# ASYMMETRIC SYNTHESIS OF AMINO ACIDS BY CATALYTIC REDUCTION OF AZALACTONES OF SUBSTITUTED ACYLAMINOACRYLIC ACIDS.

## COMMUNICATION 10. INFLUENCE OF SOLVENT ON REACTION MECHANISM IN REDUCTIVE AMINOLYSIS OF 4-ISOPROPYLIDENE-5-OXAZOLONE

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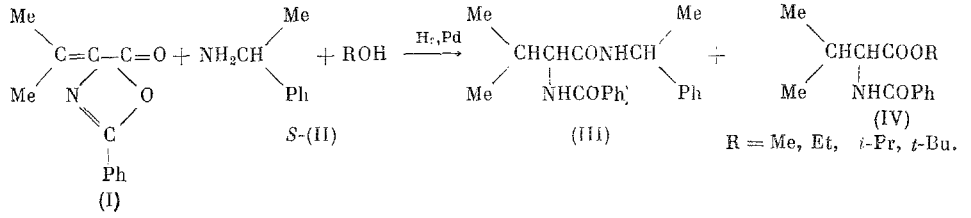
In [1] we described the reaction of reductive aminolysis of 4-isopropylidene-5-oxazolones in 1,2-dimethoxyethane (DME) under the influence of a chiral catalytic system based on $PdCl_2$ and S-($\alpha$)-phenylethylamine. In the work reported here, we investigated the effects of various types of solvents on the stereoselectivity and kinetics of the process of reductive aminolysis of 2-phenyl-4-isopropylidene-5-oxazolone (I).

## DISCUSSION OF RESULTS

When an alcohol is used as the solvent in a reaction of reductive aminolysis, the aminolysis of the 5-oxazolone may be accompanied by its alcoholysis [2] in accordance with the reaction equation shown below.




The hydrogenation was performed in a static unit at 20°C with a hydrogen gauge pressure of 0.2-0.3 kgf/cm$^2$. The reaction rate was judged from the rate of $H_2$ uptake. The reaction mixtures were analyzed by means of PMR, GLC, and spectropolarimetry [1]. The rate of hydrogenation of (I) follows a first-order equation with respect to the oxazolone (Fig. 1); in the case of the MeOH and DME, the dependence of $-\ln C$ on time remains linear all the way up to 85-90% conversion. In the other cases, after 50-60% conversion has been reached, deviations from linearity are observed. In Table 1, along with the composition of the reaction mixture, we have listed the hydrogenation rate constants calculated by the use of the equation

$$\ln C_0 - \ln C = kt \qquad (1)$$

where $C_0$ and C are the initial and instantaneous concentrations of (I) as calculated on the basis of $H_2$ uptake; only the initial linear section was used in the calculation.

It can be seen from Table 1 that the hydrogenation rate depends on the nature of the solvent. The process rate is the highest in MeOH; in alcohols with higher molecular weights (from EtOH to t-BuOH), the hydrogenation proceeds at the same rate, which is only one-fifth that in the MeOH. In the dipolar aprotonic solvent DMFA, the hydrogenation proceeds at the same rate as in EtOH. When the change is made to the low-polarity aprotonic DME, the rate drops in half. The ratio of the processes of aminolysis and alcoholysis in the alcohols depends on the acidity of the alcohol. In the MeOH, the main product is the methyl ester of N-benzoylvaline; in EtOH and i-PrOH, equal quantities of the amide (III) and ester (IV) are obtained, and in t-BuOH, the main product is

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TABLE 1. Hydrogenation of 2-Phenyl-4-isopropylidene-5-oxazolone (I) in Various Solvents (0.18 mmole $PdCl_2$, 1 mmole (I), 1.5 mmoles S-(II), 15 ml solvent)

| Solvent | Reaction product, % | | Excess of SS-diastereomer of (III), % | k, $min^{-1}$ |
|---|---|---|---|---|
| | ester (IV) | amide (III) | | |
| MeOH | 95 * | 5 | | 0,116±0,004 |
| EtOH | 50 | 50 | | 0,022±0,004 |
| *i*-PrOH | 45 | 55 | | 0,021±0,001 |
| *t*-BuOH | 8 | 92 | 25 | 0,021±0,002 |
| DMFA | – | 100 | 10 | 0,017±0,001 |
| DME | – | 100 | 4,6 | 0,011±0,001 |

*Optical yield (p) of methyl ester of benzoyl-R-valine 5%.

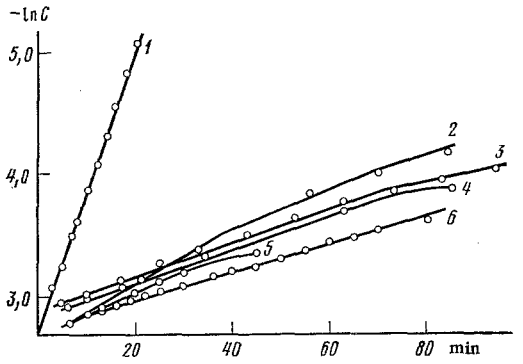
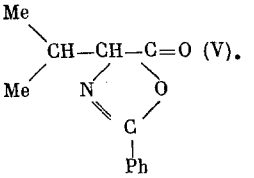



Fig. 1. Hydrogenation of 2-phenyl-4-isopropylidene-5-oxazolone (I) in various solvents: 1) MeOH; 2) i-PrOH; 3) t-BuOH; 4) EtOH; 5) DMFA; 6) DME.

(III) (see Table 1). A similar relationship was observed in [2]. The stereoselectivity in the formation of (III) is also dependent on the nature of the solvent; the excess of the SS-diastereomer (ED) that is obtained increases from DME to t-BuOH. In the t-BuOH, the ED has already reached 25-30%, which made it possible, by analogy with [3], to obtain S-valine with an optical yield p = 90%. The separation of the diastereomers of (III) was performed either by crystallization or by liquid chromatography on silica gel.

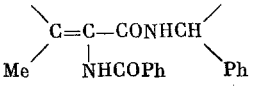
Attempts to achieve a further increase in the stereoselectivity of the process of reductive aminolysis in t-BuOH by lowering the temperature to 10°C did not give the desired results; the use of various additives to lower the melting point of the t-BuOH either lowered the stereoselectivity in spite of the lower temperature (this was the case when $H_2O$ or primary alcohols were added) or left the stereoselectivity unchanged (when sec-hexyl alcohol was added). Increases in the concentration of (II) led to a slight increase in stereoselectivity (Table 2). The sharp increase in stereoselectivity when the DME is replaced by t-BuOH suggests a change in reaction mechanism due to the action of the solvent.

A study of the process stages of the reaction in DME [1] showed that the reductive aminolysis of (I) bypasses the stages of formation of either the unsaturated amide or the saturated oxazolone




(V).

Since the unsaturated amide

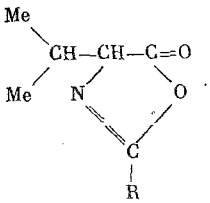



in t-BuOH is not hydrogenated under the conditions of the reductive aminolysis reaction, we can eliminate the possibility of its intermediate formation. However, the formation of the amides (III) with a single configuration in carrying out the reductive aminolysis of (I) and the aminolysis of the saturated azalactone (V) [4] in t-BuOH suggest that in t-BuOH, the process goes through the inter-

TABLE 2. Influence of Concentration of S-(−)-α-Phenylethylamine (II) on Stereoselectivity of Reductive Aminolysis of 2-Phenyl-4-isopropylidene-5-oxazolone (I) in t-BuOH (0.067 mole/liter (I))

| Conc. of (II), moles/liter | $k \cdot 10^2$, moles/liter·min | Excess of SS-diastereomer of (III), % |
|---|---|---|
| 0,1 | 0,20±0,01 | 22–24 |
| 0,2 | 0,11±0,01 | 25 |
| 0,3 | 0,11±0,01 | 27 |
| 0,4 | 0,09±0,01 | 28 |

TABLE 3. Aminolysis of Saturated 4-Isopropyl-5-oxazolones by S-(−)-α-phenylethylamine S-(II)



(1 mmole (V), 1.5 mmoles S-(II), 15 ml solvent)

| R | Method of obtaining sat. azalactone (V) | Solvent | Excess of SS-diastereomer of (III), % |
|---|---|---|---|
| Ph | A * | t-BuOH | 24*SS* |
| Ph | B† | t-BuOH | 16,5*SS* |
| Ph | A | DME | 8,0*RS* |
| Ph | B | DME | 4,6*RS* |
| Me | B | t-BuOH | 14,0*SS* |
| Me | B | DME | 6,2*RS* |

*Method A is the hydrogenation of the oxazolone (I) in the presence of $PdCl_2$ and $Et_3N$.
†Method B is the cyclization of the N-acylvaline by N,N'-dicyclohexylcarbodiimide.

mediate formation of (V) (Table 3). In order to test this hypothesis, we investigated the kinetics of reductive aminolysis of (I) and 2-methyl-4-isopropylidene-5-oxazolone (VI) in DME and in t-BuOH for comparison with the kinetics of aminolysis of the corresponding saturated oxazolones [4]. We pointed out previously (see Fig. 1) that the reductive aminolysis of (I) in DME is a first-order reaction with respect to the oxazolone. In t-BuOH, the linear character of the dependence of ln C on t is observed only up to 55% conversion. The best results are obtained by working up the data on the basis of the second-order equation

$$\ln \frac{C+\Delta}{C} - \ln \frac{C_0+\Delta}{C_0} = \Delta kt \qquad (2)$$

where Δ is the difference between the concentrations of (II) and (I). In this case, linearity is preserved up to 90% conversion (Fig. 2). A change of the initial concentration of the amine (II) from 0.2 to 0.4 mole/liter showed

TABLE 4. Rate Constants for Reductive Aminolysis of 4-Isopropylideneoxazolones (k), and for Aminolysis ($k_a$) and Racemization ($k_r$) of 4-Isopropyloxazolones (0.067 mole/liter oxazolone, 0.1 mole/liter S-(II))

| Oxazolone | Solvent | k, min$^{-1}$ | k, liters/mole·min | $k_a$, liters/mole·min | $k_r$, min$^{-1}$ |
|---|---|---|---|---|---|
| (I) (R=Ph) | DME | 0,01 | – | 0,05 | 12,4 |
| | *t*-BuOH | – | 0,2 | 0,1 | 70 |
| (VI) (R=Me) | DME | – | 0,3 | 0,006 | 0,15 |

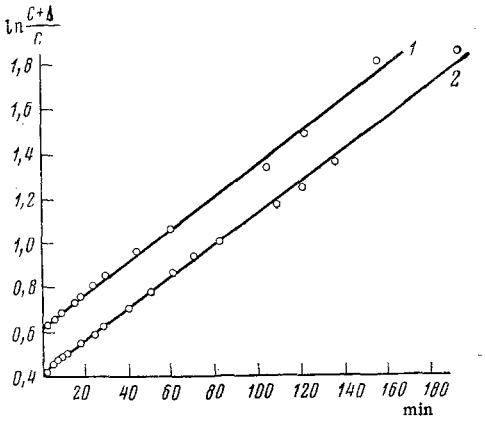



Fig. 2. Reductive aminolysis of 4-isopropylidene-5-oxazolones: 1) 2-methyl-4-isopropylidene-5-oxazolone (VI) in DME; 2) 2-phenyl-4-isopropylidene-5-oxazolone (I) in t-BuOH.

that the constant retains a satisfactory constancy (see Table 2). The slight increase of the constant at an amine (II) concentration of 0.1 mole/liter can be explained on the basis that with the given ratio of concentrations of $PdCl_2$ and (II), the catalyst activity has not yet become independent of the concentration of (II).

A workup of kinetic data on the reductive aminolysis of (VI) in DME [1] in accordance with Eqs. (1) and (2) showed that Eq. (2) gives a better representation of the data (see Fig. 2). In Table 4 we have listed values of the rate constants for the reductive aminolysis of (I) and (VI) and for the processes of racemization and aminolysis of the corresponding saturated 4-isopropyloxazolones (V). In Table 5 we show the rates of these reactions at the instant of half-conversion for (I) and (VI) in DME.

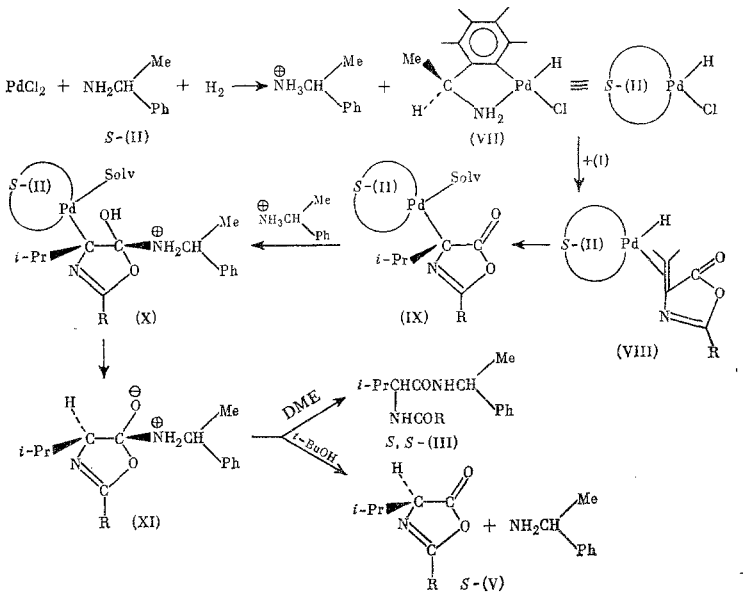
A comparison of the kinetic and stereochemical data for the processes of reductive aminolysis of (I) and the racemization and aminolysis of the saturated oxazolone (V) lead to the following hypotheses relative to the mechanism of the reductive aminolysis process (see scheme). By the interaction of $PdCl_2$, S-(II), and $H_2$, a chiral catalytic system (VII) is formed, activating the hydrogen molecule in a heterolytic manner, the proton acceptor being the chiral amine (II). The possibility of heterolytic activation of hydrogen on a number of Pd complexes has been examined in [5, 6]. It was suggested in [7, 8] that the catalytically active complex has a chelate structure. The addition of a hydride ion to a $\pi$-type-coordinated molecule of the oxazolone (VIII) leads to the species (IX), which is similar in properties to the carbanion of the oxazolone. In the species (IX), the oxazolone is chiral. Subsequent addition of S-$\alpha$-phenylethylammonium proceeds on the least hindered side of the ring plane, in the trans position relative to the Pd atom of (X). The introduction of a proton at the Pd–C bond leads to the species (XI), which was regarded as an intermediate in the aminolysis of (V) [4]. It can be converted either into SS-(III) in DME, or into S-(I) and S-(II) in t-BuOH. In the case of the DME, the stereoselectivity of the process is determined by the enanthioselectivity of the catalyst and the strength of the Pd–oxazolone bond (the capability of the latter for racemization).

In the reductive analysis of 2-methyl-4-isopropylideneoxazolone in DME, the rate of racemization of the saturated oxazolone is of the same order of magnitude as the rate of reductive aminolysis (see Table 4). It appears likely that in the sphere of the Pd complex, the Pd–C bond is quite strong, and the degree of inversion will be low. Therefore, high stereoselectivity of the process is observed, with ED SS-(III) = 40%. The fact that

TABLE 5. Reaction Rates in Reductive Aminolysis of 4-Isopropylidene-5-oxazolones (w) and for Processes of Aminolysis ($w_a$) and Racemization ($w_r$) of Saturated Oxazolones at $\tau_{1/2}$ in 1,2-Dimethoxyethane

| Oxazolone | Reaction rate w·10⁴, moles/liter·min | | |
|---|---|---|---|
| | reductive aminolysis w | aminolysis $w_a$ | racemization $w_r$ |
| (I) | 3,63 | 1,03 | 415 |
| (VI) | 6,6 | 0,3 | 6,81 |

the process is second-order suggests that the limiting stage is the conversion of (IX) to (X). When the change is made to (I), the Pd–C bond is weaker because of the phenyl group; the rate of racemization is two orders of magnitude greater than the rate of reductive aminolysis (see Table 5), and the stage of protonation proceeds with dissociation of the complex, leading to low stereoselectivity. The observed first order of the reaction indicates that the limiting stage is the formation of (IX).



In the case of t-BuOH, the process goes forward through the intermediate formation of (V). Here, the enanthioselective properties of the catalyst play a subordinate role, and the stereoselectivity of the reaction is determined by the ratio of the rates of aminolysis of the enanthiomers of (V) under the influence of the S-(II). This view is supported by the similar kinetic and stereochemical characteristics of the processes of reductive aminolysis of (I) and aminolysis of (V).

## EXPERIMENTAL

The PMR spectra were taken in a Varian DA-60-IL radiospectrometer, internal standard HMDS. The spectropolarimetric measurements were performed in a Spectropol-1 instrument. The 2-phenyl-4-isopropylidene-5-oxazolone (I) was obtained in accordance with [1], m.p. 97.5-98°C (from absolute alcohol); the 2-methyl-4-isopropylidene-5-oxazolone (VI) was obtained in accordance with [1], oil; the S-(–)-α-phenylethylamine had $[\alpha]_D$ –39° (without solvent). The S-α-phenylethylamide of β,β'-dimethylacrylic acid was obtained in accordance with [1]. The reaction of reductive aminolysis was performed in a thermostated glass reactor at 20°C with a hydrogen gauge pressure of 0.2-0.3 kgf/cm². To 0.035 g $PdCl_2$ and 5 ml t-BuOH, 0.2 ml S-(II) was added. After reduction of the catalyst, a solution of 0.2 g (I) and 10 ml t-BuOH was introduced. The hydrogenation rate was

judged from the rate of $H_2$ uptake. At the end of the reaction, the catalyst was removed by centrifuging, and the solution was evaporated to dryness. The residue was dissolved in $CHCl_3$, and the amine was extracted by 2 N HCl and water. The mixture of diastereomers of the amides (III) was crystallized from absolute ethyl acetate or absolute benzene, with the SS-(III) being accumulated in the mother liquor. After several crystallizations, a product was obtained that according to the PMR spectrum was 100% SS-(III) with m.p. 199-200°C, $[\alpha]_{365}$-229°, $[\alpha]_{400}$-173°, $[\alpha]_{350}$-119°, $[\alpha]_{530}$-76.7° (C 0.97, $CHCl_3$). The RS-(III) was isolated by means of LC. The liquid adsorption chromatography of (III) was carried out on 5-40 $\mu$m silica gel. In a column (2.8 × 27.5 cm) that had been equilibrated with the solvent system $CH_2Cl_2$/ethyl acetate/hexane/MeOH (4/1/5/0.02), 5 ml of a 1% solution of (III) in the same solvent system was introduced. The elution rate was 5 ml/min under a nitrogen gauge pressure of 1 kgf/cm$^2$. The fraction volume was 10 ml. The optical density of the fraction was measured in an SF-4 spectrophotometer at a wavelength $\lambda$ = 260 nm. The separation of (III) by means of TLC was performed on Silufol UV-254 plates in the same solvent system as that used in the column chromatography. Clean separation of the diastereomers of (III) was achieved in 18 h. RS-(III), m.p. 198.5-201.5°C, $[\alpha]_{350}$-185°, $[\alpha]_{400}$-131°, $[\alpha]_{450}$-84.6° (C 0.52, $CHCl_3$). The SS-(III) was hydrolyzed by 6 N HCl [1]. A workup of the hydrolyzate gave S-valine with p = 90%.

The reductive aminolysis in two stages was performed in accordance with [1]; the reductive methanolysis of (Ia) was performed in accordance with [3]. The reaction mixture was worked up in the same manner as in the case of the reductive aminolysis. The product recrystallized twice from hexane, according to PMR data, is the methyl ester of benzoyl-R-valine without any admixture of (IIIa):: $[\alpha]_{589}$-2.77° (C 2.9, $CHCl_3$), $[\alpha]_{365}$-58° (C 2.9, $CHCl_3$), p = 4.5%. For the methyl ester of benzoyl-R-valine, $[\alpha]_{365}$-176° (C 2.9, $CHCl_3$).

## CONCLUSIONS

1. The replacement of 1,2-dimethoxyethane (DME) by t-BuOH in the reaction of reductive aminolysis of 2-phenyl-4-isopropylidene-5-oxazolone leads to a considerable increase in the stereoselectivity, so that the S-valine can be obtained with an optical yield up to 90%.

2. On the basis of stereochemical and kinetic data, it is suggested that the reaction proceeds through the intermediate formation of the saturated oxazolone when t-BuOH is used as the solvent, and without the intermediate formation of the saturated oxazolone when DME is used.

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