STEREOCHEMISTRY OF ELECTROPHILIC SUBSTITUTION IN β-LACTAM SYSTEMS (REVIEW)

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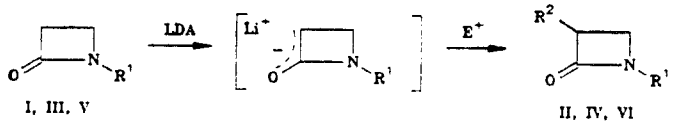
The literature data on the synthesis of 3-monosubstituted and 3,3-disubstituted β-lactams on the basis of reactions of lithium derivatives of 2-azetidinones with electrophiles are systematized.

The search for β-lactam antibiotics of a new generation that have a broad spectrum of antimicrobial activity and simultaneously are β-lactamase inhibitors has recently become one of the most important scientific and practical tasks of medicine [1, 2]. The complex relationships between the structure and biological activity of preparations of this class [3] require the development of the specific synthesis of compounds that model the pharmacologically active biomolecules. A correlation of the literature data on methods for the introduction of various substituents into the 3 position of the azetidine ring and the stereochemistry of this process (in the case of both monocyclic and condensed β-lactam systems) seems of interest in this connection.

1. ELECTROPHILIC SUBSTITUTION IN MONOCYCLIC β-LACTAMS

1.1. N-Monosubstituted 2-Azetidinones

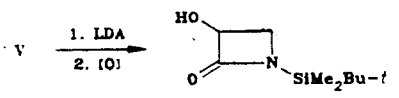
At the beginning of the 1970s a group of Canadian chemists, under the supervision of Durst, developed a method for the synthesis of 3-substituted 2-azetidinones that has currently become a universally recognized method [4]. The essence of this method consists in the action of various electrophiles on lithium derivatives of 2-azetidinones obtained by the action of lithium diisopropylamide (LDA). In particular, a preparative method for the synthesis of 1,3-disubstituted 2-azetidinones such as II (in ~100% yield), IV (55% yield), and VI (96% yield) has been developed on the basis of this [5-7].



I, III, V — II, IV, VI

I, II R^1 = Ph; R^2 = $SiMe_3$, III, IV R^1 = 4-$CH_3OC_6H_4$, R^2 = $CH(OH)C_6H_4NO_2$-2; V, VI R^1 = $SiMe_2Bu$-*t*; R^2 = $SiMe_3$

In 1989, the hydroxylation of the lithium derivative of the enolate of azetidinone V was accomplished using the MoO_5·Py·HMPT complex as the oxidizing agent [8]:



VII

The methylation of the lithium derivative of azetidinone VIII, which has an exocyclic chiral center with an (S) configuration, proceeds stereoselectively: A mixture of the (1'S,3S) and (1'S,3R) diastereomers of 3-methyl-1-(α-methylbenzyl)-2-azetidinone (IX) is formed in a ratio of 2:1 [9, 10]:

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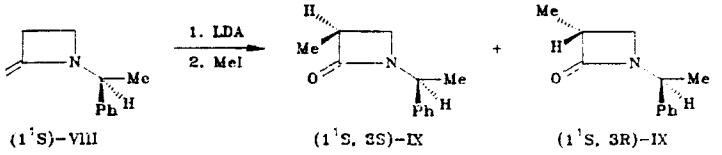
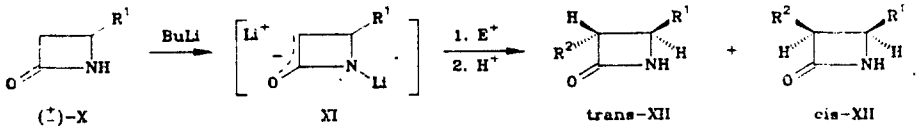


1.2. 4-Monosubstituted 2-Azetidinones

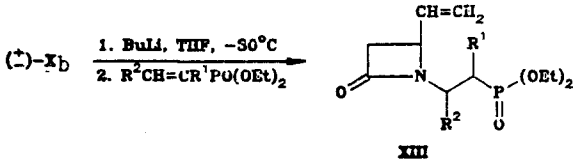
The metallation of 2-azetidinones that are not substituted at the nitrogen atom and in the 3 position leads to the formation of 1,3-dilithium derivatives, the subsequent reactions of which with electrophiles in the overwhelming majority of cases lead to the formation of 3-substituted 2-azetidinones, despite the existence of two reaction centers in intermediate XI.

It is known [11, 12] that 3,4-disubstituted azetidinones XII are formed in good yields when azetidinones X are treated successively with two equivalents of butyllithium at 0°C in THF and then with the electrophile (see Table 1).*



The regiospecificity of these reactions was confirmed by data from the IR spectra of the resulting β-lactams XII, in which bands of NH stretching vibrations at 3360-3400 cm^{-1} are present.

The only known example of reaction at the nitrogen atom is the formation of XIII in the reaction of the metallated 4-vinyl-2-azetidinone with diethyl vinylphosphonate [13]:



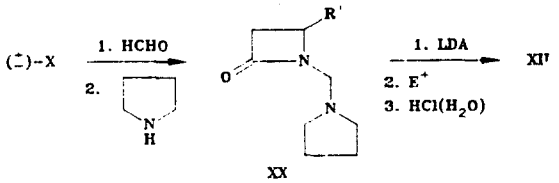
The stereochemical compositions of the azetidinones formed were evaluated on the basis of PMR data; a criterion of the stereochemical assignments in the spin-spin coupling constants (SSCC) of the trans- and cis-oriented protons of the β-lactam ring ($^3J_{34}$ = 2-3 Hz and 5-6 Hz, respectively) [14].

A general tendency toward trans stereochemistry of the substitution is evident from an analysis of the data in Table 1, as one should have expected from steric considerations; thus, 100% trans stereoselectivity is observed for 4-vinyl- (Xb) and 4-ethyl-2-azetidinone (Xc), and 80-91% trans stereoselectivity is observed for 4-phenyl-2-azetidinone (Xa) [11]. At the same time, stereoselectivity is absent in the case of 4-(3-butenyl)-2-azetidinone (Xd) [12]. Hamlet and Durst [12] explain this fact by the greater reactivity of the dilithium derivative of starting azetidinone Xd as compared with the monolithium derivative of 4-(3-butenyl)-2-azetidinone XXb, which has a protective group attached to the nitrogen atom.

1.3. 1,4-Disubstituted 2-Azetidinones

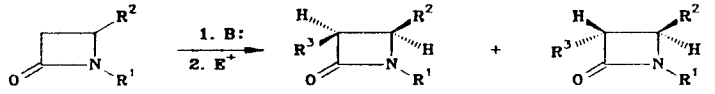
For β-lactams the ideal protective group, which is stable to the action of organometallic compounds and is then easily removed (by heating in a solution of hydrogen chloride in methanol), is the tert-butyldimethylsilyl group [7, 8, 15, 16, 19-22]. As in the case of 4-monosubstituted acetidinones X, their N-silylated analogs display a tendency toward stereoselective trans substitution. Thus, the formation of only trans-3,4-disubstituted derivatives was observed in the carboxylation [15], ethylation [16], and silylation [7] of N-(tert-butyldimethylsilyl)azetidinones XIV, XVI, and XVIII (Table 1).

A fundamentally new N-protective group, viz., the dialkylaminomethyl group, which, like the tert-butyldimethylsilyl group, is introduced and removed under mild conditions, was proposed in [12].



*For brevity here and subsequently, the diastereomeric racemates are represented by one of the enantiomers in the scheme.

TABLE 1. Stereochemical Composition of the Products of Electrophilic Substitution in Monocyclic β-Lactams



X, XIV, XVI, XVIII, XX, XXII — XII, XV, XVII, XIX, XXI, XXIII

Compound		R^1	R^2	R^3	Yield, %	Ratio		Reaction conditions		Literature
starting	formed					trans	cis	B:	T, °C	
Xa	XIIa	H	Ph	$Me_2C(OH)$	55	83	17	BuLi	0	[11]
Xa	XIIb	H	Ph	Me	53	80	20	BuLi	0	[11]
Xa	XIIc	H	Ph	Bu	66	91	9	BuLi	0	[11]
Xb	XIId	H	CH_2=CH	Bu	77	100	0	BuLi	0	[11]
Xb	XIIe	H	CH_2=CH	i-Pr	45	100	0	BuLi	0	[11]
Xc	XIIf	H	Et	Bu	65	100	0	BuLi	0	[11]
Xd	XIIg	H	CH_2=$CH(CH_2)_2$	$Me_2C(OH)$	75	50	50	BuLi	0	[12]
XIV	XV	t-$BuMe_2Si$	$HOOCCH_2$	COOH	35	100	0	LDA	−30	[15]
XVI	XVII	t-$BuMe_2Si$	CH_3CH=CH—	Et	79	100	0	LCIA	−70	[16]
XVIIIa	XIXa	t-$BuMe_2Si$	Et	Me_3Si	83	100	0	LDA	−78	[7]
XVIIIb	XIXb	t-$BuMe_2Si$	SPh	Me_3Si	75	100	0	LDA	−78	[7]
XXa	XXa	Pyrrolidinomethyl	CH_2=CH	Ac	63	100	0	LDA	−70	[16]
XXa	XXIb	Pyrrolidinomethyl	CH_2=CH	$Ph_2C(OH)$	83	100	0	LDA	−78	[12]
XXa	XXIc	Pyrrolidinomethyl	CH_2=CH	$Me_2C(OH)$	52*	97	3	LDA	−78	[12]
XXb	XXId	Pyrrolidinomethyl	CH_2=$CH(CH_2)_2$	$Me_2C(OH)$	68	97	3	LDA	−78	[12]
XXb	XXIe	Pyrrolidinomethyl	CH_2=$CH(CH_2)_2$	Ac	79	100	0	LDA	−78	[12]
XXc	XXIf	Pyrrolidinomethyl	Ph	Me	69	100	0	LDA	−78	[7]
XXIIa	XXIIIa	Me	CH_2=CH	$Me_2C(OH)$	80	100	0	LDA	−78	[4]
XXIIa	XXIIIb	Me	CH_2=CH	Me	59	100	0	LDA	−78	[4]
XXIId	XXIIIc	Me	Ph	$Ph_2C(OH)$	50	100	0	LDA	−78	[4]
XXIIa	XXIIId	Ph	Ph	$Me_2C(OH)$	58	100	0	LDA	−78	[4]
XXIIb	XXIIIe	Ph	Ph	$Me_2C(OH)$	62	100	0	LDA	−78	[17]
XXIIb	XXIIIf	Ph	Ph	$(CH_2)_5C(OH)$	41	100	0	LDA	−78	[4]
XXIIb	XXIIIg	Ph	Ph	Bz	61	100	0	LDA	−78	[4]
XXIIc	XXIIIh	CH_2=CH	Me	Me_3Si	55	100	0	LDA	−50	[18]
XXIIc	XXIIIi	CH_2=CH	Me	2-Pyridyl	28	80	20	LDA	−50	[18]

*The overall yield with respect to electrophilic substitution and removal of the substituent from the nitrogen atom is presented.

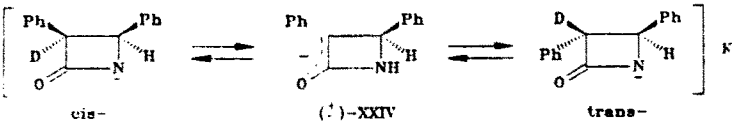
As in the case of N-silyl derivatives XIV, XVI, and XVIII, electrophilic substitution for azetidinones XX is a trans-stereoselective process. In all of the investigated reactions of N-dialkylaminomethyl derivatives XXa-c trans-3,4-disubstituted azetidinones XXIa-f are formed either as the only product or (in reactions with acetone) are the predominant products (97% trans-XXIc and trans-XXId) (see Table 1).

N-Methyl, N-phenyl, and N-vinyl derivatives XXII belong to the same class of 1,4-disubstituted 2-azetidinones.

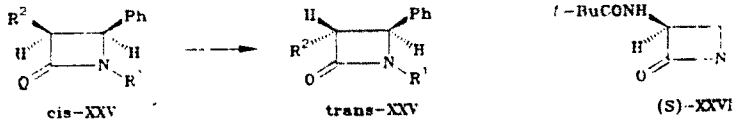
When various substituents are present in the 4 position, reactions with the most diverse electrophiles proceed trans-stereoselectively (Table 1) [4, 17, 18]. The only exception is the reaction with pyridine N-oxide, which leads to the formation of a mixture of trans and cis isomers (XXIIIi) in a ratio of 4:1 [18].

In concluding this section, it seems expedient to attempt to ascertain the factors that affect the stereochemistry of the electrophilic substitution of metallated derivatives of 4-mono- and 1,4-disubstituted 2-azetidinones. According to the data in Table 1, neither the nature of the electrophile and the substituents nor the reaction conditions have virtually any effect on the trans selectivity. Thus, for example, cases of 100% selectivity are observed for both N-substituted β-lactams (XIV, XVI, XX, XXII) and for N-unsubstituted azetidinones, as well as for compounds for aliphatic (XIIf, XIXa, XXIIIh), aromatic (XXIf, XXIIIc-g), and vinyl (XIId, e, XVII, XXIa, b, XXIIIa, b) substituents in the 4 position in reactions with electrophiles with different chemical natures, viz., alkyl halides (XIId-f, XVII, XXIf, XXIIIb), trimethylchlorosilane (XIXa, b, XXIIIh), ketones (XXIb, XXIIIa, c-f), acid esters (XXIa, e, XXIIIg), and carbon dioxide (XV), and with different steric requirements, viz., methyl iodide, ethyl iodide, and isopropyl bromide (XXIf, XXIIIb, XVII, XIIe). It should be noted that an increase in the temperature from –78°C to 0°C does not decrease the selectivity of the process, which also is not affected by varying the metallating agents (BuLi, LDA, LCIA*).

One can only certify the decreased (to 80%) trans stereoselectivity of the reactions of N-unsubstituted 4-phenyl-2-azetidinone (Xa → XIIa-c) and the absence of stereoselectivity in the formation of XIIg from 4-(3-butenyl)-2-azetidinone (Xd). The decrease in the stereoselectivity of the electrophilic substitution reactions is possibly associated with epimerization at the asymmetric $C_{(3)}$ center. Instances of cis,trans isomerization of 3,4-disubstituted 2-azetidinones are known. Thus it was established by PMR data that an equilibrium mixture of the cis and trans forms is formed in a solution of the potassium salt of cis-3,4-diphenyl-2-azetidinone (XXIV) in D_2O; the deuterium label is detected in the 3 position of the azetidinone [23].



cis,trans Isomerization is also observed for azetidinones XXV in the presence of catalytic amounts of LDA in a mixture of THF and hexametapol (isomerization does not occur in the absence of hexametapol) or in tert-BuOD in the presence of tert-BuOK [24].

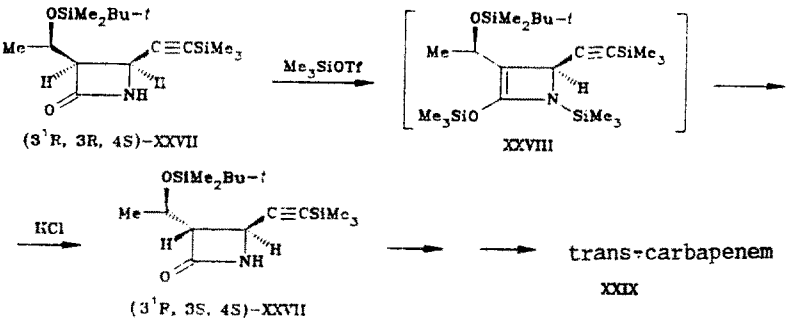


R^1 = 4-$CH_3OC_6H_4$, $SiMe_3$; R^2 = $SiMe_2Ph$

The tendency for epimerization evidently depends on the character of the substituent attached to the $C_{(3)}$ atom, and racemization of azetidinone XXVI therefore does not occur in the presence of sodium methoxide [25], while instances of epimerization, even under the influence of a weaker base, are known (see following page).

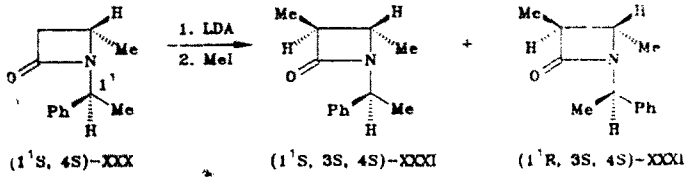
* LCIA is lithium cyclohexylisopropylamide.

The ability of cis-azetidinone XXVII to undergo isomerization in the step involving the formation of intermediate XXVIII in the case of silylation with triflat in the presence of triethylamine (20°C, 48 h) was used in the synthesis of trans-carbapenem antibiotics [26].



On the other hand, trans-azetidinone XXIf undergoes partial epimerization at the $C_{(3)}$ atom in an attempt to silylate its lithium derivative in the presence of tetramethylethylenediamine (TMEDA) [7].

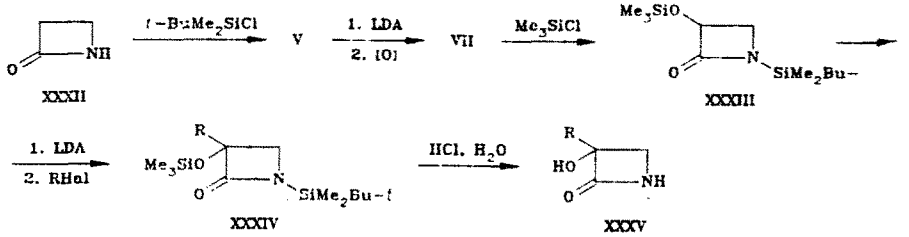
The joint action of the two inducing centers $C_{(1')}$ and $C_{(4)}$ ensures the complete trans stereospecificity of processes involving methylation at the $C_{(3)}$ atom of the (1^1S,4S) and (1^1S,4R) diastereomers of 4-methyl-1-(α-methylbenzyl)-2-azetidinone (XXX) [27, 28]. Only the $C_{(1')}$ exocyclic chiral center undergoes epimerization, while the asymmetric centers of the azetidinone ring are not involved:



It seemed evident that the tendency for epimerization at the $C_{(3)}$ atom should be determined by its CH acidity; however, 100% trans stereoselectivity is observed even in the formation of XXIIIg and XV with acceptor substituents such as benzoyl and carboxy groups. This fact, and all of the data on the stereochemistry of the products of similar reactions presented in Table 1, make it possible to assume that epimerization does not make a substantial contribution to the stereochemical result of the reactions of lithium derivatives of 2-azetidinones with various electrophiles.

1.4. 1,3-Disubstituted 2-Azetidinones

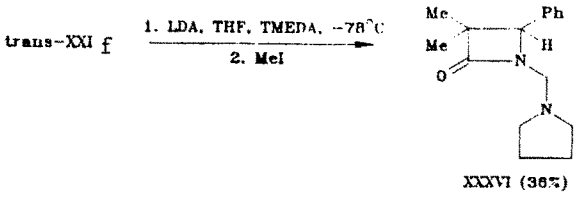
A preparative method for the synthesis of 3-hydroxy-3-alkyl-2-azetidinones XXXV from the commercially accessible (Aldrich) azetidinone XXXII was developed on the basis of the reaction of alkyl halides with the lithium derivatives of 3-trimethylsilyloxyazetidinone XXXIII [8]:



RHal	Yield of XXXIV, %	RHal	Yield of XXXIV, %
CH_3I	73	t-BuMe$_2$SiOCH$_2$CH$_2$I	83
CH_2=CHCH$_2$Br	85	1,2-Isopropylidenedioxy-4-iodobutane	72
CH_2=CH(CH$_2$)$_4$Br	52		

1.5. 1,3,4-Trisubstituted 2-Azetidinones

The introduction of a second substituent into the 3 position of 3,4-trans-disubstituted azetidinones proved to be a difficult problem. Ogilvie and Durst [7] assert that the anion of trans-azetidinone XXIf is not formed at all under the standard metallation conditions (LDA, 78°C, THF). However, the addition of one equivalent of TMEDA leads to the formation of an anion, by metallation of which 3,3-dimethyl derivative XXXVI was obtained:



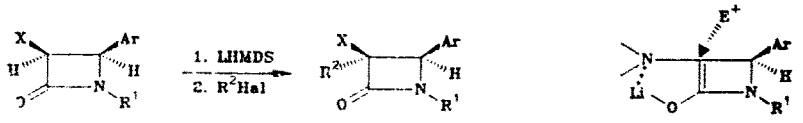
XXXVI (36%)

If, however, an allyl group is located in the 3 position of the azetidinone ring, the presence of TMEDA is not required for the formation of lithium enolate XXXVIII. The hydroxylation of lithium derivatives of azetidinones XXXVII with molybdenum peroxide was carried out under standard conditions; the hydroxy group in the 3,3-disubstituted XXXIX obtained is always trans-oriented with respected to the $C_{(4)}$ atom [7]:

XXXVII XXXVIII XXXIX

R=H (67%), R=Alk (37...53%)

A high degree of stereoselectivity of asymmetric alkylation (>99.5%) is observed for optically active 1,3,4-trisubstituted azetidinones XL and XLII with a cis orientation of the substituents. Here, lithium hexamethyldisilazide (LHMDS) was used as the metallating agent [29].



(3S, 4R)-XL; (3S, 4R)-XLII XLIIa,b XLIII XLIV

94...95%

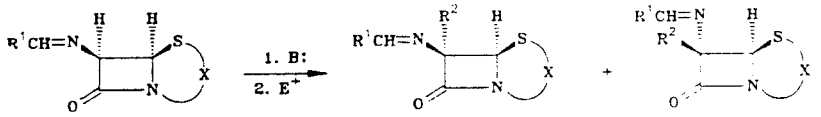
XL, XLI: X = N = $CHCH_2Ph$; Ar = Ph, R^1 = (R)-1-benzyloxymethyl-3-methylbutyl; XLI: a) R^2 = Me; b) $R^2 = CH_2CH{=}CH_2$; XLII, XLIII: X = (R)-2-oxo-4-phenyl-3-oxazolidinyl, Ar = $C_6H_3(OMe)_2$-3,4, $R^1 = CH_2Ph$, R^2 = Me.

Ojima and coworkers [29] explain the stereospecificity of the reactions by the possible formation of rigid, chelated, lithium enolates XLIV, the electrophilic attack on which is possible only from the side opposite the bulky aryl substituent in the 4 position.

2. ELECTROPHILIC SUBSTITUTION IN BICYCLIC β-LACTAM SYSTEMS

One of the most important methods for expanding the number of synthetic analogs of natural β-lactam antibiotics is the chemical stereochemical modification of natural penicillins XLV and cephalosporins XLVI in the 3 position of the β-lactam ring (the 6 position of penicillin, and the 7 position of cephalosporin).

TABLE 2. Stereochemistry of the Products of Electrophilic Substitution in Azomethine Derivatives of Esters of Penicillanic (XLIX) and Cephalosporanic (L) Acids

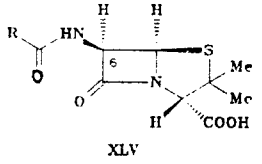


(6R)-XLIX, (7R)-L α-LI, α-LII β-LI, β-LII

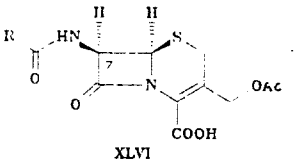
XLIX, LI X = $CMe_2CH(COOR)$; L, LII X = $CH_2C(CH_2OOCMe)=C(COOR)$

No.	Compounds: starting	Compounds: formed	R¹	R²	Reaction conditions: B	Reaction conditions: t, °C	Reaction conditions: solvent	Ratio: α	Ratio: β	Literature
1	XLIXa	LIa	Ph	Me	NaH	0	Dimethoxyethane	100	0	[31]
2	La	LIIa	Ph	Me	NaH	0	Dimethoxyethane	100	0	[31]
3	XLIXa	LIa	Ph	Me	PhLi	−78	THF-DMFA	100	0	[32]
4	La	LIIa	Ph	Me	PhLi	−78	THF-DMFA	100	0	[32]
5	XLIXb	LIb	4-$NO_2C_6H_4$	Cl_3CCH_2OCO	LDA	−78	THF-DMFA	100	0	[33]
6	Lb	LIc	4-$NO_2C_6H_4$	$PhCOCH_2$	LDA	−78	THF-DMFA	100	0	[33]
7	Lb	LId	4-$NO_2C_6H_4$	Alk	LDA	−78	THF-DMFA	100	0	[33]
8	Lb	LIe	4-$NO_2C_6H_4$	$CH_2=CHCH_2$	LDA	−78	THF-DMFA	100	0	[33]
9	Lb	LIIb	4-$NO_2C_6H_4$	Cl_3CCH_2OCO	LDA	−78	THF-DMFA	100	0	[33]
10	Lb	LIIc	4-$NO_2C_6H_4$	$PhCOCH_2$	LDA	−78	THF-DMFA	100	0	[33]
11	Lb	LIId	4-$NO_2C_6H_4$	Alk	LDA	−78	THF-DMFA	100	0	[33]
12	Lb	LIIe	4-$NO_2C_6H_4$	$CH_2=CHCH_2$	LDA	−78	THF-DMFA	100	0	[33]
13	XLIXa	LIa	Ph	Me	t-BuOK	−40	Anhydrous glyme	95	5	[34]
14	La	LIIa	Ph	Me	t-BuOK	−30	Anhydrous glyme	97	3	[34]
15	La	LIIf	Ph	Me_2NCH_2	t-BuOK	−30	Anhydrous glyme	50	50	[34]
16	XLIXb	LIf	4-$NO_2C_6H_4$	$NCCH_2CH_2$	LDA catalysis	20		100	0	[35]

Thus, for example, epimerization, which occurs under mild conditions (aqueous alkali, 20°C), makes it possible to make the transition from the natural antibiotic chetacillin (XLVII), with a cis orientation of the substituents attached to the $C_{(3)}$ and $C_{(4)}$ atoms, to the isomeric antibiotic epichetacillin (XLVIII), with a trans orientation of these substituents [30].



XLV

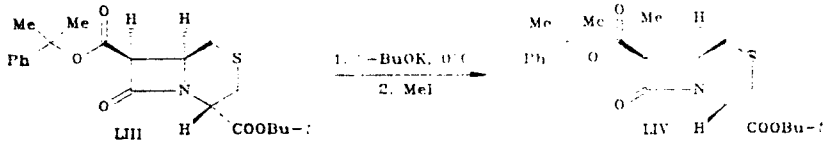


XLVI

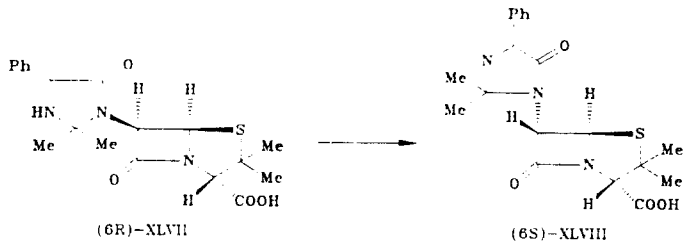
One of the forms of chemical modification of penicillin systems is the introduction of a second substituent into the 6 position through their metallated derivatives.

The electrophilic attack on azomethine derivatives of esters of 6-aminopenicillanic and 7-aminocephalosporanic acids in the presence of a base generally takes place on the sterically less-hindered α side with the formation of the α isomer (in most natural β-lactam antibiotics the five- or six-membered ring annelated with the azetidinone ring is oriented on the β side). The structures of the 6,6-disubstituted derivatives were established not only by means of PMR data, but also, for many of them, using x-ray diffraction analysis. The results of the electrophilic substitution reactions of metallated derivatives of penicillin and cephalosporin systems have been investigated (Table 2).

Under similar conditions α-methyl derivative LIV was obtained as the oily product on the basis of the synthetic β-lactam system LIII, which differs from cephalosporins with respect to the presence of an ester grouping in the 3 position of the β-lactam ring and the position of the sulfur atom in the thiazine ring [36].

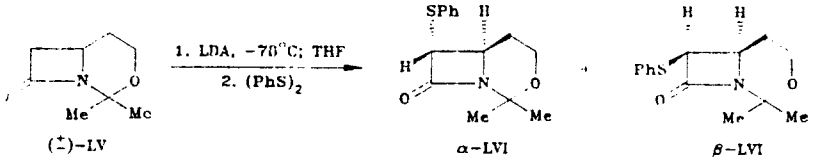


LIII LIV

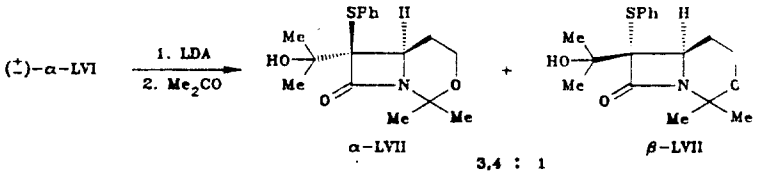


A general tendency in electrophilic substitution reactions in natural and synthetic bicyclic β-lactam systems is retention of the stereochemistry of the starting substrate with an α orientation of the substituent entering the 3 position (Table 2; also see [36]). The only exception is the complete absence of stereoselectivity in carrying out the Mannich reaction with La (No. 15 in Table 2); this is probably associated with the nature of the electrophilic agent.

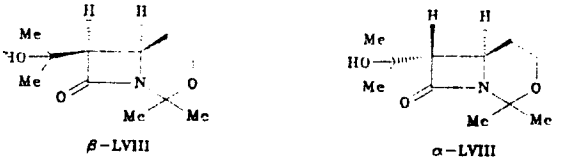
The electrophilic substitution reactions of bicyclic systems that are not substituted in the 3 position of the β-lactam ring also proceed selectively with the formation of the α isomers (which corresponds to trans stereochemistry in the monocyclic analogs). Thus, for example, the principal product of the reaction of the lithium derivative of (±)-LV with diphenyl disulfide is the α isomer of LVI (α:β = 10:1) [37].



The possibility of the facile reductive elimination of the phenylthio group stimulated an attempt to use it as a stereochemical protective group for the α side of the β-lactam ring in the synthesis of β isomers that are not accessible under the conditions of direct electrophilic substitution. However, the reaction of the lithium derivative of the α isomer of LVI with acetone under standard conditions leads to the formation of LVII isomers with preponderance of the product of attack by the new electrophile on the α side* (α:β = 3.4:1) [37]:



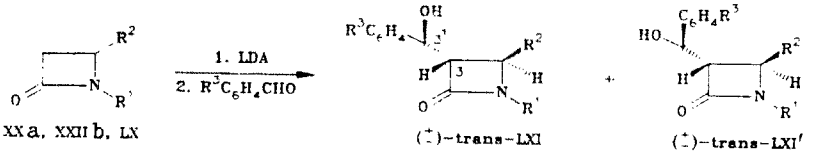
Although attempts to directly use stereochemical protection of the α side to obtain the β isomer have not been successful, encouraging results were obtained in a study of the stereochemistry of the reductive elimination of the phenylthio group. Whereas reduction with the participation of Raney nickel proceeds with retention of the configuration of the starting azetidinone LVII, reduction of the α and β isomers of LVII by means of tin hydrides leads to the formation of primarily the β isomer of LVIII. The maximum enrichment of the mixture in the β isomer of LVIII was achieved when triphenylstannane was used [37]:



Starting LVII isomer	Reagent	Overall yield, %	LVII isomer ratio	
			β	α
α-LVII	Raney Ni	68	1	2.2
β-LVII	Raney Ni	93	3.2	1
α-LVII	Bu_3SnH	94	3.3	1
β-LVII	Bu_3SnH	93	3.2	1
α-LVII+β-LVII (3.4 : 1)	Bu_3SnH	94	3.7	1
α-LVII+β-LVII (20:1)	Ph_3SnH	96	4.8	1

*Here, α,β isomerism with respect to the α-hydroxyethyl substituent is examined.

TABLE 3. Stereochemistry of the products of the trans-α-Hydroxybenzylation of 2-Azetidinones

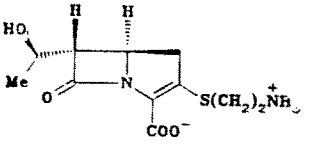


Compound		R¹	R²	R³	Yield, %	Ratio		Literature
starting	formed					LXI	LXI'	
XXIIb	LXI[a]	Ph	Ph	H	25	67	33	[17, 38]
XXIIb	LXIb	Ph	Ph	4-Cl	65	67	33	[38]
XXIIb	LXIc	Ph	Ph	4-NO_2	90	67	33	[38]
XXIIb	LXId	Ph	Ph	4-Br	68	67	33	[38]
XXIIb	LXIe	Ph	Ph	4-OH	32	67	33	[38]
XXIIb	LXIf	Ph	Ph	4-NMe_2	70	67	33	[38]
XXIIb	LXIg	Ph	Ph	4-Me	62	67	33	[38]
XXIIb	LXIh	Ph	Ph	2-NO_2	80	100	0	[38]
XXIIb	LXIi	Ph	Ph	3-NO_2	57	100	0	[38]
XXIIb	LXIj	Ph	Ph	2-Cl	86	67	33	[38]
LX	LXI[k]	4-BrC_6H_4	Ph	4-NO_2	71	70	30	[17]
LX	LXI[l]	4-BrC_6H_4	Ph	2-Cl	45	100	0	[17]
LX	LXI[m]	4-BrC_6H_4	Ph	4-Cl	32	100	0	[12]
XXa	LXI[n]	Pyrrolidinomethyl	CH_2=CH	H	81	67	33	[7]

Despite all of the complexity of this reaction sequence, it can be used to obtain difficult-to-obtain (by other methods) β isomers of bicyclic β-lactam systems.

3. STEREOCHEMISTRY OF α-HYDROXYALKYLATION REACTIONS WITH THE DEVELOPMENT OF AN EXOCYCLIC CHIRAL CENTERS

The synthesis of thienamycin (LIX), which is a natural β-lactam antibiotic of a new generation, and its structural analogs required the development of methods for the stereospecific introduction of an α-hydroxyalkyl group into the 3 position of the β-lactam ring. In this connection, the reaction of lithium derivatives of 2-azetidinones with aldehydes, as a result of which, in addition to the chiral center at the $C_{(3)}$ atom, an additional (exocyclic) asymmetric center develops, became especially important. In this connection, in analyzing the stereochemistry of α-hydroxyalkylation reactions one must consider both the cis,trans orientation of the substituents in the ring and the configuration of the developing exocyclic chiral center.



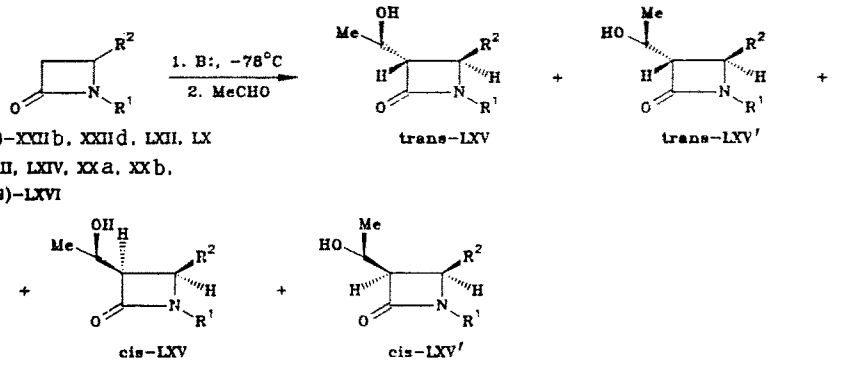
(+)-LIX

3.1. Reactions of 2-Azetidinones with Benzaldehydes

All of the research carried out thus far provides evidence for the trans-3,4-stereospecificity of the reaction of lithium derivatives of 1,4-diaryl- and 1-dialkylaminomethyl-4-vinyl-2-azetidinones with aromatic aldehydes (Table 3) [7, 12, 17, 38].

Mixtures of unequal amounts of diastereomeric racemates LXI and LXI' (characterized by $^3J_{33}$ = 3.4 and 6.5 Hz), which differ with respect to the absolute configuration of the exocyclic $C_{(31)}$ center vis-à-vis a trans orientation of the substituents in the ring, are usually formed in these reactions; the preponderant (67-70%) isomer has a lower $^3J_{33}$ value; complete stereospecificity in the development of an exocyclic chiral center is observed only in a few cases (LXIh, i, l, m).

TABLE 4. Stereochemical Composition of the Products of α-Hydroxyethylation of 2-Azetidinones



Compound		R^1	R^2	Yield, %	Ratio*		B:	Literature
starting	formed				trans-LXV	cis-LXV		
XXIIb	LXVa	Ph	Ph	70	100 (3:2)	—	LDA	[17]
XXIId	LXVb	Me	Ph	63	100 (3:2)	—	LDA	[17]
XXIId	LXVb	Me	Ph	72	100 (2:1)	—	LCIA	[16]
LXII	LXVc	*i*-Pr	Ph	64	100 (3:2)	—	LDA	[17]
LX	LXVd	4-BrC_6H_4	Ph	55	100 (4:1)	—	LDA	[17]
XIV	LXVe	*t*-$BuMe_2Si$	$HOOCCH_2$	70	100**	—	LDA	[15]
LXIII	LXVf	Ph_3P= =$CHCOOCH_2Ph$	CH_2= =$CHCH_2$	65	76	24	LCIA	[39]
LXIV	LXVg	*t*-$BuMe_2Si$	CH_2=CH	98	85 (46:37)	15 (7:1)	LDA	[19]
XXa	LXVh	Pyrrolidinomethyl	CH_2=CH	58***	100 (1:1)	—	LDA	[12]
XXb	LXVi	Pyrrolidinomethyl	CH_2= =$CH(CH_2)_2$	74***	100 (1:1)	—	LDA	[12]
(4S)-LXVI	LXVj	*t*-$BuMe_2Si$	(2-Trimethylsilyl-1,3-dithian-2-yl)-methyl	97	>95 (1:1)	<5	LDA	[20]

*The ratio of the diastereomeric racemates is given in parentheses.

**The ratio of the diastereomeric racemates in the mixture was not determined.

***The overall yield (with respect to electrophilic substitution and removal of the protective group from the nitrogen atom) is presented.

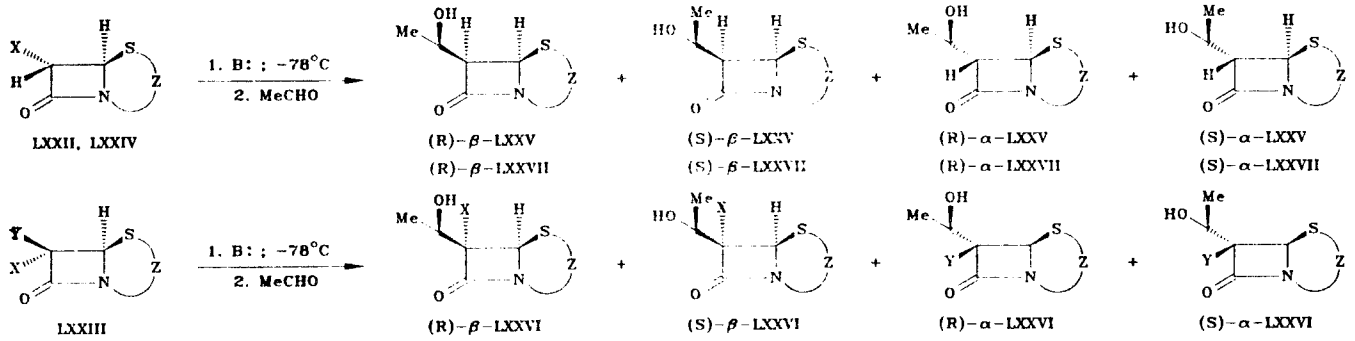
3.2. Reactions of 2-Azetidinones with Acetaldehyde

The stereocontrolled introduction of an α-hydroxyethyl group into the 3 position of 2-azetidinones through their lithium derivatives has become the most important reaction in the chemistry of thienamycin (LIX). Despite the significantly smaller steric requirements of acetaldehyde (as an electrophile) as compared with benzaldehydes, the α-hydroxyethylation reactions proceed with high trans-3,4-selectivity (Table 4).

A number of azetidinones with various substituents attached to the nitrogen atom (aromatic, aliphatic, dialkylaminomethyl) and in the 4 position (aromatic and alkenyl) form only trans-3,4-substitution products in reactions of this type. However, in the remaining cases (for example, in the reaction with LXIV), α-hydroxyethyl derivative LXVg is produced in the form of a mixture of trans and cis isomers in a ratio of 5.7:1 [19].

Even lower trans-stereoselectivity of α-hydroxyethylation was observed in the reaction with azetidinone LXIII; the ratio of the trans and cis isomers of LXV formed (~3:1) was established by means of the PMR spectra from the composition of the products of their subsequent intramolecular condensation (LXVII) [39].

TABLE 5. Stereochemical Composition of the Products of α-Hydroxyethylation of Metallated 3-Halo and 3,3-Dihalo Derivatives of Bicyclic β-Lactams LXXII-LXXIV

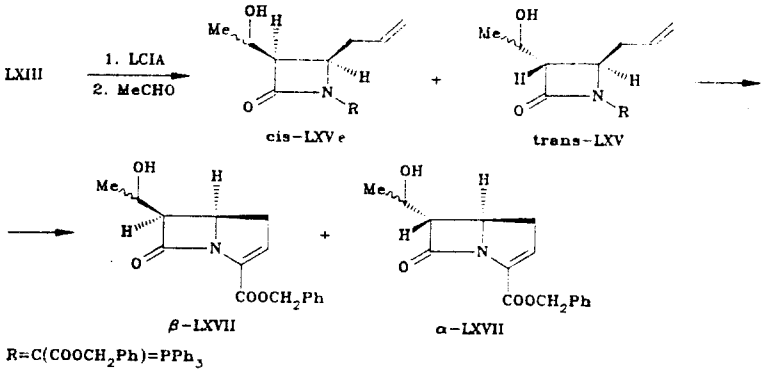


No.*	Compound**		B	Solvent	Yield, %	Percentage of isomers, %			
	starting	formed				(R)-β	(S)-β	(R)-α	(S)-α
1	LXXII	LXXV	BuLi	THF	21	21	—	32	47
2	LXXII	LXXV	BuLi	Ether	50	18	—	47	35
3	LXXII	LXXV	MeMgBr	THF	80	27	—	24	49
4	LXXIV	LXXVII	MeMgBr	Ether	—	40	—	60	
5	LXXIII[a]	LXXVIa	BuLi	THF	41	67	—	33	
6	LXXIIIa	LXXVIa	MeMgBr	THF	95	75	—	25	
7	LXXIIIa	LXXVIa	MeMgBr	THF	85	75	—	25	
8	LXXIIIa	LXXVIa	BuLi	Toluene	89	39	1	30	30
9	LXXIIIa	LXXVIa	BuLi	THF	—	80		20	
10	LXXIIIa	LXXVIa	BuLi	Toluene***	40	<5		—	>95
11	LXXIIIb	LXXVIb	MeMgI	THF	82	100	—	—	—
12	LXXIIIc	LXXVIc	MeMgI	THF	89	33	—	67	

*Data from [42] are presented for compounds Nos. 1-6; data from [44] are presented for compounds Nos. 7, 11, and 12; and data from [43] are presented for compounds Nos. 8-10.

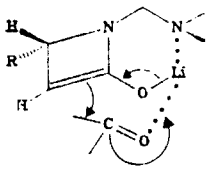
**LXXII (LXXV), LXXIIIa (LXXVIa); X = Br; LXXIV (LXXVII), LXXIIIb (LXXVIb), X = I; LXXIIIc (LXXVIc), X = Cl; LXXIIIa (LXXVIa), Y = Br; LXXIIIb, c (LXXVIb, c), Y = I; LXXII, LXXIII, Z = $CMe_2CH(COOCH_2Ph)$; LXXIV, Z = $CH_2C(CH_2OOCCH_2)=C(COOBu\text{-}tert)$.

***With the addition of Zn^{2+} ions (concentrated anhydrous solution in THF, 0.5-1.0 equivalent of $ZnCl_2$).



The selection of the protective group plays a substantial role in the development of methods for the synthesis of (±)-thienamycin LIX and its analogs on the basis of 4-vinylazetidinone Xb and 4-(3-butenyl)azetidinone XIIg. In the case of a trialkylsilyl protective group in azetidinone LXIV only 85% trans-3,4-stereoselectivity of α-hydroxyethylation was achieved (Table 4) [19]. It should be noted that, by varying the nature of the substituent attached to the $C_{(4)}$ atom while maintaining the same protective group (in the reactions of XIV and LXVI) one can achieve virtually complete trans-3,4-stereoselectivity (LXVe, j).

Complete trans-3,4-stereoselectivity was also observed in reactions of azetidinones XXa, b, which have a dialkylaminomethyl protective group attached to the nitrogen atom [12]; this is associated with the chelated state of lithium in intermediate LXVIII. In the opinion of Hamlet and Durst [12], electrophilic attack on the enolate system of the β-lactam on the side of the chelate group is facilitated in this case; this promotes trans-stereoselective substitution.

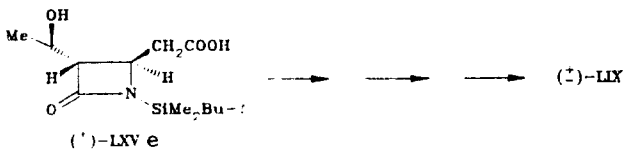


LXVIII

Thus, the α-hydroxyethylation of 1,4-disubstituted monocyclic β-lactams, like other electrophilic substitution reactions in these systems, displays a distinct tendency for trans-3,4-stereoselectivity, while α-hydroxybenzylation proceeds trans-stereospecifically. In the opinion of Ogilvie and Durst [7], this is determined by the fact that, of the two possible pathways of attack, the one in which steric interaction of the substituents attached to the $C_{(4)}$ atom and in the electrophile is realized.

In discussing the stereochemistry of the formation of the exocyclic $C_{(3)}$ center in α-hydroxyethylation reactions one must note the appreciably lower diastereoselectivity of this process as compared with α-hydroxybenzylation. Nowhere (Table 4) is 100% diastereoselectivity observed: The ratios of the trans-3,4-diastereomers vary from 4:1 (LXVd) to 1:1 (LXVh, i). It might be assumed that the absence of stereoselectivity in the latter case is associated with the smaller steric requirements of the methyl group of acetaldehyde as compared with the substituted phenyl ring of benzaldehydes. The greater diastereoselectivity of the formation of cis-3,4-diastereomers (in a ratio of 7:1 in the case of LXVg) is evidently due to the drawing together in space of the developing α-hydroxyethyl center and the substituent attached to the $C_{(4)}$ atom within the framework of the overall cis geometry of the molecule.

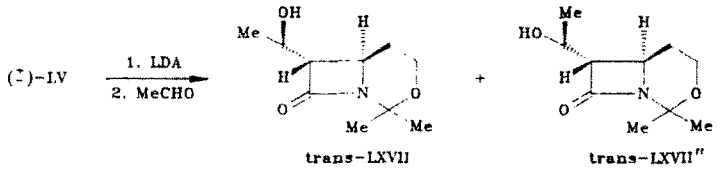
The use of the traditional method for establishing the stereochemistry of the $C_{(31)}$ center of α-hydroxyethyl derivatives of azetidinones from the SSCC is hindered in many cases by the small differences in the values of these constants ($^3J_{331}$ = 5.0 and 5.5 Hz) in the PMR criteria by means of chemical correlations seems particularly important. Thus, only one of the two trans-diastereomeric racemates LXVe was converted to (±)-thienamycin LIX [15]:



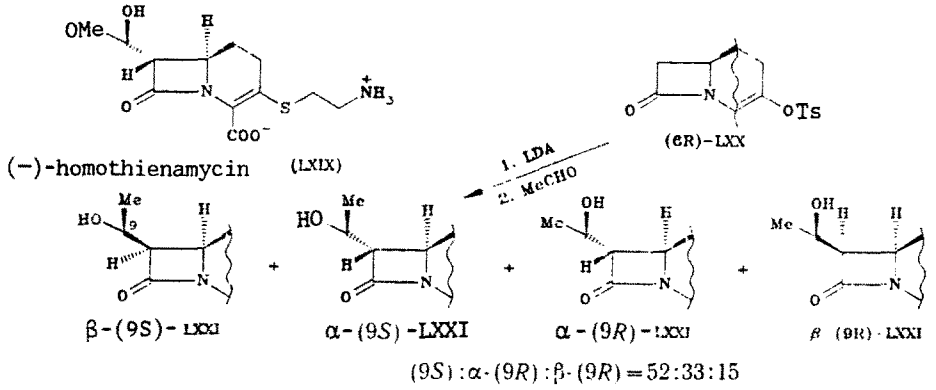
Thus, in contrast to the high trans-3,4-selectivity of reactions involving the α-hydroxyalkylation of monocyclic β-lactams, the diastereoselectivity of the formation of the exocyclic chiral center is extremely moderated: 67-70% in the case of α-

hydroxybenzylation (100% stereoselectivity was observed in only three cases, while it reaches 75-80% in α-hydroxyethylation.

Spectral studies [17] have shown that the spatial orientation of the substituents with respect to the plane of the β-lactam ring and the configuration of the asymmetric $C_{(3)}$ center in the primarily formed trans isomer of azetidinone LXVa call to mind the stereochemistry of the β-lactam fragment of the thienamycin LIX molecules. Thus, the α-hydroxyethylation of condensed β-lactam system LV was accomplished in developing approaches to the synthesis of (±)-thienamycin under standard conditions [4]; 7-α-hydroxyethyl derivative LXVII, which, according to PMR data, contains two diastereomeric racemates in a ratio of 3:2, was isolated in 89% yield by means of preparative chromatography [40]:



A mixture of 7α and 7β isomers of LXXI, in which the percentage of the necessary (9R)-trans isomer is 33%, was isolated in the synthesis of (–)-homothienamycin under the same conditions of α-hydroxyethylation of optically active LXX [41]:

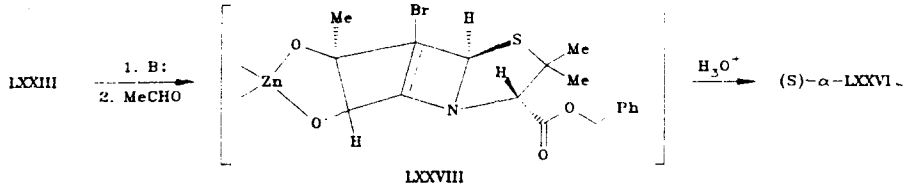


In most cases, metallated derivatives of optically active bicyclic β-lactam systems are obtained not on the basis of azetidinones themselves, but rather on the basis of their monohalo and dihalo derivatives with respect to the 3 position of the four-membered ring; not only the traditional butyllithium but also methylmagnesium bromide are used as bases. Let us note that when dihalo derivatives are used, the α-hydroxyethylation products contain a reactive halogen atom in the 3 position. In particular, 6α-halo- (LXXII), 6,6-dihalopenicillanic (LXXIII), and 7α-halocephalosporanic (LXXIV) acid esters react successively with the base and acetaldehyde to give mixtures of diastereomers of the α and β forms in various ratios (Table 5).

On the whole, an impression of low α,β-stereoselectivity of processes of this type is created on the basis of the data in Table 5: The percentage of the β isomer in the mixtures ranged from 18% (No. 2) to 80% (No. 9) and varies as a function of the degree of halogenation of the starting azetidinone (21% and 80% for monobromo- and dibromo-substituted compounds Nos. 1 and 9, respectively) and the nature of the halogen (27% and 40% in the case of bromo and iodo derivatives Nos. 3 and 4, respectively) and the solvent (67% and 40% when the reaction is carried out in THF and toluene, respectively, Nos. 5 and 8); the nature of the base has virtually no effect on the α,β-stereoselectivity (Nos. 1 and 3 and 5 and 6). The 100% β stereoselectivity observed in the reaction of diiodo derivative LXXIIIb (No. 11) constitutes an exception.

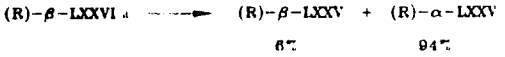
In contrast to the low α,β stereoselectivity, one's attention is drawn to the diastereospecificity of the development of the exocyclic chiral center within the framework of the β form – only the (R)-β isomer is formed in virtually all cases (Table 5). On the other hand, the formation of the diastereomers of the α form does not proceed stereoselectively.

Carrying out the reaction in the presence of Zn^{2+} ions opens up an interesting possibility for modification of the stereochemistry of the α-hydroxyethylation process [43]. Whereas all four possible stereoisomers, viz., the (R)-β, (S)-β, (R)-α, and (S)-α isomers in a ratio of 39:1:30:30, are formed in the reaction of dibromo derivative LXXIIIa in toluene, the same reaction in the presence of zinc ions makes it possible to obtain >95% of the (S)-α isomer (Nos. 8 and 10, Table 5). Aimetti and Kellogg [43] link the high diastereoselectivity of the formation of the (S)-α isomer of LXXVIa with the formation of chelate intermediate LXXVIII, which provides evidence for the preferableness of the pro-(S) configuration of the exocyclic chiral center in the α isomer of LXXVIa:



The development of preparative methods for the highly stereoselective synthesis of bicyclic α-hydroxyethylated monohalo-substituted azetidinones (R)-β-LXXVIb and (S)-α-LXXVIa was the result of detailed investigations of the stereochemistry of reactions involving the α-hydroxyethylation of lithium derivatives of dihalo-substituted bicyclic structures.

It is interesting to note that the electrolytic dehalogenation of an individual isomer of one compound of this type, viz., (R)-β-LXXVIa, is accompanied by inversion of the configuration at the $C_{(3)}$ center of the β-lactam with the primary formation of the (R)-α isomer of bicyclic system LXXV [42]:



In summing up this analysis of the results of investigation of electrophilic substitution reactions of metallated derivatives of mono- and bicyclic azetidinones, it may be noted that, at the present time, this process opens up extensive possibilities for modification of the structures of β-lactams; the general tendency toward trans stereochemistry of the introduction of substituents into the 3 position is particularly valuable.

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