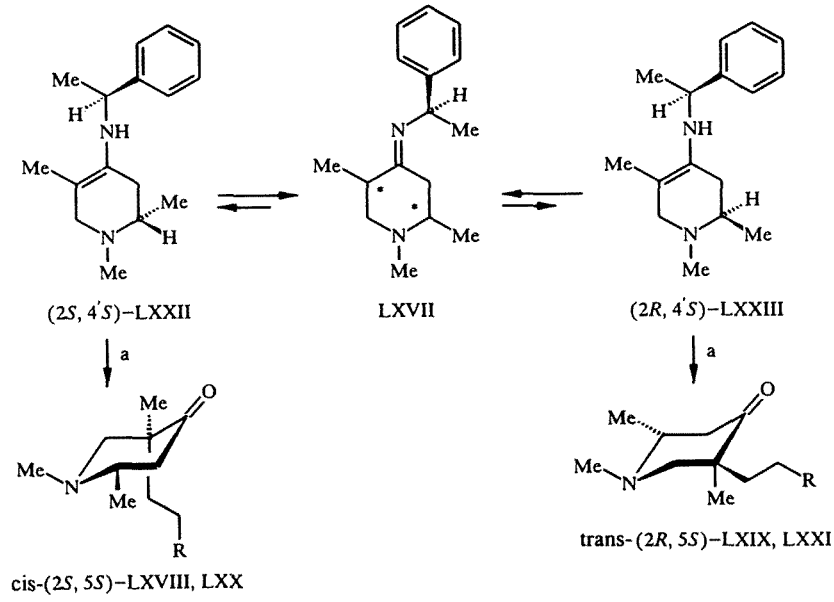


LXV LXVI

2,5,5-Trisubstituted 4-Piperidones

On the basis of the topological scheme 11, the stereochemical result was predicted for the deracemizing Michael alkylation of the chiral imine 1,2,5-trimethyl-4-piperidone (LXVII) [60]. The experiments demonstrated 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-piperidones LXVII/LXIX and LXX/LXXI, respectively (Scheme 12). In each case, the ratio of cis-trans diastereomers was 3:1. The enantiomeric purity of the 4-piperidones was as follows: LXVII 80%, LXIX 66%, LXX 86%, and LXXI 70%.

Scheme 12



(2*S*, 4'*S*)−LXXII LXVII (2*R*, 4'*S*)−LXXIII

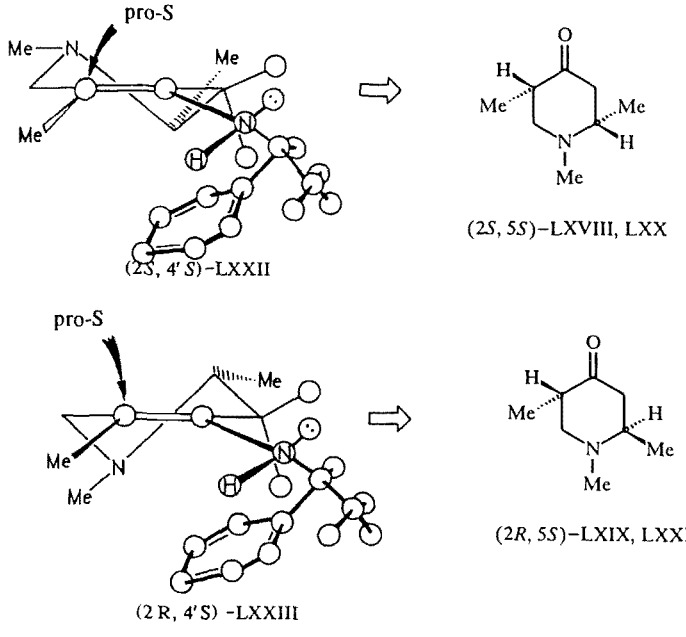
cis-(2*S*, 5*S*)−LXVIII, LXX trans-(2*R*, 5*S*)−LXIX, LXXI

3 : 1

LXVIII, LXIX R=CN; LXX, LXXI R=COOMe

Reagents and conditions: a) CH_2=CH−R, THF, Δ, 72 h

In the molecule of the reaction form of the secondary enamine – the tautomer of the chiral imine LXVII – two asymmetric atoms are present, namely $C_{(2)}$ and (S)-$C_{(4')}$; and hence it exists in the form of a mixture of two diastereomers (2S,4'S)-LXXII and (2R,4'S)-LXXIII. It is important for the prediction that the diastereomeric enamines LXII and LXXIII interact with the electron-deficient alkene as individual compounds. Then, within the framework of the topological scheme 11, the new quaternary center $C_{(5)}$ that arises in the course of alkylation of the enamines (2S)-LXXII and (2R)-LXXIII should have the (S) configuration, while the configuration of the chiral center $C_{(2)}$ in this case will remain the same as in the original enamines. Then, with attack by olefins on the prochiral double bond $C_{(4)}=C_{(5)}$, there should be formed from the enamine (2S,4'S)-LXXII the cis-(2S,5S) isomer of 5,5-disubstituted 4-piperidones LXVIII and LXX, and from the enamine (2R,4'S)-LXXIII the trans-(2R,5S) isomers LXIX and LXXI. Exactly this stereochemistry was established experimentally by means of NMR spectroscopy and stereochemical correlation for the preferentially formed and minor stereoisomers of 5,5-disubstituted 4-piperidones.



Thus, the strategy that has been developed for stereoselective synthesis in the 4-piperidone series, as described in the works we have cited, offers a means for obtaining a broad series of diverse chiral 4-piperidones in high optical purity and with the required stereochemistry, and it opens up the prospect of using these compounds as chirons in fine organic synthesis.

DIASTEREOSELECTIVE 1,4-HYDRIDE ADDITION TO ENAMINOKETONES

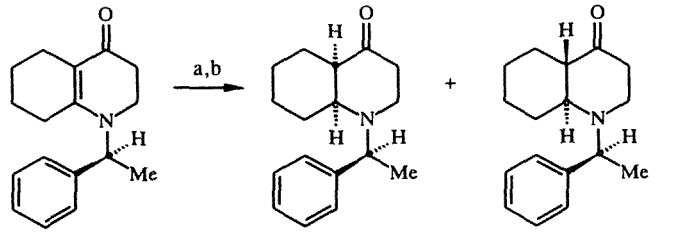
Cycloalkano-2,3-4-piperidones

Efficient diastereoselective synthesis of chiral cis and trans isomers of decahydro-4-quinolinones, octahydro-4-pyridones, and 2,3-cycloheptano-4-piperidones has been accomplished by using as the substrates the bicyclic enaminoketones LXXIV-LXXVI, in the molecules of which the chiral substituent with the (S) configuration is located on the nitrogen atom; i.e., the asymmetrizing center in this case is part of the substrate molecule. Reduction of the enaminoketones LXXIV-LXXVI by lithium aluminum hydride proceeds as an asymmetric 1,4-hydride addition to the enaminoketone fragment. In the resulting cycloalkano-2,3-4-piperidones, two new chiral centers are created.

The stereochemistry of this process was examined in detail in the example of the enaminoketone LXXIV [61-63]. Upon reduction of this compound, (1'S)-1-(1-phenylethyl)decahydro-4-quinolinone was obtained with a 69% yield in the form of a mixture of the two isomers LXXVII and LXXVIII (Scheme 13). The presence of the isomer LXXVIII in the process of reduction was detected chromatographically only in trace quantities. However, by column chromatography on the reaction mixture, the isomers LXXVII and LXXVIII were recovered in a 3:1 weight ratio. This means that the formation of the (1'S)-1-(1-phenylethyl)decahydro-4-quinolinone (LXXVII) proceeds as a result of kinetically controlled stereoselective reduction of

the enaminoketone LXXIV by lithium aluminum hydride. The formation of the (1'S)-1-(1-phenylethyl)-decahydro-4-quinolinone (LXXVIII) is a consequence of isomerization that takes place upon contact with the sorbent, owing to enolization of the carbonyl group. The isomers LXXVII and LXXVIII, thus, are epimers with respect to the $C_{(10)}$ center. The diastereomeric purity of the isomers LXXVII and LXXVIII that were recovered in individual form, as established by ^1H NMR data, was 97%.

Scheme 13

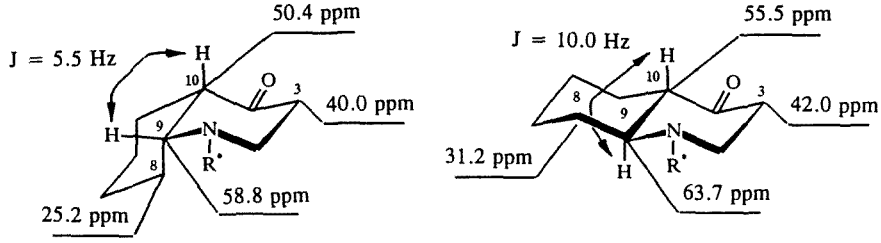


LXXIV (−)- cis- LXXVII (+)- trans- LXXVIII

3 : 1

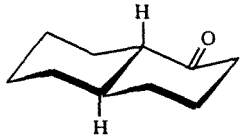
Reagents and conditions: a) $LiAlH_4$, ether, 25°C, 3 h; b) SiO_2

The steric structure and the preferred conformations of the decahydro-4-quinolinones LXXVII and LXXVIII were established by means of ^1H and ^{13}C NMR spectroscopy [64, 65]. It was found that the chemical shifts of the $C_{(3)}$, $C_{(8)}$, $C_{(9)}$, and $C_{(10)}$ atoms are characteristic and can serve as a criterion for assignment of the isomers of the decahydro-4-quinolinones to the cis and trans series.



cis-(9*S*, 10*R*)-LXXVII trans-(9*S*, 10*S*)-LXXVIII

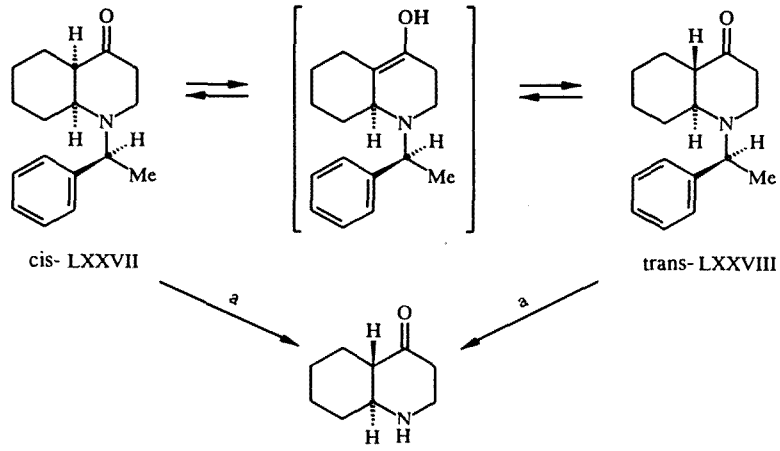
The absolute configuration of the new chiral centers $C_{(9)}$ and $C_{(10)}$ in the cis and trans isomers of the decahydro-4-quinolinones LXXVII and LXXVIII were established by stereochemical correlation methods, using as the comparison standard trans-(−)-(3S,4R)-decalin-1-one (LXXIX) [63].



LXXIX

The process of diastereoselective reduction of the enaminoketones LXXIV is confirmed by removal of the (S)-phenylethyl substituent in the individual cis and trans decahydro-4-quinolinones LXXVII and LXXVIII by hydrogenolysis in the presence of palladium black. The result was dramatic: From the cis-LXXVII and the trans-LXXVIII, exactly the same compound was obtained, the thermodynamically more stable (+)-(9S,10S)-trans-decahydro-4-quinolinone (LXXX). These data confirm beyond a doubt the genetic link between the members of the stereochemically labile epimeric pair of diastereomers LXXVII and LXXVIII, which differ only in absolute configuration of the $C_{(10)}$ center (Scheme 14).

Scheme 14



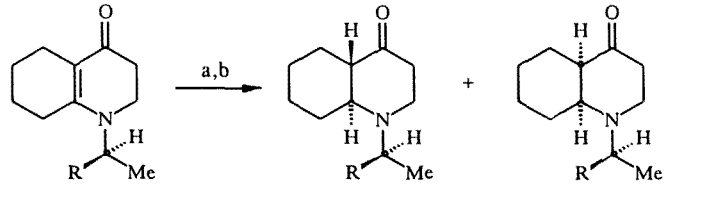
(+)– trans- (9*S*, 10*S*)–LXXX

Thus, 1,4-hydride addition of lithium aluminum hydride to the enaminoketone LXXIV is an asymmetric, kinetically controlled process, and it leads to formation of the cis-(−)-(9S,10R)-decahydro-4-quinolinone LXXVII with very nearly 100% diastereoselectivity. Subsequently, as a result of internal stereochemical lability due to enolization of the carbonyl group, the cis-(−)-(9S,10R)-LXXVII, under conditions of thermodynamic control, is epimerized at the $C_{(10)}$ center with the formation of an equilibrium mixture of the isomers LXXVII and LXXVIII with a 3:1 composition. Consequently, the optical yield of the reaction in this case is close to 100%.

It is important to emphasize that cis isomers of racemic N-alkyldecahydro-4-quinolinones had not been described in the literature [66, 67].

The stereochemistry of 1,4-hydride addition to the enaminoketones LXXV and LXXVI, which have alkyl (S)-1-benzylethyl and (S)-sec-butyl substituents on the nitrogen atom, proved to be the opposite [68]. Reduction of the enaminoketones LXXV and LXXVI is also asymmetric, but it leads to the formation of essentially only trans-(+)-(1'S,9S,10S)-isomers of 1-(1-benzylethyl)-decahydro-4-quinolinones (LXXXI) and 1-(1-sec-butyl)-decahydro-4-quinolinones (LXXXIII) (Scheme 15). The cis-(9S,10R)-decahydro-4-quinolinones LXXXII and LXXXIV, although they were registered chromatographically, were not actually recovered. Consequently, the optically active trans-decahydro-4-quinolinones LXXXI and LXXXIII, which have N-alkyl substituents, are formed in the process of asymmetric reduction of the enaminoketones LXXV and LXXVI with practically 100% diastereoselectivity. The stereochemistry and the absolute configuration of the trans-decahydro-4-quinolinones LXXXI and LXXXIII were established by means of ^1H and ^{13}C NMR spectroscopy [64, 68] and by stereochemical correlation methods [68].

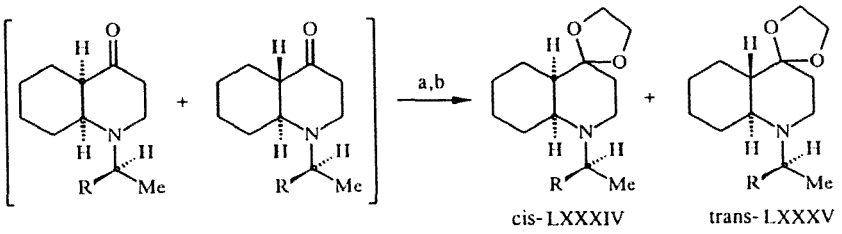
Scheme 15



Reagents and conditions: a) $LiAlH_4$, ether, 25°C, 3 h; b) SiO_2

The differing thermodynamic stabilities of the cis and trans diastereomers of decahydro-4-quinolinones having N-alkyl and N-phenylethyl substituents on the nitrogen atom were demonstrated by using them to synthesize the stereochemically stable aminoketals cis-LXXXIV and trans-LXXXV (Scheme 16). The ratio of these cis and trans ketals that are formed under conditions of thermodynamic control reflects the composition of the original decahydro-4-quinolinones within the pairs N-1-phenylethyl- (LXXVII, LXXVIII), N-1-benzylethyl- (LXXXI, LXXXII), and N-sec-butyl- (LXXXIII, LXXXIV) decahydro-4-quinolinones. It is important that the cis-decahydro-4-quinolinone LXXVII, will also remain stable under the rather severe conditions of ketal formation.

Scheme 16

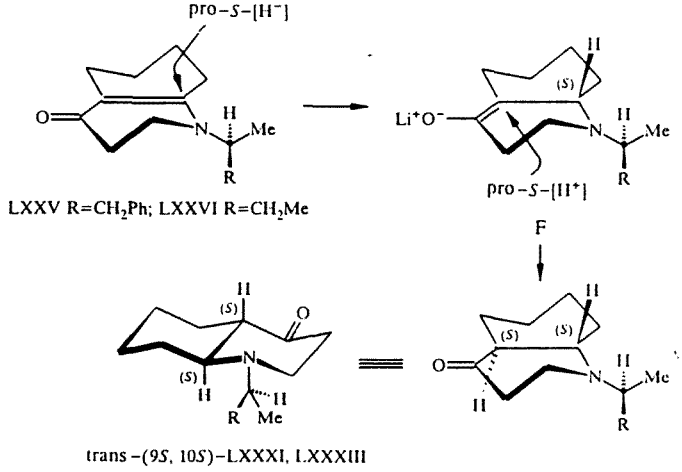


LXXVII, LXXVIII R=Ph	7 : 1
LXXXII, LXXXI R=CH_2Ph	1 : 6
LXXXIV, LXXXIII R=CH_2Me	1 : 5

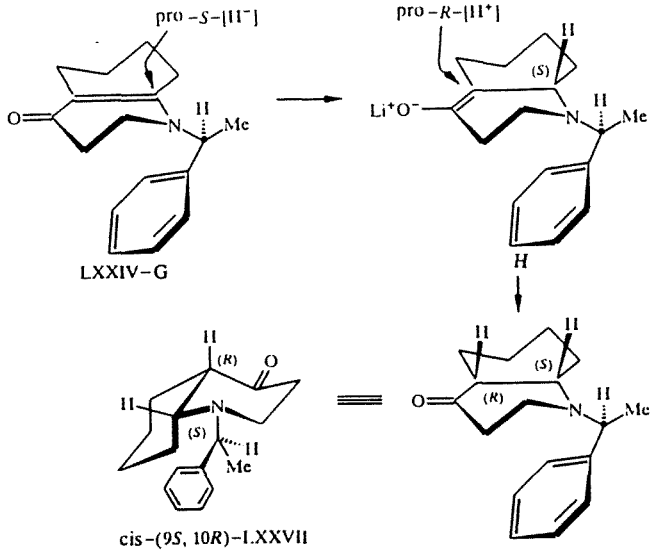
Reagents and conditions: a) $HOCH_2CH_2OH$, p-TsOH, benzene, Δ, 3 h; b) SiO_2

In accordance with the stereochemistry of the trans-decahydro-4-quinolinones LXXXI and LXXXIII that were obtained, the scheme of asymmetric 1,4-hydride addition to the enaminoketone fragment appears as follows (Scheme 17). The key stereoselective stage of this process is the approach of the hydride ion to the prochiral bond $C_{(9)}$=$C_{(10)}$ of the enaminoketones LXXV and LXXVI from the sterically unhindered pro-(S) side. This leads to the creation of a new chiral center $C_{(9)}$ with the (S) configuration in the enolate F that is formed in this reaction. The second stage – the formation of a chiral center $C_{(10)}$ with the (S) configuration upon approach of a proton from the pro-(S) side of the enolate F upon ketonization – is controlled by the thermodynamic stability of the trans-diastereomer of the 2,3-cycloalkano-4-piperidone that is formed in this reaction. Consequently, the formation of only the conformationally fixed trans isomers LXXXI and LXXXIII of the N-alkyl-substituted 4-piperidones is the result of concerted control of the 1,4-hydride addition to the enaminoketone fragment by kinetic and thermodynamic factors.

Scheme 17



Scheme 18

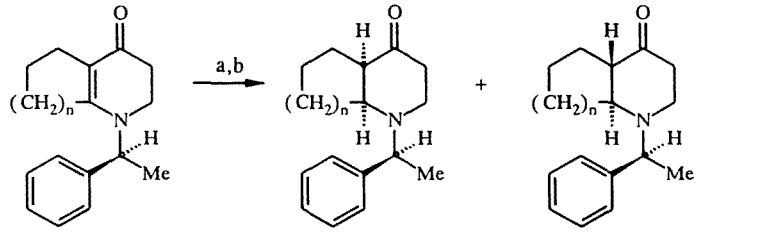


On the basis of an analysis of spectral and chiroptic data [69-71], along with conformational modeling by the molecular mechanics method [72], it was established that for the bicyclic enaminoketone LXXIV, which contains on the nitrogen atom an (S)-phenylethyl substituent, the conformer G is predominant in the conformational equilibrium. The great preference for the compact conformation G is related to intramolecular homoconjugation of the enaminoketone and phenyl chromophores [73]. Exactly this conformation of the enaminoketone LXXIV is reduced by lithium aluminum hydride.

The formation of a new chiral center $C_{(9)}$ with the (S) configuration in the cis-decahydro-4-quinolinone LXXVII suggests that the asymmetric reduction of the enaminoketone LXXIV in the first stage proceeds within the framework of the topological scheme 17, predicting preferential formation of the chiral center $C_{(9)}$ with the (S) configuration. However, protonation of the resulting enolate H proceeds preferentially from the pro-(R) side, leading to the formation of the cis-(9S,10R) isomer LXXVII (Scheme 18). It is important to emphasize that in this case, the stereochemical result of the reaction is controlled specifically by stereoelectronic factors.

The stereochemical direction of 1,4-hydride addition to the $\Delta^{8,9}$-hexahydro-4-pyridone (LXXXVI) and 2,3-cyclohepteno-4-piperidone (LXXXVII), which have an (S)-1-phenylethyl substituent on the nitrogen atom, is completely preserved. The corresponding 2,3-cycloalkano-piperidones are also formed as a mixture of cis- LXXXVIII, and trans-LXXXIX (or cis-XC and trans-XCI) isomers, with a considerable predominance of the cis isomer in each case (Scheme 19) [74]. The cis-(8S,9R)-LXXXVIII and trans (8S,9S)-LXXXIX isomers of 1-(1-phenylethyl)octahydro-4-piperidone were recovered in an 8:1 ratio. Their absolute configuration was established by stereochemical correlation [74].

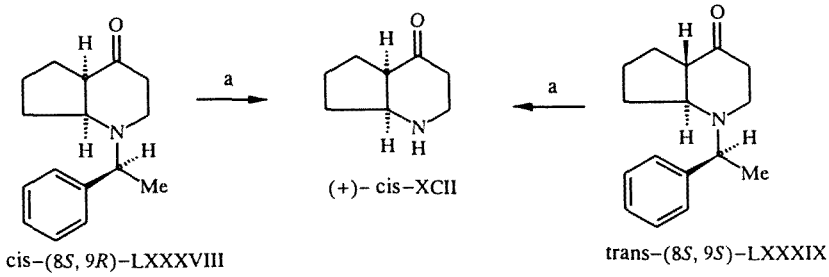
Scheme 19



Reagents and conditions: a) $LiAlH_4$, ether, 25°C, 2 h; b) SiO_2

Removal of the asymmetrizing marker in each of the isomers LXXXVIII and LXXXIX gave exactly the same (more thermodynamically stable) (+) enantiomer, the cis-octahydro-4-piperidone XCII (Scheme 20) [74]. This proves the genetic link between the cis and trans isomers of the octahydro-4-piperidone LXXXVIII and LXXXIX, which are epimers with respect to the center $C_{(9)}$.

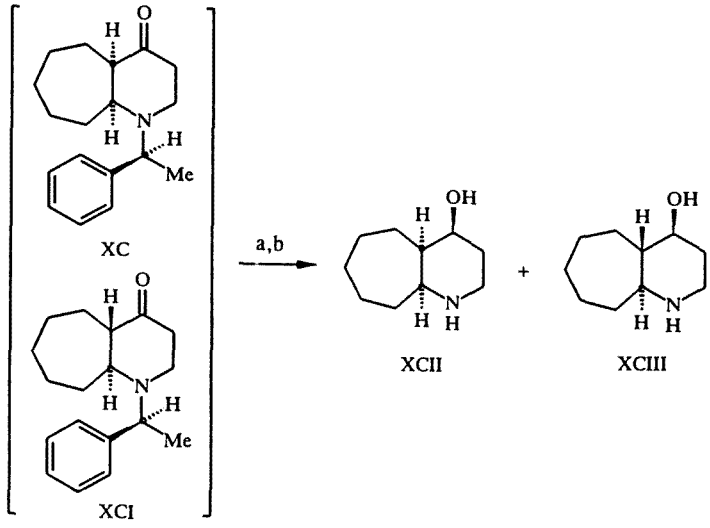
Scheme 20



Reagents and conditions: a) H_2, Pd, CH_3COOH, 25°C, 3 h; then NaOH

The cis-trans pair of 1-(1-phenylethyl)-2,3-cycloheptano-4-piperidone XC and XCI, owing to the facile mutual convertibility, was not separated into the individual isomers. However, it was shown that the ratio of isomers after contact with sorbents, according to ^1H NMR data, was 1:1.

Scheme 21



Reagents and conditions: a) $NaBH_4$, C_2H_5OH—H_2O (1:1), 25°C, 1 h;
b) H_2, Pd, C_2H_5OH, 25°C, 3 h

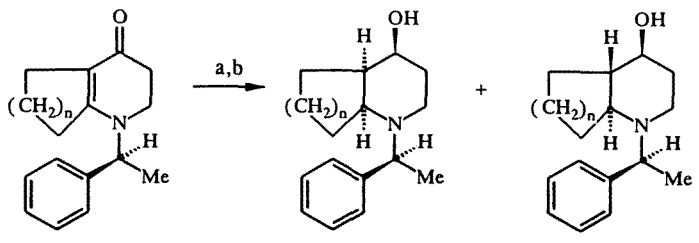
Confirmation of the asymmetric character of the reduction of the enaminoketones LXXXVI and LXXXVII with the formation of stereochemically labile 2,3-cycloheptano-4-piperidones XC and XCI is provided by the fact that the optically active 2,3-cycloheptano-4-piperidols XCII and XCIII are obtained upon reducing a mixture of the cis and trans isomers XC and XCI (Scheme 21).

TOTAL REDUCTION OF ENAMINOKETONE FRAGMENT

2,3-Cycloalkano-4-piperidols

Total asymmetric reduction of the enaminoketone fragment takes place when the enaminoketones LXXIV, LXXXVI, and LXXXVII interact with sodium borohydride; this leads to the formation of the optically active 2,3-cycloalkano-4-piperidols XCIV-XCIX (Scheme 22) [75].

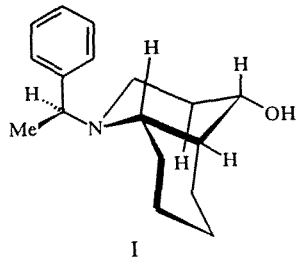
Scheme 22



Reagents and conditions: a) $NaBH_4$, C_2H_5OH—Py 1:1, Δ, 10 h; b) SiO_2

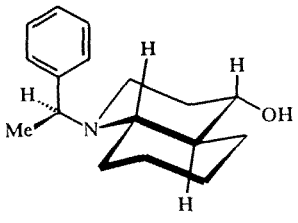
In the process of reduction of the enaminoketones LXXIV, LXXXVI, and LXXXVII, three new asymmetric centers appear, and hence we can expect the formation of four diastereomeric pairs of 1,4-aminoalcohols. The result of the reaction is the preferential formation of only one cis-trans diastereomeric pair of the 2,3-cycloalkano-4-piperidols.

According to x-ray diffraction and ^{13}C NMR data, the cis-decahydro-4-quinolinol (XCIV) has the (1'S,4S,9S,10R) configuration, and it exists in the crystal and in solution primarily in conformation I. The minor conformationally fixed trans-(1'S,4S,9S,10S)-decahydro-4-quinolinol (XCV), according to ^{13}C NMR data, exists in conformation J. The steric structure of the cis-trans diastereomeric pairs of the perhydro-4-pyridol XCVI/XCVII and 2,3-cycloheptano-4-piperidinol XCVIII/XCIX was established by stereochemical correlation, using as the reference compounds the cis and trans isomers of the decahydro-4-quinolinols XCIV/XCV.



I

cis-(4*S*, 9*S*, 10*R*)-XCIV

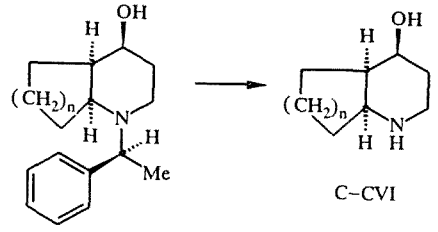


J

trans-(4*S*, 9*S*, 10*S*)-XCV

Upon removal of the chiral (S)-phenylethyl group in the cis and trans isomers of the N-substituted 2,3-cycloalkano-4-piperidols XCIV-XCIX, optically active 2,3-cycloalkano-4-piperidols C-CVI were obtained, once more confirming the asymmetric character of reduction of the enaminoketones LXXIV, LXXXVI, and LXXXVII by sodium borohydride (Scheme 23).

Scheme 23



XCIV–XCIX

C–CVI

Reagents and conditions: H_2, Pd, C_2H_5OH, 25°C, 3 h

Thus, the total reduction of the enaminoketones LXXIV, LXXXVI, and LXXXVII by sodium borohydride proceeds with a high stereoselectivity and leads to the preferential formation of previously unknown, optically active 2,3-cycloalkano-4-piperidols in the form of a single cis-trans diastereomeric pair.

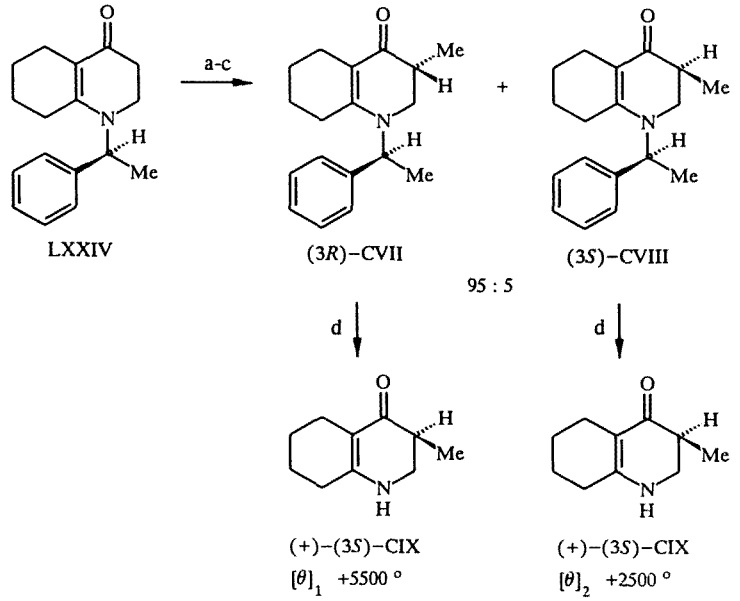
ASYMMETRIC ALKYLATION OF METALATED ENAMINOKETONES

3-Methyl-$\Delta^{9,10}$-octahydro-4-quinolinones

In [76], still another direction was worked out in the asymmetric transformations of bicyclic enaminoketones: feasibility and principle were demonstrated for performing the diastereoselective electrophilic substitution of metalated bicyclic enaminoketones at position 3. Methylation of the lithium derivative of (1'S)-1-(1-phenylethyl)-$\Delta^{9,10}$-octahydro-4-quinolinone (LXXIV) under conditions of kinetic control, with a 100% regioselectivity and 90% optical yield, leads to the

formation of (+)-(1'S,3R)-1-(1-phenylethyl)-3-methyl-$\Delta^{9,10}$-octahydro-4-quinolinone (CVII) (Scheme 24). Its absolute configuration was established by stereochemical correlation.

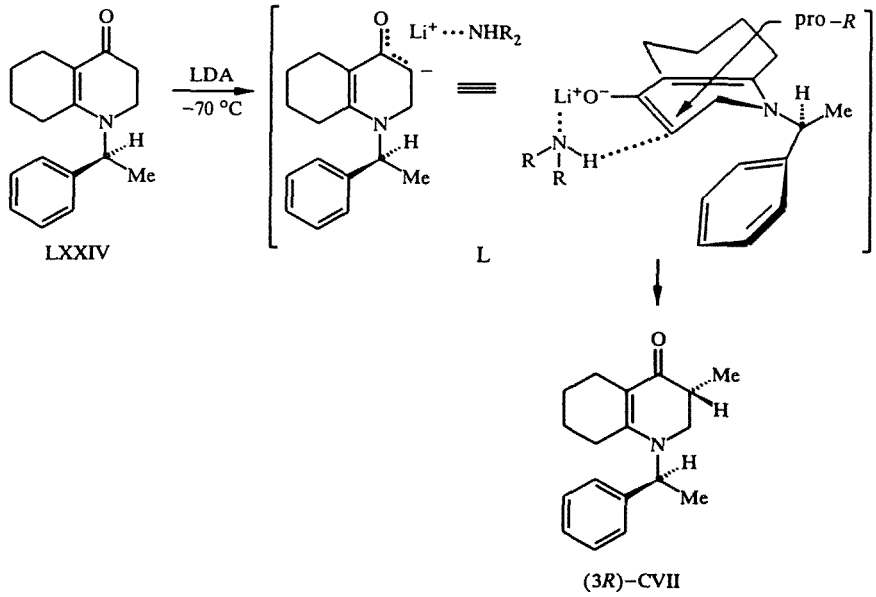
Scheme 24



Reagents and conditions: a) lithium diethylamide (2 eq), −70°C, hexane—THF 10:1, 1 h; b) CH_3I, −7°C, 30 min; c) SiO_2; d) H_2, Pd, C_2H_5OH, 25°C, 3 h

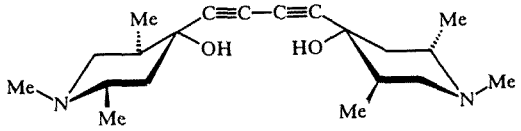
Attention is drawn to the high thermodynamic stability of the minor (1'S,3S)-1-(1-phenylethyl)-3-methyl-$\Delta^{9,10}$-octahydro-4-quinolinone (CVIII). Upon removal of the chiral marker in the diastereomers (1'S,3R)-CVII and (1'S,3S)-CVIII, one and the same (+)-(3S) enantiomer CIX is formed, but with different optical purities (Scheme 24). These data show that the hydrogenolysis process is accompanied by preliminary epimerization of the (3R) diastereomer CVII to the thermodynamically more stable (3S) diastereomer CVIII.

Thus, the preferential formation of the (3R) diastereomer CVII in the process of asymmetric alkylation is controlled kinetically, and its thermodynamic instability leads to the appearance of the (3S)-CVIII in the reaction mixture.

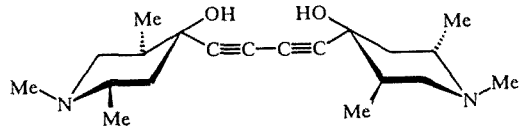


In accordance with these data, the steric direction of asymmetric alkylation of metalated enaminoketones becomes understandable: under the influence of a strong base, the kinetically controlled monodeprotonation of the enaminoketone LXXIV in position 3 leads to the formation of the aza-anion L, the conformational rigidity of which is due to coordination with diisopropylamine. In turn, this leads to differentiation of the prochiral sides of the $C_{(3)}=C_{(4)}$ bond. Attack by the alkyl halide takes place preferentially from the sterically unhindered pro-(R) side, and it ensures high stereoselectivity in the formation of the new chiral center $C_{(3)}$ with the (R) configuration.

The stereoselectivity of the process of alkylating the enaminoketone LXXIV is influenced greatly by the reaction conditions: With increasing bulk of the alkylating agent, an increase of temperature, or a change in the lithium amide/substrate ratio, the diastereoselectivity drops off.



β-CX
(+)-(2*S*, 4*R*, 5*R*)-β-CX
and
(−)-(2*R*, 4*S*, 5*S*)-β-CX



γ-CXI
(−)-(2*S*, 4*S*, 5*R*)-γ-CXI
and
(+)-(2*R*, 4*R*, 5*S*)-γ-CXI

Concluding our analysis of the stereoselective paths of synthesis of 4-piperidones and their bicyclic analogs, let us turn again to the "chirality−activity" problem. It had been shown previously that the racemic β-(2e,4a,5e)-CX and γ(2e,4e,5e)-CXI isomers of the glycol of 1,4-bis(1,2,5-trimethyl-4-hydroxy-4-piperidyl)-1,3-butadiene stimulate the growth of plants, with the γ-glycol CXI having a higher activity than the β-isomer CX [77]. In [78], the authors showed that the (+) and (−) enantiomers of the β-glycol CX have an antagonistic effect on the respiration of tobacco and chlorella cells, whereas the (+) and (−) enantiomers of the γ-glycol CXI exhibit identical positive activity. It is entirely probable that the different growth-stimulating activities of the racemic glycols β-CX and γ-CXI are related to differences in the biological action of their (+) and (−) enantiomers.

REFERENCES

1. G. M. Whitesides and D. W. Lewis, J. Am. Chem. Soc., **92**, 6979 (1970).
2. The Merck Index, 11th Ed., Merck & Co., Rahway, N.J. (1989).
3. C. R. Ganellin and R. G. Spickett, J. Med. Chem., **8**, 619 (1965).
4. A. A. Champseix and G. R. Lefur, Eur. Pat. 12,643; Chem. Abstr., **94**, 15175 (1981).
5. S. Samczuk and H. K. F. Hermans, Ger. Pat. 2,642,856; Chem. Abstr., **87**, 53094 (1977).
6. Ciba-Geigy, Fr. Pat. 2,437,405; Chem. Abstr., **94**, 83739 (1981).
7. E. Abignente and M. Biniecka-Picazio, Acta. Pol. Pharm., **34**, 241 (1977).
8. M. Nalanishi, M. Shiraki, T. Kobayakawa, and R. Kobayashi, Jpn. Pat. 74-03987; Chem. Abstr., **81**, 120485 (1974).
9. I. N. Nazarov, N. S. Prostakov, N. A. Mikheeva, and V. N. Dobrynina, Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol., **2**, 726 (1959).
10. P. S. Portoghese, J. Pharm. Sci., **55**, 865 (1966).
11. A. Ziering and I. Lee, J. Org. Chem., **12**, 911 (1947).
12. I. Lee, A. Ziering, S. D. Heinemann, and L. Berger, J. Org. Chem., **12**, 885 (1947).

13. A. Ziering, S. D. Heinemann, and I. Lee, J. Org. Chem., **12**, 894 (1947).
14. L. Berger, A. Ziering, and I. Lee, J. Org. Chem., **12**, 904 (1947).
15. I. N. Nazarov, Selected Works [in Russian], Izd. Akad. Nauk SSSR, Moscow (1961), p. 588.
16. N. S. Prostakov and L. A. Gaivoronskaya, Usp. Khim., **47**, 859 (1978).
17. D. L. Larson and P. S. Portoghese, J. Med. Chem., **16**, 195 (1973).
18. D. S. Fries and P. S. Portoghese, J. Med. Chem., **17**, 990 (1974).
19. D. S. Fries and P. S. Portoghese, J. Med. Chem., **19**, 1155 (1976).
20. D. S. Fries, R. D. Dodge, H. Hope, and P. S. Portoghese, J. Med. Chem., **25**, 9 (1982).
21. P. S. Portoghese, Z. S. D. Gomaa, and D. L. Larson, J. Med. Chem., **16**, 199 (1973).
22. K. H. Bell and P. S. Portoghese, J. Med. Chem., **17**, 129 (1974).
23. M. Froimowitz, J. Med. Chem., **25**, 1127 (1982).
24. C. J. Barnett, C. R. Copley-Merriman, and J. Maki, J. Org. Chem., **54**, 4795 (1989).
25. D. M. Zimmerman, U.S. Pat. 4,081,450; Chem. Abstr., **89**, 109113 (1978).
26. D. M. Zimmerman, R. Nickander, J. S. Horng, and D. T. Wong, Nature, **275**, 332 (1978).
27. A. Jonczyk, M. Jawdosiuk, M. Makosza, and J. Czyzewski, Przem. Chem., **57**, 131 (1978).
28. N. Lalinde, J. Moliterni, D. Wright, H. K. Spenatr, M. N. Ossipov, T. C. Spaulding, and F. G. Rudo, J. Med. Chem, **33**, 2876 (1990).
29. J. L. Archibald, Br. Pat. 1,411,783; Chem. Abstr., **84**, 43876 (1976).
30. T. N. Riley, D. S. Hale, and M. C. Wilson, J. Pharm. Sci., **62**, 983 (1973).
31. W. F. M. van Bever, C. J. E. Niemegeers, and P. A. J. Janssen, J. Med. Chem., **17**, 1047 (1974).
32. M. Nogradi, Stereoselective Synthesis, VCH Publications, New York (1986).
33. E. A. Mystryukov and G. N. Smirnova, Tetrahedron, **27**, 375 (1971).
34. P. Geneste, J. Hugon, C. Reminiac, G. Lamaty, and J. P. Roque, Bull. Soc. Chim. Fr., No. 5-6, 845 (1976).
35. R. E. Lyle and G. G. Lyle, J. Org. Chem., **24**, 1679 (1959).
36. É. A. Mistryukov, N. I. Aranova, and V. F. Kucherov, Izv. Akad. Nauk SSSR, Ser. Khim., No. 5, 932 (1961).
37. G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, T. A. Gudasheva, I. F. Leshcheva, N. M. Sergeev, T. A. Kudryavtseva, and E. Yu. Korchagina, Khim. Geterotsikl. Soedin., No. 12, 1693 (1983).
38. G. V. Grishina, V. M. Potapov, T. A. Gudasheva, and S. A. Abdulganeeva, Khim. Geterotsikl. Soedin., No. 10, 1378 (1985).
39. G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, and E. Yu. Korchagina, Khim. Geterotsikl. Soedin., No. 12, 1648 (1985).
40. G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, T. A. Gudasheva, A. A. Karapetyan, and A. A. Espenbetov, Khim. Geterotsikl. Soedin., No. 12, 1641 (1986).
41. I. F. Leshcheva, N. M. Sergeev, G. V. Grishina, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 11, 1503 (1986).
42. A. É. Aliev, A. A. Fomichev, G. V. Grishina, Yu. I. Él'natanov, and R. G. Kostyanovskii, Izv. Akad. Nauk SSSR, Ser. Khim., No. 8, 1760 (1990).
43. S.-I. Yamada, K. Hiroi, and K. Achiwa, Tetrahedron Lett., No. 48, 4233 (1969).
44. K. Hiroi, K. Achiwa, and S.-I. Yamada, Chem. Bull. Pharm., **20**, 246 (1972).
45. J. K. Whitesell and S. W. Feiman, J. Org. Chem., **42**, 1663 (1977).
46. S. J. Blarer, W. B. Schweizer, and D. Seebach, Helv. Chim. Acta, **65**, 1637 (1982).
47. C. Stetin, B. DeJeso, and J.-C. Pommier, J. Org. Chem., **50**, 3863 (1985).
48. A. I. Meyers, D. R. Williams, and M. Druelinger, J. Am. Chem. Soc., **98**, 3032 (1976).
49. J. K. Whitesell and M. A. Whitesell, J. Org. Chem., **42**, 377 (1977).
50. D. I. Hashimoto and K. Koga, Tetrahedron Lett., No. 6, 573 (1978).
51. A. I. Meyers, D. R. Williams, G. W. Erickson, S. White, and M. Druelinger, J. Am. Chem. Soc., **103**, 3081 (1981).
52. G. V. Grishina, V. M. Potapov, and S. A. Abdulganeeva, Vestn. Mosk. Gos. Univ., Khim., **24**, 507 (1983).
53. G. V. Grishina, V. M. Potapov, and S. A. Abdulganeeva, Khim. Geterotsikl. Soedin., No. 3, 372 (1986).
54. G. V. Grishina, V. M. Potapov, S. A. Abdulganeeva, and I. A. Ivanova, Khim. Geterotsikl. Soedin., No. 11, 1510 (1983).

55. G. V. Grishina, S. A. Abdulganeeva, V. M. Potapov, I. A. Ivanova, A. A. Espenbetov, Yu. T. Struchkov, I. A. Grishina, and A. I. Dutsenko, Khim. Geterotsikl. Soedin., No. 12, 1656 (1985).
56. V. Schilay, A. Alyev, and G. Grishina, Bull. Soc. Chem. Belg., No. 8, 742 (1992).
57. G. V. Grishina and E. L. Gaidarova, Khim. Geterotsikl. Soedin., No. 8, 1072 (1992).
58. E. L. Gaidarova and G. V. Grishina, Synlett., No. 1, 89 (1992).
59. J. d'Angelo, D. Desmaele, F. Dumas, and A. Guingant, Tetrahedron: Asymmetry, **3**, 459 (1992).
60. G. V. Grishina, E. L. Gaidarova, and A. É. Aliev, Khim. Geterotsikl. Soedin., No. 10, 1369 (1992).
61. V. M. Potapov, G. V. Kiryushkina (Grishina), and G. P. Tokmakov, Khim. Geterotsikl. Soedin., No. 12, 1656 (1972).
62. V. M. Potapov, G. V. Grishina, E. A. Golov, P. B. Terent'ev, and R. Khertsshu, Khim. Geterotsikl. Soedin., No. 7, 953 (1976).
63. V. M. Potapov, G. V. Grishina, and E. A. Golov, Khim. Geterotsikl. Soedin., No. 8, 1093 (1976).
64. I. F. Leshcheva, N. M. Sergeev, G. V. Grishina, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 2, 230 (1983).
65. A. É. Aliev and G. V. Grishina, Khim. Geterotsikl. Soedin., No. 2, 271 (1989).
66. W. L. F. Armarego, in: Stereochemistry of Heterocyclic Compounds, Part I, Nitrogen Heterocycles, Wiley Interscience (1977), p. 141.
67. G. V. Grishina and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 5, 579 (1987).
68. G. V. Grishina, N. E. Agafonov, and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 4, 519 (1983).
69. G. V. Grishina, G. N. Koval', and V. M. Potapov, Khim. Geterotsikl. Soedin., No. 9, 1230 (1978).
70. V. M. Potapov, G. V. Grishina, and G. N. Koval', Khim. Geterotsikl. Soedin., No. 4, 508 (1978).
71. V. M. Potapov, G. V. Grishina, E. V. Korotkov, and G. N. Koval', Khim. Geterotsikl. Soedin., No. 4, 511 (1976).
72. L. A. Kutulya, T. V. Khandrimailova, G. V. Grishina, G. M. Makeev, and M. Yu. Kornilov, Zh. Org. Khim., **27**, 2165 (1991).
73. V. M. Potapov, G. V. Grishina, and G. N. Koval', Khim. Geterotsikl. Soedin., No. 9, 1286 (1976).
74. V. M. Potapov, G. V. Grishina, and T. A. Liberchuk, Khim. Geterotsikl. Soedin., No. 2, 240 (1978).
75. V. M. Potapov, G. V. Grishina, and T. A. Gudasheva, Khim. Geterotsikl. Soedin., No. 1, 101 (1980).
76. G. V. Grishina, V. M. Potapov, and T. V. Tyrtysh, Khim. Geterotsikl. Soedin., No. 3, 389 (1984).
77. I. N. Azerbaev, K. B. Erzhanov, T. S. Sadykov, N. P. Polatbekov, and V. P. Reshetov, Material from International Symposium of CMEA Member Countries [in Russian], Pushchino (1975), Part 1, p. 148.
78. S. A. Abdulganeeva, G. V. Grishina, V. M. Potapov, K. B. Erzhanov, and A. A. Shapovalov, Khim. Geterotsikl. Soedin., No. 4, 501 (1983).