ASYMMETRIC SYNTHESIS OF AMINO ACIDS BY CATALYTIC REDUCTION OF AZLACTONES OF SUBSTITUTED ACYLAMINOACRYLIC ACIDS. COMMUNICATION 12. AMINOLYSIS OF 4-SEC-BUTYL-5-OXAZOLONES AND MECHANISM OF REDUCTIVE AMINOLYSIS OF 4-SEC-BUTYLIDENE-5-OXAZOLONES

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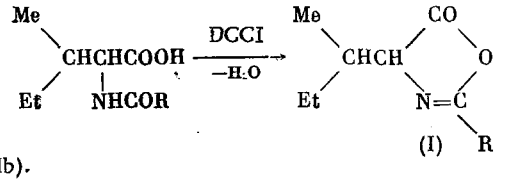
The present work describes the study of kinetics and stereochemistry of the epimerization and aminolysis reactions of 4-sec-butyl-5-oxazolones (I) under conditions corresponding to reductive aminolysis of 4-sec-butylidene-5-oxazolones (II) [1] in order to clarify the mechanism of the latter process.

DISCUSSION OF RESULTS

Saturated chiral oxazolones are obtained by cyclization of N-acylamino acids in the presence of N,N-dicyclohexylcarbodiimide (DCCI) [2]. The cyclization of SS-acylisoleucine according to [2] at 20°C is accompanied by epimerization at the α-C-center with the formation of an epimeric mixture of (I) (SS and SR). At −22 to −30°C, chiral oxazolones SS-(Ia) and SS-(Ib) were obtained



R = Me (Ia), Ph (Ib).

The product obtained was analyzed by the PMR method.

Compound (I) was epimerized either without a catalyst, or by the action of triethylamine at 20°C (Table 1).

Table 1 shows that the ratio of SS- and SR-(I) at the equilibrium established as the result of epimerization remains constant and is independent of the nature of the solvent. Replacement of the substituent at the 2-position of the oxazolone ring changes the ratio between the epimers of (I), which is the same as the ratio between the diastereomers of α-phenylethylamides of acylisoleucines (III) obtained as the result of reductive aminolysis of (II) by the action of S-(−)-α-phenylethylamine (IV) [1].

A comparative kinetic study of the epimerization and aminolysis of (I) by the action of (IV) was carried out under the conditions corresponding to those of the reductive aminolysis process, in dimethoxyethane (DME) and t-BuOH, at 20°C, at initial concentrations of (I) and (IV) of 0.067 and 0.1 mole/liter, respectively. The ratio between the diastereomers of (III) was determined by GLC. Compound (III) was also hydrolyzed, and the epimeric mixture of isoleucines (S-isoleucine and R-alloisoleucine) was analyzed by the GLC method at the chiral phase and spectropolarometrically.

The rate of the epimerization and aminolysis processes of (I) was followed from the change in the angle of optical rotation and the optical density in the IR absorption spectra at 1825 (DME) and 1835 cm^{-1} (t-BuOH).

The epimerization and aminolysis of (I) by the action of (IV) take place according to Scheme 1. The pseudo-first order rate constants of the epimerization were calculated from

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Scheme 1

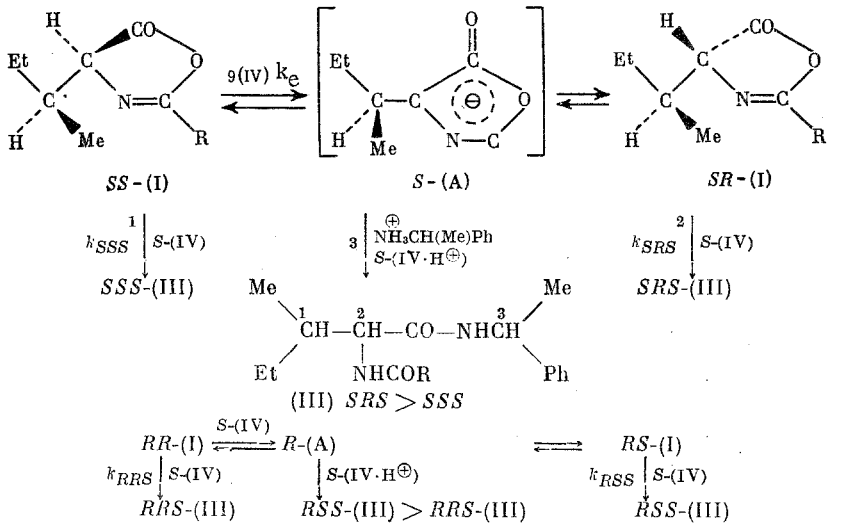


TABLE 1. Composition of Equilibrium Mixture of Epimers of 2-Methyl- (Ia) and 2-Phenyl-4-sec-butyl-5-oxazolones (Ib)*

Oxazolone	Solvent	Composition of mixture, %		K_{eq}, 20°
		SS-(I)	*SR*-(I)	
(Ia)	DME	30	70	2,33
(Ia)	*t*-BuOH	30	70	2,33
(Ib)	DME	39,5	60,5	1,53
(Ib)	*t*-BuOH	39,1	60,9	1,56

*Ratio of SS-(I) and SR-(I) was determined by the PMR method. DME = dimethoxyethane.

the equation

$$\ln(\alpha_0 - \alpha_\infty) - \ln(\alpha - \alpha_\infty) = k_{ob}t$$

where α_0, α_∞, and α are angles of rotation of initial (I), the equilibrium mixture of epimers and the mixture of epimers at moment of time t, respectively, where k_{ob} is observed rate constant of reaction. The kinetics of aminolysis obeys the equation of second order [3]. The second-order rate constants were calculated from the formula $k_e = k_{ob}/C_{IV}$. The kinetic and stereochemical data are listed in Table 2. As in the case of the racemization of 4-isopropyl-5-oxazolones, the rate of epimerization of (I) depends on the substituent at the 2-position of the oxazolone ring and on the nature of the solvent.

Replacement of the methyl group by phenyl leads to an increase in the rate of epimerization by at least two orders of magnitude, and replacement of DME by t-BuOH also accelerates the reaction. These effects are explained by the stabilization of the intermediately formed carbanion, in the first case as the result of the electron-acceptor influence of the phenyl ring, and in the second case as the result of solvation. In all cases, the rate of aminolysis is much lower than the rate of epimerization, and therefore it can be assumed that the three particles present in the equilibrium undergo hydrolysis (see Scheme 1). An examination of the mechanism of the reaction of neutral molecules of (I) with S-(VI) (paths 1 and 2) using the Dreiding and Stuart Briegleb models, as in [3], leads to the conclusion that SSS-(III)* should form at a higher rate than SRS-(III), as, in fact, is observed during the aminolysis of (I) in t-BuOH. As expected, in this case the addition of the achiral Et_3N does not influence the ratio between diastereomers of (III).

We shall evaluate the ratio of the rate constants of formation of the diastereomeric amides (III) k_{SSS}/k_{SRS} (see Scheme 1). From the expression for the rates it follows that

*SSS = 1S2S3S, SRS = 1S2R3S according to our numeration of carbon atoms in (III) (see Scheme 1).

TABLE 2. Data on Epimerization and Aminolysis of (Ia) and (Ib) by Action of S-(IV)

Oxazolone	Solvent	Epimerization		Aminolysis	Ratio of diastereomers of (III), %		Ratio of isoleucines, %		$[\alpha]_{365}$ of mixture of isoleucines
		$k_{ob} \cdot 10^2$, min^{-1}	$k_e \cdot 10^2$, liter/mole·min	$k_a \cdot 10^2$, liter/mole·min	*SSS*	*SRS*	*SS*	*SR*	
(Ia)	DME	3,7±0,4	37±4	5,8±0,4	45,7	54,3	47	53	−6,02
(Ia)	DME /Et_3N	–	–	–	48,3	51,7	–	–	–
(Ia)	*t*-BuOH	100±10	1000±100	20±5	52,2	47,8	–	–	–
(Ia)	*t*-BuOH/Et_3N	–	–	–	51,7	48,3	–	–	–
(Ib)	DME *	300±150	3000±1500	3,7±0,3	35,6	64,4	36	64	−18,7
(Ib)	DME /Et_3N	–	–	–	34,7	65,3	–	–	–
(Ib)	*t*-BuOH †	700	7000	10±2	57,0	43,0	–	–	+9,36
(Ib)	*t*-BuOH/Et_3N	–	–	–	57,6	42,4	–	–	–

*For (Ib) in DME in absence of (IV), k_{ob} is $11.2 \cdot 10^{-1}$ min^{-1}.
†Rate of epimerization is very high [reaction is completed 30 sec after introduction of (IV)].

$$\frac{d[SSS\text{-(III)}]}{dt} = k_{SSS}[SS\text{-(I)}][\text{IV}], \quad \frac{d[SRS\text{-(III)}]}{dt} = k_{SRS}[SR\text{-(I)}][\text{IV}],$$

$$\frac{[SR\text{-(I)}]}{[SS\text{-(I)}]} = K_{eq}$$

where K_{eq} is equilibrium constant of epimerization.

$$\frac{d[SSS\text{-(III)}]}{d[SRS\text{-(III)}]} = \frac{k_{SSS}}{k_{SRS}} \frac{1}{K_{eq}}$$

whence

$$\int_0^t d[SSS\text{-(III)}] = \frac{1}{K_{eq}} \frac{k_{SSS}}{k_{SRS}} \int_0^t d[SRS]$$

since at t = 0

$$[SSS\text{-(III)}] = [SRS\text{-(III)}] = 0$$

$$\frac{k_{SSS}}{k_{SRS}} = \frac{[SSS\text{-(III)}]}{[SRS\text{-(III)}]} \cdot K_{eq}$$

Similarly

$$\frac{k_{RSS}}{k_{RRS}} = \frac{[RSS\text{-III}]}{[RRS\text{-III}]} \cdot \frac{1}{K_{eq}}$$

In Table 3, the values of k_{SSS}/k_{SRS} are given that were obtained in the aminolysis in t-BuOH and calculated from the data in Tables 1 and 2. From these values, it follows that the rate constant of formation of SSS-(III) is 2-2.5 times higher than the rate constant of formation of SRS-(III).

In analogy with [3], it can be assumed that in DME, path (3) is the main one, despite the fact that the influence of Et_3N is in this case not clearly expressed (see Table 2). This may be due to the influence of a chiral β-center in the carbanion. It has been shown in [3] that when the reaction proceeds by path (3), amide with the 2R3S configuration is preferentially formed.

The reaction of the chiral carbanion S-(A) with S-α-phenylethylammonium ($IV \cdot H^{\oplus}$) also leads to the preferential formation of thermodynamically more stable SRS-(III). Similarly R-(A) should lead to an excess of RSS-(III). Table 4 shows that the enantioselectivity of the reaction of R-(Aa) with ($IV \cdot H^{\oplus}$) is higher than that for S-(Aa). This leads to an overall excess of the R-α-C-center in (IIIa) observed during the aminolysis of the mixture of four diastereomers of (I), as confirmed by negative dispersion of optical rotation (DOR) of the corresponding mixture of isoleucines [1].

In the case of (Ab), the enantioselectivity of the aminolysis for the two antipodes is the same, within the limits of experimental error. However, the observed negative DOR of the

TABLE 3. Ratio of Rate Constants of Aminolysis of Diastereomers of (I) in t-BuOH

Oxazolone	k_{SSS}/k_{SRS}	k_{RSS}/k_{RRS}	$k_{SSS}\cdot10^2$	$k_{SRS}\cdot10^2$
(Ia) *	2,54	–	14,3	5,7
(Iб) *	1,99			
(Iб) †	1,99	2,23	6,6	3,4

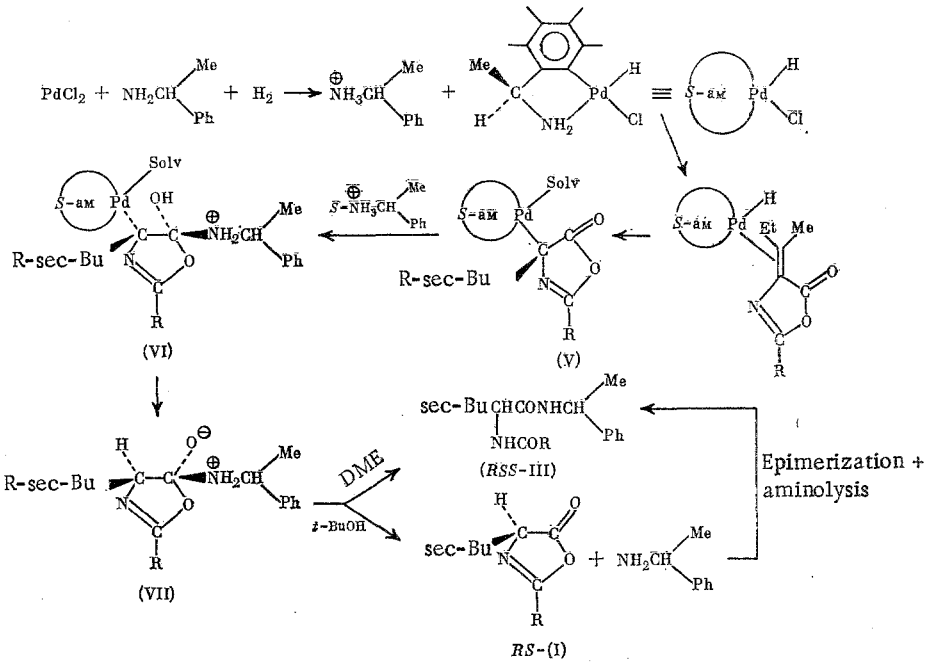
*Calculation according to the data of the present work.
†Calculation according to the data of Table 5 in [1].

TABLE 4. Ratio of Diastereomers of (III) Obtained during Aminolysis of (I) in DME

Oxazolone	SRS/SSS	RSS/RRS
(Ia) *	1,18	–
(Iь) *	1,81	–
(Ia) †	2,5	4,1
(Iб) †	2,0	2,2

See notes in Table 3.

Scheme 2



mixture of isoleucines indicates a higher enantioselectivity in the case of S-(Ab).

From the data obtained in [1] and those in the present work, the following scheme on the mechanism of the reductive aminolysis can be assumed (Scheme 2), in which, for the sake of simplicity, the transformations of Z-(II) are considered. In general outline, Scheme 2 resembles the scheme given in [4]. During reaction of $PdCl_2$, S-(IV), and hydrogen, a chiral hydride complex with Pd is formed, with S-(IV) being the proton acceptor in this case. Unsaturated Z- and E-oxazolones add to the chiral catalytic particle from one and the same side of the ring plane [1]. The addition of the hydride ion to the β-C-atom leads to particle (V) (see Scheme 2), resembling a carbanion in its properties. The reaction with the Z-isomer of the unsaturated oxazolone (70%) leads to a particle with an R-configuration of the β-center; the attack of $(IV\cdot H^{\oplus})$ on the carbonyl group from the side opposite to the Pd atom leads to the formation of RSS-(III) (attack from the side of the Pd atom is sterically less favorable). The reaction with the E-isomer (30%) at the same approach should lead to SSS-(III). However, in this case we can expect an increase in the role of the attack of $(IV\cdot H^{\oplus})$ from the side of the Pd atom, since a thermodynamically more stable SRS-(III) is thus formed. Therefore, a decrease in the stereoselectivity of the reductive aminolysis of 2-methyl-4-sec-butylidene-5-oxazolone is observed, compared with 2-methyl-4-isopropylidene-5-oxazolone. Since the rates of the reductive aminolysis of 2-methyl-4-butylidene-5-oxazolone and of epimerization of (Ia) differ little, it can be assumed that the transition from (VI) to (VII) proceeds with the entry of a proton at the Pd–C bond, and not via the preliminary dissociation of this bond.

Replacement of the methyl group by phenyl at the 2-position of the oxazolone ring leads to weakening of the Pd–C bond (rate of epimerization of saturated oxazolone increases

sharply), and the protonation is accompanied by the dissociation of the complex. In t-BuOH, at the stage of (VI) or (VII), splitting of the amine fragment occurs, and the total reaction proceeds through the intermediate formation of (I), as confirmed by similar kinetic and stereochemical characteristics of the aminolysis of (I) and reductive aminolysis of (II) processes in this solvent. Similar conclusions were reached in [4].

EXPERIMENTAL

The PMR spectra were run on the "Tesla BS-497" radiospectrometer (100 MHz) in $CDCl_3$ with HMDS as internal standard. The dispersion of optical rotation and the epimerization kinetics were studied on the "Spectropol-1" spectropolarimeter. The IR spectra were run on the UR-20 spectrophotometer. The GLC was carried out on the "Khrom-5" and LKhM-8MD apparatus with PID.

The GLC of (III) was carried out on a 1.2 m × 3 mm column filled with chromosorb WNP with 5% OV-17, with He as gas carrier. Compound (IIIa) was analyzed at 210°C, and (IIIb) at 280°C. The retention times of the SRS diastereomers are shorter than those for the SSS-diastereomers. The GLC analysis of the mixture of the isoleucines in the form isopropyl esters of trifluoroacetyl derivatives was carried out on a 3 m × 0.2 cm column with a stationary phase consisting of Chromaton N-super with 3% of tert-butylamide of docosanoyl-S-valine, at 102°C, at a flow rate of 60 ml/min.

SS-2-Methyl-4-sec-butylidene-5-oxazolone (Ia). A 5-mmole portion of DCCI in 50 ml of THF was added at –25 to –30°C to a solution of 5 mmoles of SS-acetylisoleucine in 100 ml of THF. The mixture was stirred for 3.5 h, dicyclohexylurea was filtered, and the filtrate was evaporated in vacuo in the cold. The residue was dissolved in petroleum ether (bp 40-70°C), filtered, and evaporated in vacuo. SS-(Ia) was obtained in the form of the oil, yield 96%. PMR spectrum ($CDCl_3$, δ, ppm): 0.94 t (CH_3–CH_2, ^3J = 7Hz), 1.07 d (CH_3CH, ^3J = 7 Hz), 1.40 m (CH_2CH_3), 2.0 m (β-CH), 2.20 d (CH_3C=N, ^5J = 2.05 Hz), 4.15 d.d. (α-CH, ^3J = 4.4 Hz). IR spectrum (DME, ν, cm^{-1}): 1880 s (C=O), 1680 s (C=N); t-BuOH, 1835 s (C=O), 1685 s (C=N), $[\alpha]_D$ = –76° (C 2.28, THF), $[\alpha]_D$ –160°, $[\alpha]_{410}$ = –400° (C 1.02, DME), $[\alpha]_D$ = –80°, $[\alpha]_{430}$ = –206° (C 1.02, t-BuOH).

Compound SS-(Ib) was obtained in a similar way. PMR spectrum ($CDCl_3$, δ, ppm): 0.90 t (^3J = 7 Hz, CH_3CH_2), 1.02 d (^3J = 7 Hz, CH_3CH), 1.40 m (CH_2CH_3), 2.13 m (β-CH), 4.35 d (α-CH, ^3J = 4.1 Hz), 7.6 m, 8.0 m (C_6H_5). $[\alpha]_D$* = –24° (C 3.5, THF), $[\alpha]_D$ = –18°, $[\alpha]_{365}$ = –25.8° (C 1.4, DME), $[\alpha]_D$ = –25.2°, $[\alpha]_{395}$ = –49.2° (C 1.4, t-BuOH).

Aminolysis of (I). A 1.5 mmole portion of (IV) of 1.5 mmole of Et_3N and 1.5 mmole of (IV), were added to 1 mmole of (I) in 15 ml of solvent. After 30-40 h, the solvent was evaporated, the residue was dissolved in $CHCl_3$, the amines were extracted with 2 N HCl, and the solution was washed with water to a neutral reaction, and evaporated to dryness. Compound (III) was obtained. The hydrolysis of (III) and the isolation of isoleucines was carried out as described in [5].

To study the kinetics of epimerization and aminolysis of (I), we used freshly prepared samples. The change in the rotation angle of (Ia) was observed at 410 nm in DME and at 430 nm in t-BuOH; the change in the rotation angle of (Ib) was observed at 365 nm in DME, and at 395 nm in t-BuOH. The kinetic data were treated according to equations given in this paper and in [3], by the method of least squares.

The authors wish to express their gratitude to V. D. Shats for analyzing amides (III) by GLC.

CONCLUSIONS

1. It was found that SS-4-sec-butyl-5-oxazolones readily undergo epimerization. The ratio between the epimers was determined. The kinetics of epimerization and aminolysis under the action of α-phenylethylamine were studied.

2. The aminolysis of SS-4-sec-butyl-5-oxazolones in tert-butanol proceeds by the reaction of neutral oxazolone molecules with the amine, and leads to preferential formation of the SSS-amide.

3. The aminolysis of SS-4-sec-butyloxazolone in dimethoxyethane proceeds by the reaction of chiral carbanion with S-α-phenylethylammonium, with preferential formation of SRS-amide.

*Compound (Ib) epimerizes on standing and by the action of solvents.

4. A method for the reductive aminolysis of 4-sec-butylidene-5-oxazolones has been proposed.

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REARRANGEMENT OF EUCARVONE OXIDE IN THE PRESENCE OF BASES

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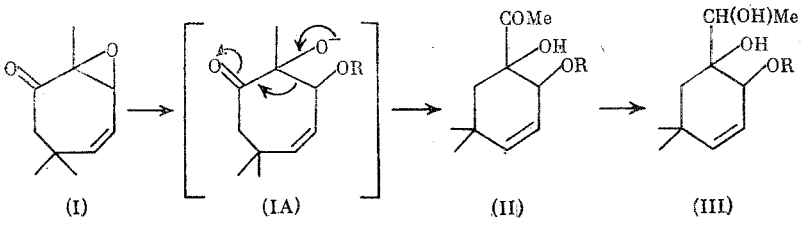
Continuing our study of the properties of α,β-epoxy ketones [1], we have studied the reaction of eucarvone oxide (I) in the presence of alcoholates (MeONa, EtONa) and alkali (KOH) in an alcohol medium (MeOH, EtOH). The reactions were carried out by boiling (I) with an equimolar amount of the alcoholate or a three- or fourfold amount of alkali



(I) (IA) (II) (III)

R = Me(a), Et(b).

The reaction of (I) with MeONa/MeOH and KOH/MeOH gave a product of composition $C_{11}H_{18}O_3$ corresponding to addition of a MeOH molecule to (I). The IR spectrum of the product contained absorption bands of the C=C bond and the C=O and OH groups. According to the data of the proton NMR spectrum, the C=C bond was disubstituted. In addition, the spectrum contained signals of the gem-dimethyl group, methoxy group, and methyl group with a chemical shift of 2.2 ppm, characteristic of methyl bonded to the C=O group, something that suggested the presence of the MeCO fragment in the product. The presence of this fragment was confirmed by the fact that during reduction of the product by $NaBH_4$ a diol was formed, in whose proton NMR spectrum we observed a shift of the signal of the corresponding methyl group (2.2 ppm) to a higher field (1.0 ppm).

The nature of the hydroxyl group was determined by recording the proton NMR spectrum of a solution of the product in deuterated DMSO [2]: The presence of a singlet at 5.0 ppm in the spectrum indicated the tertiary nature of the OH group.

Everything that has been said, taking into account the data of integration of the proton NMR spectra, made it possible to assign structure (IIa) to the obtained product and to assign structure (IIIa) to the corresponding diol.

Similar results were also obtained for the reactions of (I) with EtONa/EtOH and KOH/EtOH. In both cases, only one product was formed, namely, (IIb), whose structure, just as in the case of product (IIa), was determined according to the proton NMR spectrum. Reduction of (IIb) by $NaBH_4$ gave diol (IIIb).

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