Chemistry of Heterocyclic Compounds, Vol. 31, No. 8, 1995

SYNTHESIS AND STEREOCHEMISTRY OF CHIRAL 2-AZETIDINONES AND 2-AZETIDINETHIONES. 2.* STUDY OF THE CHIROPTICAL PROPERTIES OF SOME 2-AZETIDINONES

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Circular dichroism (CD) spectra were taken for 13 2-azetidinones with one, two, and three asymmetric sites. A possible correlation was found between the sign of the Cotton effect (CE) of the $n-\pi^*$ *transition of the amide chromophore with the absolute configuration of the endocyclic stereocenters of 3-methyl-, 4-methyl-, and 3,4-dimethyl-2-azetidinones both with and without an achiral N-α,α-dimethylbenzyl or chiral N-α-methylbenzyl substituent.*

The literature data on the chiroptical properties of the simplest monocyclic 2-azetidinones are rather sparse and limited predominantly to derivatives without substituents at the nitrogen atom [2-4] and N-aryl derivatives [5]. Somewhat greater attention has been given to bicyclic models [6, 7] and azetidinones with additional functional groups or heteroatomic substituents [7-9]. A rather extensive series of monocyclic β-lactam stereoisomers became available as the result of our previous study on the chemistry and stereochemistry of chiral 2-azetidinones. These products may be divided into three types:

1) compounds without substituents at the nitrogen atom,

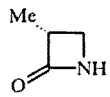
2) lactams containing an achiral α,α-dimethylbenzyl substituent at the nitrogen atom, and

3) azetidinones bearing a chiral α-methylbenzyl group at the nitrogen atom.

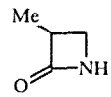
The absolute configuration for most of these compounds were established in our previous work [10, 12] as well as by Jensen [2, 14] and Kampe [15]. These findings permit us to evaluate the applicability of various sector rules for stereochemical assignment by analyzing the chiroptical properties of 2-azetidinones.

CIRCULAR DICHROISM SPECTRA OF β-LACTAMS WITH ENDOCYCLIC ASYMMETRIC CENTERS

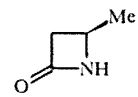
In studying the chiral properties of the 2-azetidinones synthesized in our laboratory, we began with their simplest representatives, namely, 3- (I) and 4-methyl-2-azetidinones (II), which lack substituents at the nitrogen atom.



(3*R*)-I



(3*S*)-I



(4*R*)-II

*Communication 1, see ref. [1].

M. V. Lomonosov Moscow State University, 119899 Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1059-1077, August, 1995. Original article submitted July 29, 1995.

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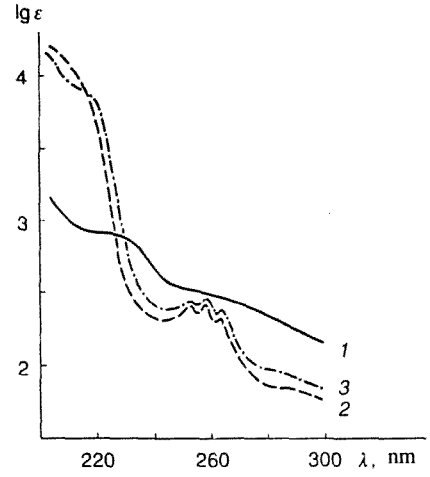
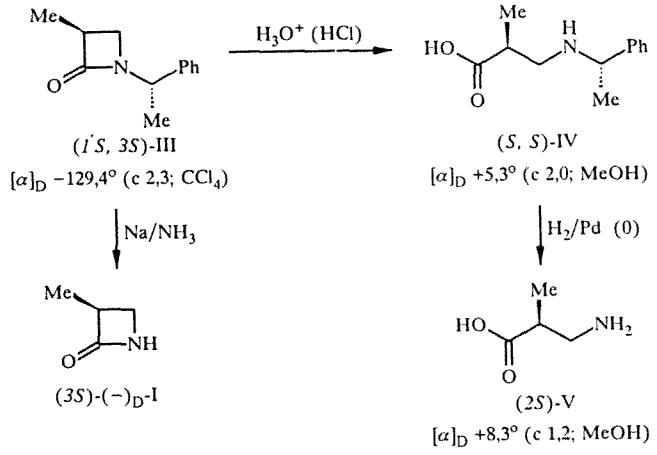


Fig. 1. Electronic absorption spectra of 3-methyl-2-azetidinone (I) (*1*), 1-(α-methylbenzyl)-2-azetidinone (XIV) (*2*), and 4-methyl-1-(α-methylbenzyl)-2-azetidinone (XIV) (*3*) taken in hexane.

Both enantiomers of II have already been isolated [14, 15] and their CD spectra have been described [2]. Enantiomer (*4R*)-II [12] was used here for comparison. Both enantiomers of 3-methyl-2-azetidinone I were first obtained in our laboratory [11, 13] although a brief communication concerning the synthesis of racemic β-lactam (*R,S*)-I without spectral data was published initially by Okano et al. [16].

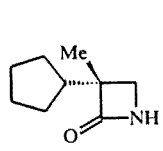
In order to establish the absolute configuration of the enantiomers of this azetidinone, $(+)_D$-I and $(-)_D$-I, we carried out the hydrolytic cleavage of the β-lactam ring of N-(*S*)-α-methylbenzyl diastereomer $(+)_{235}^{CD}$-III, which is related to $(-)_D$-I (see Scheme 1). Subsequent removal of the N-(*S*)-methylbenzyl substituent in the N-substituted β-amino acid IV obtained in the first step by its hydrogenolysis over Pd(0) leads to the $(+)_D$ enantiomer of β-aminoisobutyric acid V, whose (*S*) configuration has been established by Okamoto et al. [17].

Scheme 1

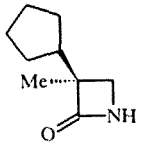


Since none of the transformations in the above scheme affects the asymmetric site at $C_{(3)}$, this permits us to assign absolute configuration (*1S,3S*)-III and (*1'S,2S*)-IV to starting isomer $(+)_{235}^{CD}$-III with specific rotation $[\alpha]_D = -129.4°$ and intermediate N-substituted β-amino acid $(+)_D$-IV, respectively. The removal of the chiral substituent at the nitrogen atom in azetidinone $(+)_{235}^{CD}$-III by the action of sodium in liquid ammonia gives $(-)_D$-I, which is the basis for assigning (*3S*) configuration to this derivative. Thus, the $(+)_D$ enantiomer of 3-methyl-2-azetidinone I has (*3R*) configuration.

We should note that the chiroptical properties of 3-monosubstituted azetidinones lacking a substituent at the nitrogen atom have not yet been studied. CD spectra have been reported only for two enantiomers of a 3,3-disubstituted β-lactam, namely, 3-methyl-3-cyclopentyl-2-azetidinone (VIa,b), whose absolute configurations are unknown [3].



VIa



VIb

Compounds such as I, II, and VI contain only the amide chromophore within the four-membered ring. Theoretical analysis and experimental study of the electronic absorption, optical rotary dispersion (ORD), and CD spectra of amides, in general [18-20], and lactams, in particular [7, 21-23], predict two major bands corresponding to the $n-\pi^*$ (210-230 nm) and $\pi-\pi^*$ transitions (175-200 nm) of the amide chromophore in the UV region available for measurement. In some cases, an additional band arises in the intermediate region (205-215 nm), whose assignment has been the subject of discussion [6, 7, 24]. This band may be either an $n-\sigma^*$ transition [25] or Ridberg $n-3s$ absorption [26]. This appearance of this "mystery band" is probably a consequence of amide aggregation since it disappears upon dilution [25, 27].

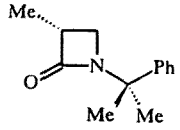
Taking account of this behavior and the low concentration of the solutions used in our spectral studies, the well resolved shoulder at 220-230 nm in the absorption spectrum of azetidinone (*R,S*)-I measured in hexane (Fig. 1, curve *1*) may be assigned to the $n-\pi^*$ transition of the amide chromophore. The relatively high intensity of this shoulder ($\log \varepsilon \sim 2.93$) is a consequence of the strong $\pi-\pi^*$ transition band of the amide group, whose maximum is probably below 200 nm.

The CD spectra of the two enantiomers of 3-methyl-2-azetidinone (*3S*)-I and (*3R*)-I show positive and negative dichroic absorption at 200-250 nm, respectively (Fig. 2, curves *1* and *2*). Despite the unfavorable ratio of the relatively weak dichroic and strong isotropic absorption, a negative maximum at 204 nm with $\Delta\varepsilon = -0.9$ may be observed in the CD spectrum of (*3R*)-I taken in methanol. We may assume that this dichroic maximum is a consequence of the $n-\pi^*$ transition of the amide chromophore. This is in accord with the assignment of the negative dichroic maximum at 216 nm in CD spectrum of methylazetidinone (*4R*)-II, which has similar electronic structure, taken in heptane to the $n-\pi^*$ transition. For convenience of comparison, the CD spectrum of β-lactam (*4R*)-II taken in methanol is shown in Fig. 2 (curve *3*). The long-wavelength dichroic maximum in the CD spectrum of (*4R*)-II undergoes a hypsochromic shift with increasing solvent polarity from 216 nm in heptane [2] to 211 nm in methanol ($\Delta\varepsilon \sim 2.1$), which is evidence for its assignment to an $n-\pi^*$ transition. An additional argument for this assignment is found in the dichroic extrema in the CD spectra of the indicated two enantiomers of the fully aliphatic 3,3-disubstituted β-lactam VIa and VIb, corresponding to $n-\pi^*$ (213 nm) and $\pi-\pi^*$ transitions (186 nm). These extrema have opposite signs and significantly different intensity (for one of the enantiomers of VI, $\Delta\varepsilon_{213}$ 0.65, $\Delta\varepsilon_{186}$ −2.83) [3].

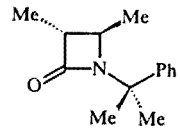
Since the absolute configuration of (*3S*)-I was established in our laboratory independently (see Scheme 1), we may conclude that the $n-\pi^*$ transition of the amide chromophore has positive rotatory strength in the case of the (*3S*) enantiomer of I and negative rotatory strength in the case of (*3R*)-I as in the case of (*4R*)-II [2].

The low optical activity of compounds such as I, II, and VI is readily explained if we take account of the virtually planar structure of the four-membered β-lactam ring, which was demonstrated by the x-ray diffraction structural analysis of several compounds of this class [28, 29], the small volume of the methyl group, which distorts the chromophore symmetry, and the significant overlap of the two close-lying dichroic bands with opposite signs. The latter was confirmed both theoretically [7] and experimentally for several N-substituted mono- and bicyclic β-lactams.

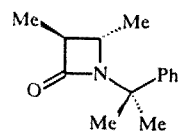
Let us now examine the chiroptical properties of several 2-azetidinones containing an achiral α,α-dimethylbenzyl substituent at the nitrogen atom with one (VII) or two substituents (VIII) in the β-lactam ring. We should note that these compounds are by-products of methylation at $C_{(3)}$ of the β-lactam ring of the lithium derivatives of the corresponding homochiral N-α-methylbenzyl-2-azetidinones [11, 12]. The absolute configuration of the two enantiomers of *trans*-3,4-dimethyl-β-lactams VIII was established in our laboratory [11, 12], while the configuration of one of the enantiomers of $(-)^{CD}_{220}$-VII is unknown.



$(-)_{220}^{CD}$-VII



(*3R, 4R*)-VIII



(*3S, 4S*)-VIII

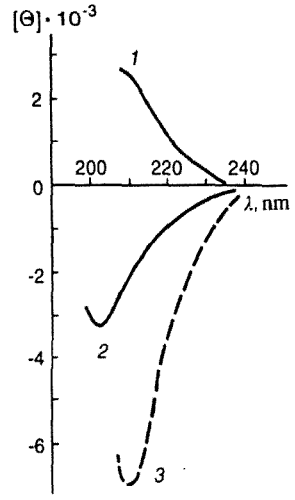
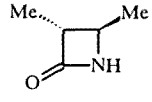


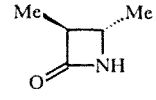
Fig. 2. CD spectra of (*3S*)- (*1*) and (*3R*) enantiomers (*2*) of 3-methyl-2-azetidinone (I) and of (*4R*)-methylazetidinone (II) (*3*) taken in methanol.

Azetidinones VII and VIII contain an aromatic chromophore in the exocyclic N-substituent in addition to the amide chromophore. This aromatic chromophore is seen, for example, in the absorption spectrum of azetidinone VII as characteristic elements of the vibrational structure on the weak band of the aromatic ^1L_b transition at 250-270 nm (Fig. 3).

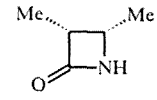
A rather favorable ratio of the intensities of the dichroic and isotropic absorption obtains in the case of 3,4-disubstituted 2-azetidinones containing an achiral N-substituent such that the maximum of the band corresponding to the $n-\pi^*$ transition may be measured entirely for both enantiomers of *trans*-3,4-dimethyl derivatives (*3S,4S*)-VIII and (*3R,4R*)-VIII (Fig. 4, curves 2-5) despite the reduced optical purity of the (*3R,4R*) enantiomer. The characteristic hypsochromic shift of this band with increasing solvent polarity from 232 nm in heptane (curves *2* and *4*, respectively) to 223 nm in methanol (curves *3* and *5*, respectively) justifies the assignment of these dichroic extrema to the $n-\pi^*$ transition. For comparison, the dichroic maximum at 218 nm in the CD spectrum taken in heptane was assigned to the $n-\pi^*$ transition for the two enantiomers of the corresponding *trans*-3,4-dimethylazetidinone IX not substituted at the nitrogen atom [2].



(*3R, 4R*)-IX



(*3S, 4S*)-IX



(*3R, 4S*)-IX

Unfortunately, the optical activity of the ^1L_b transition of the aromatic chromophore could not be reliably established in any of these cases, possibly as a consequence of its considerable distance from the stereogenic centers in VII and VIII.

A negative dichroic maximum shifted to 217 nm is found in the CD spectrum of N-(α,α-dimethylbenzyl) β-lactam $(-)_{220}^{CD}$-VII (Fig. 4, curve *1*), which has much lower intensity ($\Delta\varepsilon$ −0.8 in methanol) than for analogs with disubstituted rings. This intensity is close to that found for N-unsubstituted azetidinone (*3R*)-I (Fig. 2, curve *2*). By analogy with I, II, and VIII examined above, this extremum should be assigned to an $n-\pi^*$ transition.

We might think that the increase in the rotatory strength of the $n-\pi^*$ transition in the case of 3,4-disubstituted VIII is due to slight chiral twisting of the amide chromophore induced by the *trans* arrangement of the substituents in the ring and steric repulsion between the bulky N-substituents and close-lying methyl group at $C_{(4)}$. Indeed, the analogous N-α,α-dimethylbenzyl derivative of 3-monomethyl-2-azetidinone $(-)_{220}^{CD}$-VII, in which the substituents at the nitrogen atom and $C_{(3)}$ do not interact sterically, has very low dichroic absorption (see Fig. 4, curve *1*). On the other hand, Rehling and Jensen [2] have reported that the dichroic maximum at 218 nm in the CD spectra of the enantiomers of N-unsubstituted *trans*-3,4-dimethylazetidinones (*3S,4S*)-IX and (*3R,4R*)-IX, corresponding to the $n-\pi^*$ transition, has high intensity: $\Delta\varepsilon = +4.3$ and -4.6, respectively, in comparison with $\Delta\varepsilon = +1.2$ for *cis*-dimethyl-2-azetidinone (*3R,4S*)-IX, in which chiral twisting of the ring is impossible.

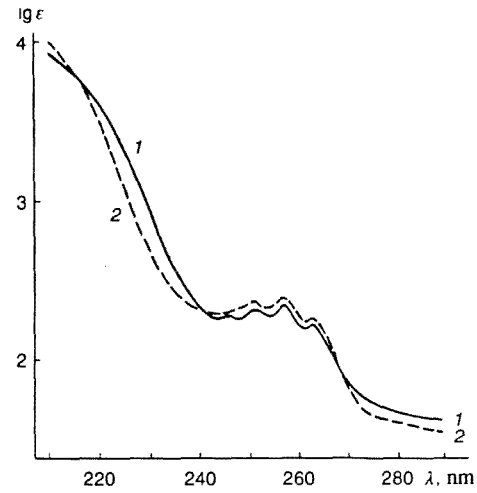


Fig. 3. Electronic absorption spectra of 3-methyl-1-(α,α-dimethylbenzyl)azetidinone VII taken in methanol (*1*) and cyclohexane (*2*).

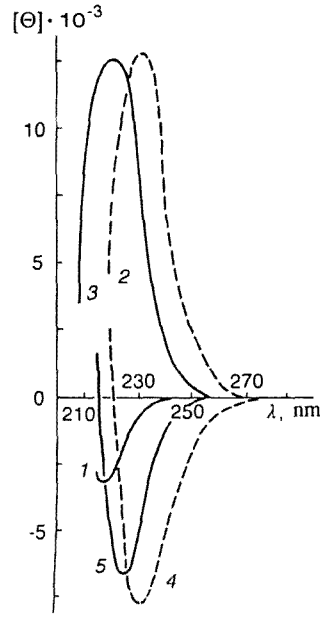
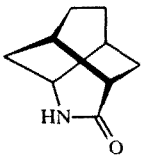


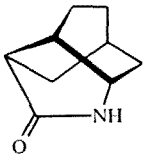
Fig. 4. CD spectra of the $(-)_{220}^{CD}$ enantiomer of 3-methyl-1-(α,α-dimethylbenzyl)azetidinone VII in methanol (*1*) and of the (*3S,4S*) (*2, 3*), and (*3R,4R*) enantiomers (*4, 5*) of *trans*-3,4-dimethyl-(α,α-dimethylbenzyl)azetidinone VIII taken in heptane (*2, 4*) and methanol (*3, 5*).

The significant effect of twisting of the amide chromophore in four-, five-, and six-membered lactams on their optical activity has been confirmed both by quantum chemical calculations for the dependence of the rotatory strength on the $C_{(3)}-C_{(2)}-N-C_{(1')}$ [7, 30] and experimentally, for example, by studying the chiroptical properties of two tricyclic lactams, namely, (−)-(*3S*)-4-azatricyclo[4.4.0.$0^{3,8}$]decan-5-one (*5S*)-X [31] and (+)-(*3S*)-4-azatricyclo[4.3.1.$0^{3,7}$]decan-5-one (*3S*)-XI [26], for which this angle is 14.5° and 1.2°, respectively, as indicated by x-ray diffraction structural analysis.



(−)-(3*S*)-X

ω 14,5°



(+)-(3*S*)-XI

ω 1,2°

Such distortions convert the formally achiral planar amide chromophore into an internally disymmetric twisted chromophore. This effect is especially pronounced in the case of six-membered δ-lactams [30].

Analysis of the chiroptical properties of our compounds shows that the same correlation of the sign of the Cotton effect of the $n-\pi^*$ transition with the absolute configuration of the endocyclic stereocenters is found for *trans*-3,4-dimethyl-2-azetidinones VIII containing an achiral N-α,α-dimethylbenzyl substituent as for the corresponding compounds lacking substituents at the nitrogen atom. Specifically, the sign of the Cotton effect of the $n-\pi^*$ transition is negative in the CD spectra of (*3R,4R*)-VIII, while the Cotton effect for the same transition is positive for (*3S,4S*)-VIII.

Analysis of the ellipticity at the maximum corresponding to the $n-\pi^*$ transition in pairs of 2-azetidinones with and without an N-substituent indicates that, for all types of ring substitution (3-Me, 4-Me, and 3,4-Me_2), the introduction of an N-α,α-dimethylbenzyl group has a relatively weak effect on the chiroptical properties of β-lactam compounds. In the case of compounds both with and without an achiral N-substituent, the Cotton effect of the $n-\pi^*$ transition in the CD spectra of 3- and 4-alkyl 2-azetidinones with (*S*) configuration and *trans*-3,4-dialkyl-2-azetidinones with (*S,S*) configuration should have a positive sign, while it should be negative in the spectra of (*3R*), (*4R*), and *trans-(3R,4R)* antipodes. This behavior may then be used for determining the absolute configuration of new alkyl-substituted β-lactams assuming reliable identification of the $n-\pi^*$ transition in their CD spectra. Thus, for example, we may assume that the $(-)_{220}^{CD}$ enantiomer of 3-monomethyl β-lactam with an achiral N=α,α-dimethylbenzyl substituent VII displaying a negative Cotton effect in the CD spectrum (Fig. 4, curve 1) has (*3R*) absolute configuration.

APPLICATION OF CHIRALITY RULES FOR ESTABLISHING THE ABSOLUTE CONFIGURATION OF N- AND/OR C-SUBSTITUTED 2-AZETIDINONES

An accepted approach for establishing the absolute configuration of various types of compounds involves use of the corresponding semiempirical chirality rules relating the sign of the Cotton effect of a given electronic transition in a chromophore group to the position of the substituents perturbing the symmetry of this chromophore [32].

Considerable attention has been given to theoretical analysis of the chiroptical properties of compounds with the amide chromophore beginning with the classic studies of Schellman [18-20] since the optical activity of this chromophore is often used in studying the stereochemistry of polypeptide structures. Several empirical and semiempirical pathways have been proposed for cyclic amides (lactams) for correlating the sign of the Cotton effect of the $n-\pi^*$ transition of the amide group with absolute configuration [23, 24, 30, 33].

These approaches include the Schellman quadrant rule for the amide chromophore [19, 34] based on the perturbation theory of an internally symmetrical (C_{2v}) chromophore. This rule was tested initially for a five-membered lactam, namely, 3-amino-2-pyrrolidone [19] and later extended to β-lactams [2]. It is a simplified variant of the octant rule for carbonyl compounds [32, 33], in which only four distant octants are examined (Fig. 5*a*). Subsequently, Weigang et al. [24] proposed a modification of this rule taking account of the actual reduction in symmetry of the amide chromophore (to C_S) in comparison with the carbonyl chromophore, which required replacement of one of the nodal planes by a spherical surface. This variant of the modified quadrant rule was tested for five- and six-membered lactams.

In order to apply the quadrant rule to 2-azetidinone, the four-membered ring is placed in one of two mutually perpendicular planes (dividing all space into quadrants of alternating signs) such that the symmetry axis of the carbonyl group coincides with the intersection of these nodal planes, while the amide nitrogen atom is located to the right (Fig. 5*a*). The substituents lying in the upper right and lower left sectors should give a negative contribution to the optical activity, while the upper left and lower right sectors should give a positive contribution. We should note that, as a result of the difference in bond lengths, which is obvious *a priori* and confirmed by an x-ray diffraction structural analysis of several N-aryl- [29] and N-aroyl-2-azetidinones [28], the β-lactam ring is deformed such that $C_{(4)}$ is outside the nodal plane of the *n*-orbitals of the car-

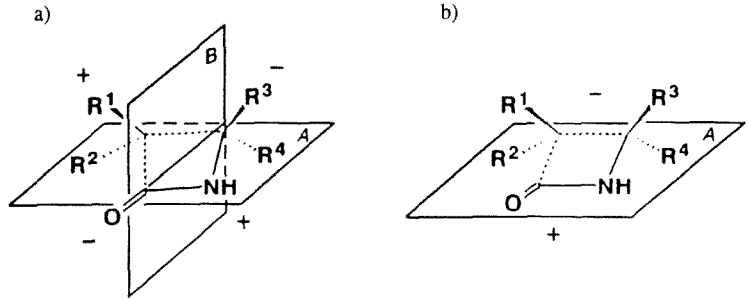


Fig. 5. Application of the quadrant (*a*) and lactam chirality rules (*b*) for 2-azetidinone with an unsubstituted nitrogen atom.

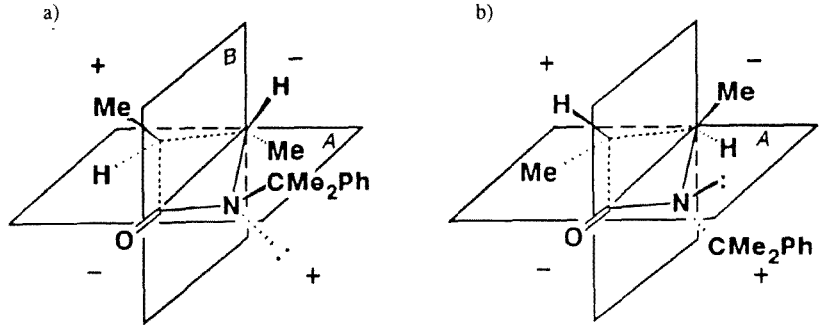


Fig. 6. Application of the quadrant chirality rule for *(3S,4S) (a)* and *(3R,4R)* enantiomers (*b*) of *trans*-3,4-dimethyl(α,α-dimethylbenzyl)azetidinone (VIII).

bonyl group (plane *B*, Fig. 5*a*). As a consequence, substituents located at $C_{(4)}$ of the β-lactam ring may also make a contribution to the optical activity [2].

A natural limitation of the quadrant rule is its inapplicability to *cis*-3,4-disubstituted 2-azetidinones with the same substituents at adjacent stereocenters. In this case, the substituents perturbing the symmetry of the chromophore lie in sectors with opposite signs and their contributions compensate for each other, leading to the prediction of zero optical activity, which is not observed [2, 35].

A second, simpler sector rule proposed by Ogura and coworkers for four-, five-, and six-membered cyclic amides [35-38] has been termed the lactam rule. In the particular case of β-lactams [35, 37], the four-membered ring is placed in a single zero plane (*A*) such that the amide nitrogen atom is in front of the observer from the right, while the carbonyl group is in front of the observer from the left (Fig. 5*b*). The substituents located above this plane make a negative contribution to the optical activity of the $n-\pi^*$ transition of the amide chromophore, while substituents below the plane make a positive contribution. The chiroptical properties of *trans*-3,4-disubstituted 2-azetidinone with the same substituents cannot be examined in the framework of this rule due to mutual compensation of the contributions of the two identical groups located in sectors with opposite signs.

Thus, neither the lactam rule nor the quadrant chirality rule can be considered general. Each of these rules is operative only for certain types of ring substitution. Hence, determination of the applicability of the reported sector rules for simple 3-monosubstituted β-lactams and their N-substituted derivatives is an outstanding problem.

In accord with the data of Jensen [2] and Ogura [35], both the lactam and quadrant rules lead to the proper prediction of the sign of the Cotton effect of the $n-\pi^*$ transition for enantiomers of 4-methyl-2-azetidinone (II): a negative sign for the *(4R)* configuration [Fig. 5*a,b*, R^3 = Me (here and subsequently, substituents R^n = H) unless otherwise indicated] and a positive sign for *(4S)*-II (Fig. 5*a,b*; R^4 = Me).

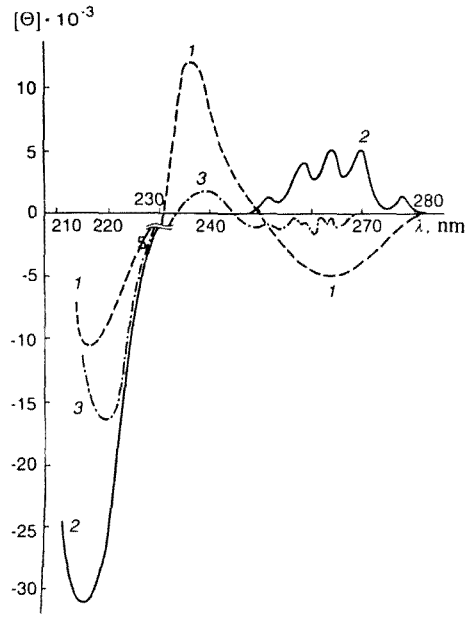


Fig. 7. CD spectra of *(1'S)*-(α-methylbenzyl)azetidinone (XIV) taken in heptane *(1)*, methanol *(2)*, and dioxane *(3)*. The long-wavelength fragments of the spectra are given with 20-fold enlargement.

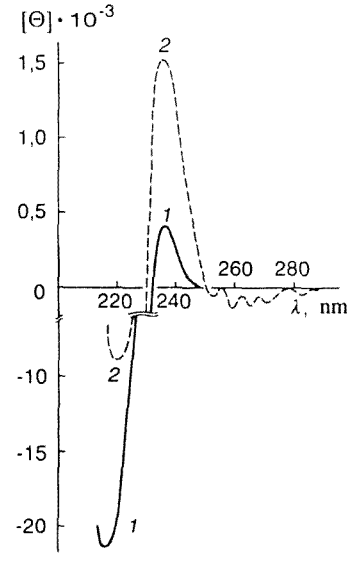


Fig. 8. CD spectra of *(1'S,3S)*-3-methyl-1-(α-methylbenzyl)azetidinone (III) taken in dioxane *(1)* and heptane *(2)*. The long-wavelength fragments of the spectra are given in 10-fold enlargement.

The absolute configuration of *trans*-3,4-dialkyl-substituted 2-azetidinones may be predicted using the quadrant rule [2]. However, its applicability for N-substituted analogs of such structures has not yet been examined. We were able to fill this gap using CD data for two enantiomers of N-(α,α-dimethylbenzyl)-*trans*-3,4-dimethylazetidinone VIII obtained from compounds with known absolute configuration [12].

The quadrant rule predicts a positive Cotton effect for the *(3S,4S)* enantiomer of β-lactam VIII since both the 3-Me and 4-Me ring substituents fall in positive sectors (Fig. 6*a*). If the nitrogen atom has sp^2 hybridization, the α-benzyl carbon

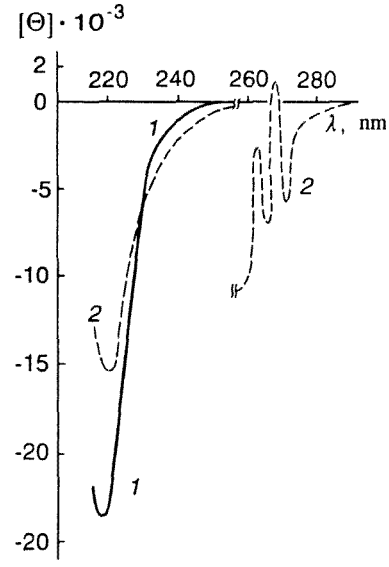


Fig. 9. CD spectra of *(1'S,3R)*-3-methyl-1-(α-methylbenzyl)-azetidinone (III) taken in dioxane *(1)* and heptane *(2)*. The long-wavelength fragment of curve *2* is given in 200-fold enlargement.

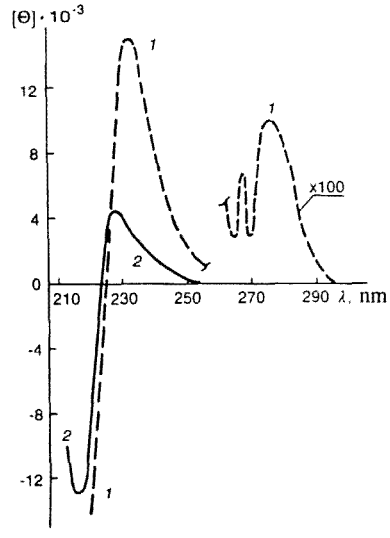
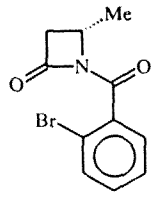


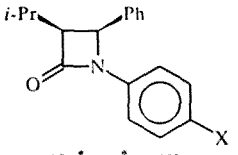
Fig. 10. The CD spectra of *(1'S,4S)*-4-methyl-1-(α-methylbenzyl)-azetidinone (XV) taken in heptane *(1)* and methanol *(2)*. The long-wavelength part of curve *1* is enlarged by 100-fold.

of the N-(α,α-dimethyl)benzyl group should lie in nodal plane *A*. In this case, with an equal population of rotamers of the N-substituent, it should not make a contribution to the optical activity.

The situation is somewhat different if the hybridization of the nitrogen atom is altered from sp^2 to sp^3, i.e., with some pyramidalization of its environment. Evidence for the possibility of such distortions is found in the results of the x-ray diffraction structural analysis of the following N-aroyl- [28] and N-arylazetidinones [29].



(*4S*)-XII



(*3S**, *4R**)-XIII

a X = Cl, b X = Br

The angle in *(4S)*-XII and *(3S*,4R*)*-XIII formed by the exocyclic $N-C_{(1')}$ bond with the plane of the β-lactam ring varies from 7.7 to 9.3° despite the greater tendency of these compounds to retain sp^2 hybridization due to conjugation than for N-alkylazetidinones. This departure from planarity may be related to steric interactions between the substituents at the nitrogen atom and at $C_{(4)}$. Evidence for the effect of distortion of the amide chromophore on chiroptical properties is found in the above-mentioned tricyclic model of the twisted six-membered lactam *(3S)*-X, in which this angle is 14.5° [31].

It is reasonable to assume that such departures from planarity are also possible in the case of N-(α,α-dimethylbenzyl)-*trans*-3,4-dimethyl-2-azetidinones VIII examined in our laboratory. As a result of the extrusion of the substituent at the nitrogen atom from the zero plane *A*, it may give an additional contribution to the optical activity. In the special case of *(3S,4S)*-VIII, the presence of a substituent at $C_{(4)}$ should dictate favored transoid arrangement of the N-(α,α-dimethyl)benzyl fragment relative to the methyl group at $C_{(4)}$ in the negative sector (Fig. 6*a*). This should lead to some decrease in the positive Cotton effect in the CD spectrum of β-lactam *(3S,4S)*-VIII in comparison with the value reported for N-unsubstituted *trans-(3S,4S)*-3,4-dimethyl-2-azetidinone IX [2]. This hypothesis is in complete accord with the experimental dichroic absorption at the maximum of the band for the $n-\pi^*$ transition: $\Delta\varepsilon = +3.8$ for *(3S,4S)*-VIII in comparison with $\Delta\varepsilon = +4.3$ for *(3S,4S)*-IX.

Analogously, the quadrant rule predicts the negative Cotton effect for the *(3R,4R)* enantiomer of VIII (Fig. 6*b*), which is in accord with the experimental data (Fig. 4, curves *4*, *5*).

Since the absolute configurations of the *(3R,4R)* and *(3S,4S)* enantiomers of VIII were determined independently in our laboratory [12], we may conclude that the quadrant rule is applicable not only for azetidinones with *trans*-3,4 configuration not substituted at the nitrogen atom but also for analogous β-lactam structures with an achiral benzyl substituent at the nitrogen atom. Although the contribution to the optical activity of this class is opposite to the contribution from the two endocyclic stereocenters, since this value is slight even for such a bulky substituent as the α,α-dimethylbenzyl group, we may propose that the applicability of the quadrant rule for N-substituted azetidinones should obtain for a rather broad range of N-substituent structures.

As noted above, the chiroptical properties of 3-monosubstituted 2-azetidinones have not been described previously and, thus, the question of the applicability of sector rules for such systems has naturally not been discussed.

An attempt to apply Ogura's lactam rule [35, 37] for the two enantiomers of 3-methyl-2-azetidinone (I) gave signs for the Cotton effect opposite to the experimental signs. Thus, the lactam rule predicts a positive Cotton effect for the *(3R)* enantiomer of I (Fig. 5*b*, R^2 = Me), while a negative long-wavelength dichroic maximum is observed in the CD spectrum of *(3R)*-I (Fig. 2, curve *2*). Analogously, the predictions of the lactam rule for the *(3S)* enantiomer of I are also not in accord with the experimental values (Fig. 2, curve *1*).

On the other hand, the quadrant rule is entirely applicable for predicting the correlation between the absolute configuration of the $C_{(3)}$ site and the sign of the Cotton effect of the $n-\pi^*$ transition of the amide chromophore in the case of 3-monosubstituted 2-azetidinone I. This rule predicts a negative Cotton effect for the *(3R)* enantiomer of I (Fig. 5*a*, R^2 = Me) and the opposite Cotton effect for the *(3S)* enantiomer of I (Fig. 5*a*, R^1 = Me), which is in accord to the experimentally observed signs of the dichroic absorption at 220-240 nm (Fig. 2, curves *2* and *1*, respectively).

Since the absolute configurations of both enantiomers of 3-methyl-2-azetidinone I were established in our laboratory by chemical methods, we may conclude that their optical activity may be correctly described only in the framework of the quadrant rule, while the simple lactam rule is inapplicable for 3-monosubstituted 2-azetidinones. This result is probably a consequence of the specific features of the four-membered cyclic amides since the correlation of the sign of the Cotton effect of the $n-\pi^*$ transition with the absolute configuration for five-, six-, and seven-membered lactams is usually carried out in the framework of the simple lactam rule [30, 33, 35, 38].

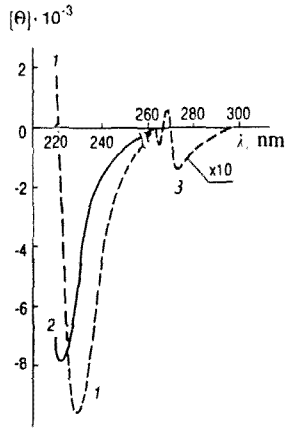


Fig. 11. CD spectra of *(1'S,4R)*-4-4-methyl-1-(α-methylbenzyl)-azetidinone (XV) taken in heptane *(1)*, methanol *(2)*, and dioxane *(3)*. The long-wavelength fragment of curve *3* is enlarged by 10-fold.

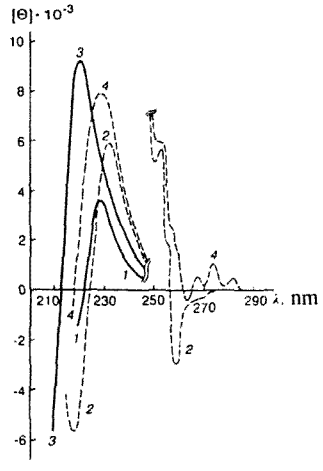


Fig. 12. CD spectra of *(1'S,3S,4S)* *(1, 2)* and *(1'R,3S,4S)* diastereomers *(3, 4)* of *trans*-3,4-dimethyl-1-(α-methylbenzyl)-azetidinone (XVI) taken in heptane *(1, 3)* and methanol *(2, 4)*. The long-wavelength fragments of curves *2* and *4* are enlarged 10-fold.

In light of the applicability of the quadrant rule for 3-monosubstituted azetidinones lacking a substituent at the nitrogen atom as well as the only slight effect of the N-(α,α-dimethyl)benzyl substituent on the chiroptical properties even for *trans*-3,4-disubstituted β-lactams, we may use this rule for evaluating the absolute configuration of $(-)_{220}^{CD}$-3-methyl-1-(α,α-dimethylbenzyl)azetidinone (VII) formed in the asymmetrical methylation of *(1'S)*-N-α-methylbenzyl-2-azetidinone XIV [11]. The quadrant rule predicts a negative Cotton effect for the *(3R)* enantiomer of VII (Fig. 6*b*, R^2 = Me), while a positive Cotton effect should be expected for the *(3S)* enantiomer VII (Fig. 6*b*, R^1 = Me). The experimentally observed negative dichroic extremum in the CD spectrum for $(-)_{220}^{CD}$-VII at 220-240 nm (Fig. 4, curve *1*) permits assignment of the *(3R)* configuration.

We should note that the quantitative similarity of the CD spectra of *(3R)*-VII and 2-azetidinone *(3R)*-I lacking a substituent at the nitrogen atom (Figs. 4 and 2, respectively). This reconfirms the insignificance of the effect of the N-(α,α-dimethyl)benzyl substituent, which does not interact with the distant asymmetric center at $C_{(3)}$, to the optical activity.

TABLE 1. Parameters of the Band for the $n-\pi^*$ Transition in the CD Spectra of N- and/or C-Substituted 2-Azetidinones ($\Delta\varepsilon$ and λ_{max})

Compound	$\Delta\varepsilon$	λ_{max}, nm	Solvent	Compound	$\Delta\varepsilon$	λ_{max}, nm	Solvent
(*3S*)-I	> +0,8*[3]	< 210*[3]	Methanol	(*1'S,4S*)-XV	+4,6	232	Heptane
(*4S*)-II*[1]	+2,1	216	Heptane		+1,5	233	Dioxane
(*3S,4S*)-V*[2]	+4,3	218	Heptane		+1,2	225	Methanol
(*3R,4S*)-V*[1]	+1,2	219	Heptane	(*1'S,3S,4S*)-XVI	+1,8	232	Dioxane
(*3R*)-I	-0,9	204	Methanol		+1,1	227	Methanol
(*4R*)-II*[1]	-2,3	216	Heptane	(*1'R,3S,4S*)-XVI	+3,6	230	Heptane
	-2,1	211	Methanol		+2,4	228	Dioxane
(*3S,4S*)-VIII	+3,9	232	Heptane		+2,8	220	Methanol
	+3,8	223	Methanol	(*1'S,3R*)-III	(-)*[4]		Heptane
(*3R*)-VII	-0,8	217	Methanol		(-)*[4]		Dioxane
(*3R,4R*)-VIII	-2,4	232	Heptane	(*1'S,4R*)-XV	-2,9	230	Heptane
	-2,0	225	Methanol		-2,4	222	Methanol
(*1'S*)-XIV	+0,23	238	Heptane				
	+0,03	242	Dioxane				
(*1'S,3S*)-III	+0,45	236	Heptane				
	+0,12	236	Dioxane				
	+0,25	246	Methanol				

*[1]Data from Jensen [2].

*[2]Data from Busson [8].

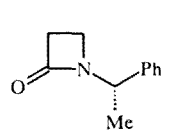
*[3]The dichroic maximum could not be measured due to unfavorable ratio of the dichroic and isotropic absorption.

*[4]The negative dichroic extremum is overlapped by the stronger band for the ^1L_a transition of the same sign.

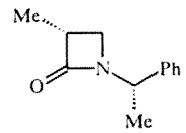
Thus, these results enable us to correlate the sign of the Cotton effect of the $n-\pi^*$ transition of the amide chromophore with the absolute configuration of monoalkyl- and *trans*-3,4-dialkyl-2-azetidinones both lacking a substituent at the nitrogen atom and with an achiral N-substituent in the framework of the quadrant rule.

CD SPECTRA OF 2-AZETIDINONES WITH EXO AND ENDO STEREOCENTERS

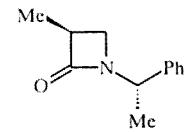
Let us now examine the chiroptical properties of N-(α-methylbenzyl)-2-azetidinones both lacking stereogenic sites in the ring such as XIV and with one endocyclic stereocenter at $C_{(3)}$ (III) or $C_{(4)}$ (XV) as well as analogous compounds containing two *trans*-arranged substituents in the β-lactam ring (XVI).



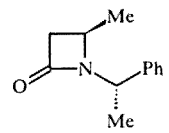
(*1'S*)-XIV



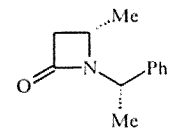
(*1'S, 3R*)-III



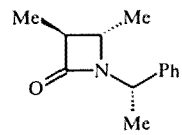
(*1'S, 3S*)-III



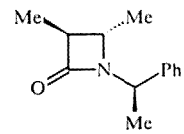
(*1'S, 4R*)-XV



(*1'S, 4S*)-XV



(*1'S, 3S, 4S*)-XVI



(*1'R, 3S, 4S*)-XVI

The spectral characteristics of azetidinones bearing the α-methylbenzyl substituent at the nitrogen atom are complicated stereochemically due to the additional exocyclic asymmetric site at $C_{(1')}$ and electronically due to the aromatic chromophore linked directly to this stereocenter. In such systems, we should expect two additional bands, namely a weak band corresponding to the ^1L_b (B_{2u}) transition and a strong band corresponding to the ^1L_a (B_{1u}) transition of the aromatic chromophore along with the band for the $n-\pi^*$ transition of the amide chromophore in the conveniently measured 210-300-nm region [32, 39, 40]. The CD spectrum of starting *(S)*-α-methylbenzylamine showed five dichroic extrema at 236-268 nm with $\Delta\varepsilon$ up to +0.18, corresponding to the ^1L_b electronic transition [41-43].

In accord with this finding, the absorption spectra of the simplest compound in this group, azetidinone XIV and its 4-methyl analog XV show a weak band (log $\varepsilon \sim 2.5$) at 245-265 nm with vibrational structure characteristic for the ^1L_b transition (Fig. 1, curves *2* and *3*). The high-intensity shoulder at 215-220 nm (log $\varepsilon > 4$) may be assigned to the allowed ^1L_a transition of the aromatic chromophore.

The $n-\pi^*$ transition of the amide chromophore cannot be observed in the absorption spectra of XIV and XV as a separate band with expected low intensity due to its overlap with the adjacent strong band of the allowed ^1L_a transition of the aromatic chromophore. The propinquity of these two bands corresponding to the $n-\pi^*$ and ^1L_a transitions also complicates the interpretation of the CD spectra of these azetidinones.

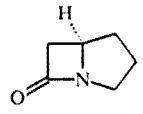
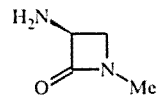
Nevertheless, despite the strong isotropic absorption, all three theoretically expected electronic transitions may be observed in the CD spectra of most of such compounds with given ratios of the absolute configurations of the endo- and exocyclic stereocenters.

Thus, for example, the CD spectra of the simplest of these azetidinones not containing a substituent in the β-lactam ring *(1'S)*-XIV (Fig. 7) contains dichroic bands corresponding to the three types of electronic transitions. The weak long-wavelength band with vibrational structure at 250-280 nm, which could not be detected in the spectra taken in methanol and dioxane, should be assigned to the prohibitted ^1L_b transition of the aromatic chromophore in light of its position, low intensity, and form. It is interesting to note that its sign as well as its intensity depend on the polarity of the solvent used and varies from negative in heptane to positive in methanol (Fig. 7, curves *1* and *2*, respectively). Such sensitivity to the nature of the solvent is probably related to change in the population of rotamers of the α-methylbenzyl group due to solvation of the carbonyl group of the azetidinone ring.

The strong short-wavelength negative dichroic extremum at 215-220 nm in the CD spectrum of model compound *(1'S)*-XIV (Fig. 7) should be assigned to the allowed ^1L_a transition of the aromatic chromophore on the basis of its intensity and position as well as in accord with its electronic spectrum (Fig. 1, curve *2*).

The $n-\pi^*$ transition of the amide chromophore in the CD spectrum of azetidinone *(1'S)*-XIV, which is most important for stereochemical correlations, is seen as a weak band in the intermediate range 235-245 nm. At first glance, the anomalous bathochromic shift of this extremum with an increase in the solvent polarity from 238 nm in heptane to 242 nm in dioxane (Fig. 7, curves *1* and *3*, respectively) and its absence in the spectrum taken in methanol (curve *2*) are attributed to the effects of overlap of two close-lying bands of opposite sign and markedly different intensity. Indeed, in such a situation, the observed position and intensity of the smaller of the two dichroic extrema of opposite signs should differ strongly from the true values due to strong deformation of the smaller band upon its fusion with the stronger neighboring band. A model of such situations of the fusion of two separate Gaussian bands with different characteristics [39] showed that the distortion of the spectral parameters of the weaker band becomes more significant with increasing approximation. Thus, the experimentally observed long-wavelength shift and decrease in the intensity of the $n-\pi^*$ transition in the CD spectrum of 2-azetidinone *(1'S)*-XIV taken in dioxane (Fig. 7, curve *3*) in comparison with the spectrum taken in heptane (curve *1*) are indirect evidence for the hypsochromic shift of this band with increasing solvent polarity expected for such electronic transitions. The finding that a Cotton effect for the $n-\pi^*$ transition could not be detected at all in the CD spectrum of this compound, *(1'S)*-XIV, taken in methanol is probably related to a further approximation of the maxima of the $n-\pi^*$ and ^1L_a transitions due to a hypsochromic shift of the former and increase in the intensity of the latter (Fig. 7, curve *2*). This leads to the complete masking of the weak positive band by the strong negative band.

Additional evidence for the identification of the $n-\pi^*$ transition is found in the circumstance that this assignment was made precisely for the dichroic band at 231 nm ($\Delta\varepsilon = -3.8$) observed in the CD spectrum of bicyclic azetidinone *(5S)*-XVII, which does not contain chromophores except for the amide group [6]. This conclusion was also supported by semiempirical quantum chemical calculations for a model N-methyl-substituted monocyclic azetidinone *(3S)*-XVIII [7].

(5S)-XVII (3S)-XVIII

Thus, the CD spectra of model compound *(1'S)*-XIV with an exocyclic stereocenter as the only source of chirality indicates that the *(S)*-α-methylbenzyl substituent at the nitrogen atom gives a positive contribution to the optical activity of the $n-\pi^*$ transition of the amide chromophore in β-lactam structures. This contribution is much less ($\Delta\varepsilon$ = 0.03-0.23) than that found previously for endocyclic stereocenters (see Table 1).

The optical activity of N-α-methylbenzyl derivatives of monomethylated azetidinones III and XV is a function of the presence of both exo- and endocyclic stereocenters. The CD spectra of the two diastereomers of 3-methyl-substituted β-lactam *(1'S,3S)*-III and *(1'S,3R)*-III, which differ in the absolute configuration of the endocyclic asymmetric carbon atom, are in accord with the hypothesis of additivity of the contributions of the $C_{(3)}$ and $C_{(1')}$ stereocenters to the optical activity of the $n-\pi^*$ transition (Figs. 8 and 9).

The CD spectra of the *(1'S,3S)* diastereomer of III (Fig. 8) are qualitatively similar to the CD spectra examined above of the simpler model with only one exocyclic stereocenter, *(1'S)*-XIV (Fig. 7). The spectrum of *(1'S,3S)*-III taken in heptane also contains the three expected bands, corresponding to the ^1L_a, $n-\pi^*$, and ^1L_b transitions at virtually the same wavelengths and with similar intensities (Fig. 8). The intensity of the positive dichroic maximum at 236 nm corresponding to the $n-\pi^*$ transition ($\Delta\varepsilon$ = 0.45) is twice that found for the model *(1'S)*-XIV with one stereocenter ($\Delta\varepsilon$ = 0.23). This indicates that the endocyclic stereocenter at $C_{(3)}$ in the case of *(S)* configuration also makes a positive contribution to the optical activity of the $n-\pi^*$ transition, whose magnitude is comparable to the positive contribution from the *(S)*-N-α-methylbenzyl substituent.

Assuming the additivity of two sources of chirality, we naturally expect that, upon change in the absolute configuration of one of the two stereocenters in III, the two contributions to the optical activity of the $n-\pi^*$ transition, which now have positive signs, may cancel each other out when they are comparable in magnitude. In complete accord with this hypothesis, the CD spectrum of diastereomer *(1'S,3R)*-III with absolute configuration at $C_{(3)}$ switched to positive does not show a dichroic band corresponding to the $n-\pi^*$ transition, which indicates a negative contribution to its optical configuration from the endocyclic stereocenter (Fig. 9). The shape, position, and intensity of the dichroic bands due to the aromatic ^1L_b and ^1L_a transitions are similar to those found for diastereomer *(1'S,3S)*-III.

The spectral characteristics of the pair of diastereomers of 4-methylazetidinone *(1'S,4S)*-XV and *(1'S,,4R)*-XV (Figs. 10 and 11) are qualitatively similar to those for the two isomers of the 3-methyl analog III examined above (Figs. 8 and 9). A significant quantitative difference is found in the intensity of the extremum related to the $n-\pi^*$ transition: $\Delta\varepsilon$ 0.45 and 4.6 for the *(S,S)* diastereomers of 3-Me and 4-Me β-lactams, respectively. This effect may be attributed to the steric interaction of the N-substituent with the 4-methyl group in *(1'S,4S)*-XV leading to restriction of the configurational mobility of the α-methylbenzyl group (rotation about the $N-C_{(1')}$ bond). Both aromatic transitions ^1L_b and ^1L_a in this case also probably have negative rotatory strength although the characteristic vibrational structure of the latter is seen in the region of positive ellipticity values due to the overlap of the ^1L_a transition on the long-wavelength branch by the stronger positive dichroic maximum of the $n-\pi^*$ transition (Fig. 10, curve *1*).

The sign of the Cotton effect of the $n-\pi^*$ transition in this pair of diastereomers is also positive in the case of the *(S)* configuration of the endocyclic center at $C_{(4)}$ (Fig. 10) and negative in the case of its *(R)* configuration (Fig. 11). As a consequence of its higher intensity and, thus, lower distortion due to overlap with the adjacent band of the aromatic ^1L_b transition, a "normal" solvent effect is observed in the CD spectra of both diastereomers of azetidinone XV: the hypsochromic shift of the maximum of the band for the $n-\pi^*$ transition by 7-8 nm occurs with increasing solvent polarity from heptane to methanol, which supports the reported assignment (Table 1).

The dichroic band corresponding to the $n-\pi^*$ transition in the CD spectra of both diastereomers with three asymmetric sites *(1'S,3S,4S)*-XV and *(1'R,3S,4S)*-XVI (Fig. 12), which differ only in the absolute configuration of the α-methylbenzyl substituent, in all cases, has positive rotatory strength in accord with the *(S)* configuration of the endocyclic stereocenters and independently of the absolute configuration of the exocyclic center. The short-wavelength shift of its maximum with increasing solvent polarity by 6-10 nm (Table 1) supports this assignment. The type of change in the ellipticity at the maximum of the band for the $n-\pi^*$ transition presupposes a positive contribution from the N-α-methylbenzyl substituent in the case of its *(1'R)*

configuration and negative in the case of its *(1'S)* configuration. The change in the sign of the contribution to the optical activity from the conformationally labile N-substituent in comparison with the previously found positive contribution for the ring-unsubstituted model *(1'S)*-XIV supports the possibility of a significant change in the population of the N-substituent rotamers due to its steric interaction with the 4-methyl group. Nevertheless, the magnitude of the contribution to the optical activity of the $n-\pi^*$ transition from the N-α-methylbenzyl substituent remains slight in comparison with the contribution from the endocyclic stereocenters, which determine the sign of the Cotton effect of this transition.

Thus, comparison of the chiroptical properties of azetidinones bearing an α-methylbenzyl group on the nitrogen atom with their absolute configurations established by independent methods shows a clear correlation of the sign of the Cotton effect of the $n-\pi^*$ transition of the amide chromophore with the absolute configuration of the endocyclic stereocenters, independently of the stereochemistry of the chiral N-α-methylbenzyl substituent (see, for example, Fig. 12). As in the case of azetidinones not containing a substituent at the nitrogen atom or bearing an achiral N-substituent, the $n-\pi^*$ transition has negative rotatory strength in this group of compounds with *(R)* or *(R,R)* configuration of the $C_{(3)}$ and/or $C_{(4)}$ stereocenters. However, in the case of *(S)* or *(S,S)* configuration of the endocyclic stereocenters, the Cotton effect of this transition is positive. This is entirely in accord with the predictions based on the quadrant rule (Fig. 6*a,b*) taking account of the contribution of only the asymmetric sites of the β-lactam ring.

Thus, the chiroptical properties of very different types of 3- and 4-monomethyl- and 3,4-*trans*-dimethylazetidinones both unsubstituted at the nitrogen atom and bearing an achiral or chiral N-substituent may be described using the quadrant rule on condition of reliable identification of the $n-\pi^*$ transition of the β-lactam chromophore. A study of thio analogs of 2-azetidinones has been undertaken to provide further evidence for our assignments.

EXPERIMENTAL

The CD spectra were taken on a JASCO J-20 polarimeter in cells with pathlength 10, 1, and 0.1 mm. The electronic absorption spectra were taken on a Varian Cary-15 spectrophotometer.

***(1'S,3S)*-N-(α-Methylbenzyl)-3-methyl-2-azetidinone (III)** was obtained by the method described in our previous work [10] with specific rotation $[\alpha]_D$ −129.4° (c 2.3, CCl_4).

***(3²S,2S)*-N-(α-Methylbenzyl)-β-aminoisobutyric Acid (IV).** A solution of 0.209 g (1.1 mmole) azetidinone $(-)_D$-(III) (with negative dichroic absorption at 235 nm in the CD spectrum taken in methanol) in 35 ml 6 N hydrochloric acid was heated at reflux in an argon stream for 3 h. The reaction mixture was evaporated to dryness in vacuum. The residue was dissolved in 3 ml water and placed on a 1×8-cm column packed with Serva Dowex ion-exchange resin (20/50 mesh). The column was flushed with 0.1 N hydrochloric acid and then distilled water (until chloride ion was no longer detected in the wash water). The amino acid was eluted with 0.2 N aqueous ammonia as an ammonium salt. The aqueous solution was evaporated on a rotary evaporator to give 1.60 g (66%) amino acid $(+)_D$-IV, mp 148-150°C (in a sealed capillary, from methanol−ethanol), $[\alpha]_D^{20}$ +5.3° (c 2.0, methanol), R_f 0.33 (in 16:1:3 butanol−formic acid−water).

***(2S)*-β-Aminoisobutyric Acid (V).** A solution of 0.1533 g (0.75 mmole) amino acid $(+)_D$-IV with specific rotation $[\alpha]_D$ +5.3° (c 2.0, methanol) in 5 ml glacial acetic acid was hydrogenated over freshly prepared palladium black with stirring. Standard work-up of the reaction mixture gave 0.099 g (97%) $(+)_D$-β-aminoisobutyric acid (V), mp 200-202°C (sealed capillary), $[\alpha]_D$ +8.3° (c 1.2, methanol), R_f 0.21 in 16:1:3 butanol−formic acid−water (mp 194-195°C, $[\alpha]_D^{20}$ +15.4° (c 5.0, water) [17]).

This work was carried out with the financial support of the Russian Fund for Basic Research (Project Code 93-03-4593) and General Committee of the Russian Federation for Higher Education, Science and Technology: Fine Organic Synthesis (Grant FT-28).

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