ASYMMETRIC SYNTHESIS OF AMINO ACIDS BY THE CATALYTIC REDUCTION OF AZLACTONES BY SUBSTITUTED α-ACYLAMINOACRYLIC ACIDS

1. SYNTHESIS OF S-PHENYLALANINE

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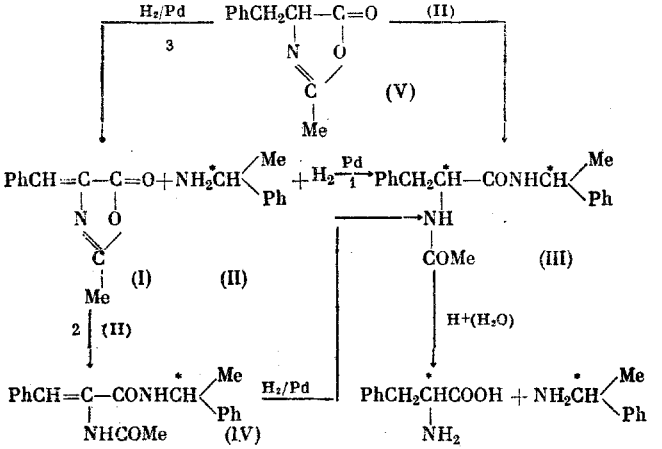
One of the methods for the enantioselective synthesis of amino acids is the reduction of azlactones of α-acylamidoacrylic acids in the presence of chiral catalysts [1]. In the presence of Pd on silk the azlactone of acetamidocinnamic acid (I) is reduced to R(+)-phenylalanine with a total yield of 16% and an optical purity of p = 35.6% [2]. The use of catalysts based on Pd and Ni and obtained by reducing complexes of them with S-tyrosine in this reaction produced S-phenylalanine with a 5-30% yield and p = 30-60% [3]. Rhodium — phosphine catalysts, which have been successfully used for the enantioselective hydrogenation of acylamidocinnamic acids [4, 5], were found to be inactive in the case of the hydrogenation of the corresponding azlactone [4]. The low yields in the case of the reduction of azlactones are apparently attributable to the resistance of the system of double bonds in the azlactone ring to reduction. Recalling the high reactivity of azlactones with respect to conversions involving the opening of the ring, we would expect some facilitation of the hydrogenation of azlactones in the presence of nucleophilic reagents. In fact, the reduction of azlactones was carried out in [6] in ethanol containing ammonia in the presence of Raney nickel, and the reaction resulted in the formation of amides of benzoylamido acids with 80-100% yields.

We previously showed that the reductive aminolysis of I by S(—)-α-phenylethylamine (II) in the presence of a Pd catalyst is stereoselective and produces N-(α'-phenylethyl)-α-acetamidohydrocinnamamide with an SS configuration, whose hydrolysis yields optically pure S-phenylalanine and S(—)-α-phenylethylamine, the latter being capable of being used again in the reaction [7]. The present investigation is devoted to a more detailed study of this reaction.

The reaction of I with II and hydrogen in aprotonic solvents was carried out in the presence of a Pd catalyst, which was obtained by the reduction of $PdCl_2$ by hydrogen (see the scheme):



The reaction products, which contained N-(α'-phenylethyl)-α-acetamidohydrocinnamamide (III) and N-(α'-phenylethyl)-α-acetamidocinnamamide (IV), were analyzed by PMR, the relative amounts of SS-III, RS-III, and IV being determined. Figure 1 presents the PMR spectrum of a mixture of the protons of the CH_3 group, the weak-field signals corresponding to the SS diastereosiomer. The assignment was made on the basis of the

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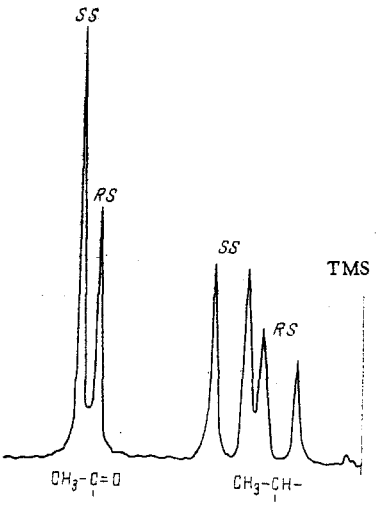

Fig. 1. Proton magnetic resonance spectrum of a mixture of the diastereoisomers of N-(α'-phenylethyl)-α-acetamidohydrocinnamamide.

TABLE 1. Effect of the Ratio between the Azlactone of Acetamidocinnamic Acid (I) and S(—)-α-Phenylethylamine (II) with Various Initial Concentrations in DME on the Nature of the Reductive Aminolysis ($PdCl_2$ = 0.2 mmole, 20°C)

Experiment number	Initial concentration, mole/liter		(II)/(I)	$\tau_{1/2}$, min	Reaction products, %		Ratio of diastereoisomers of III, %, SS : RS	Exc. S,† %
	(I)	(II)			(III)	(IV)		
1	0,07	0,07	1,0	15	80	–	59 : 41	18
2	0,07	0,105	1,50	22	75	10,5	69,5 : 30,5	39
3	0,07	0,135	1,93	42	88	12,0	71,5 : 28,5	43
4	0,07	0,206	2,95	48	63,5	28,0	70,5 : 29,5	41
5	0,07	0,25	3,57	*	60	38,5	68 : 32	36
6	0,08	0,10	1,25	39	72	7	66,6 : 33,4	33,2
7	0,05	0,10	2,00	46	72	12	71 : 29	42
8	0,033	0,10	3,0	36	85	3,3	65,5 : 34,5	31
9	0,025	0,10	4,0	39	72	7	66,6 : 33,4	33,2

*The reaction time was 5 h.
†Excess of the S enantiomer

hydrolysis of that diastereoisomer, which yielded S-phenylalanine. The production of optically pure S-phenylalanine and II as a result of the hydrolysis indicates that there is no racemization of either chiral center.

The results of the experiments in which the temperature, ratio between the components, and the solvent were varied are given in Tables 1 and 2. The investigation of the influence of the ratio between the reactants for various initial concentrations on the nature of the process (see Table 1) showed that when the concentration of the amine is increased, the reaction is slowed, and the relative concentration of the unsaturated amide (IV) in the catalysate increases (experiments 1-5). In addition, the stereospecificity increases as the amine :azlactone mole ratio is increased from 1 to 1.5 (experiments 1, 2, and 6). A further increase in this ratio to 3 has no effect on the stereospecificity. At the same time, changes in the concentration of I with a constant concentration of II have little effect on the process, although dilution lowers the stereospecificity to a slight extent (experiments 4 and 8). Thus, the optimal concentrations of I are 0.07-0.08, and those of II are 0.10-0.14 mole/liter. A comparison of three solvents [dimethoxyethane (DME), dioxane (DO), and THF] revealed that with respect to the reaction rate and stereospecificity DME has definite advantages over THF and DO (see Table 2). Increasing the temperature from 10 to 35°C causes an increase in the relative concentration of IV in the reaction mixture, whereas the stereospecificity drops sharply in dioxane. No significant changes in the course of the reaction are observed in the 10-20°C temperature range. Reduction of the amount of catalyst from 0.035 to 0.020 g has little effect on the reaction, causing only a slight decrease in the rate and stereospecificity.

Considering the step-by-step mechanism for the reductive aminolyiss of azlactones, we can draw the following paths for this reaction (see the scheme).

TABLE 2. Effect of the Temperature and the Solvent on the Reductive Aminolysis of the Azlactone of Acetamidocinnamic Acid (I) by S(—)-α-Phenylethylamine (II), 1 mmole of I, 1.5 mmole of II, 0.18 mmole of $PdCl_2$, and 15 ml of solvent

Solvent	T., °C	$\tau_{1/2}$, min	Reaction products, %		Ratio of diastereomers of III, %, SS : RS	Exc. S, %
			(III)	(IV)		
DME	11	21	98	2	70 : 30	40
"	20	22	97	3	69 : 31	38
DO	11	41	97	3	63 : 37	26
"	20	45	100	—	59 : 41	18
"	35	42	69	23	51 : 49	2
THF	11	15	96	4	58 : 42	16

TABLE 3. Hydrogenation of S(+)-N(α'-Phenylethyl)-α-acetamidocinnamamide (IV) (0.18 mmole of $PdCl_2$, 1 mmole of IV, 15 ml of solvent)

Solvent	Amine	Amount of amine, mole/mole IV	Extent of conversion of IV into III, %	$\tau_{1/2}$, min	Ratio of diastereomers of III, %, RS : SS	Exc. R, %
DO	—	—	100	19	62 : 38	24
THF	—	—	100	14	66 : 34	32
DME	—	—	97	9	60 : 40	20
"	TEA	0,72	89	51	58 : 42	16
"	"	1,60	66	54	60 : 40	20
"	*RS*-(II)	0,67	100	19	56 : 44	12
"	*RS*-(II)	1,33	65	*	53 : 47	6
"	*R*-(II)	0,67	100	36	56 : 44	12
"	*R*-(II)	2,4	No reaction			
"	*S*-(II)	0,67	100	9	70 : 30	40
"	*S*-(II)	2,0	No reaction			

*The reaction time was 160 min.

1. Synchronous interaction of the azlactone with hydrogen and the amine on the catalyst surface, which results in the formation of (III). In this case, the source of the asymmetric induction is a catalyst with a chiral amine adsorbed on its surface. This path presupposes the simultaneous occurrence of oxidation—reduction and acid—base steps on the surface of the catalyst. These steps are separate in the pathways considered below.

2. Aminolysis of the azlactone to form chiral IV followed by its hydrogenation to III. The asymmetric induction in this case is due to the asymmetric center already present in the substrate molecule (diastereoselective hydrogenation). The presence of a chiral amine can result in the modification of the Pd surface and thereby determines the contribution of the chiral catalyst to the overall stereoselectivity of the reaction.

3. Hydrogenation of azlactone I to the azlactone of acetylphenylalanine (V) followed by the aminolysis of the latter to III. In this case either enantioselective hydrogenation with the formation of chiral V followed by aminolysis or the stereoselective aminolysis of racemic azlactone V under the effects of chiral II can take place. For a number of azlactones the rate of racemization is greater than the rate of aminolysis [8], and the observed stereospecificity of the reaction of some racemic azlactones with chiral aminic esters is attributed to the fact that one of the enantiomers of the azlactone reacts with the chiral nucleophile with a greater rate than the other, which is in equilibrium with it [9].

In order to ascertain which of the paths is realized in the process under study, we undertook an investigation of the hydrogenation of unsaturated amide IV and azlactone I in the absence of S(—)-α-phenylethylamine and the aminolysis of azlactone V by S(—)-α-phenylethylamine with and without a catalyst.

The data on the hydrogenation of IV in different solvents in the presence and absence of an amine in different amounts and of varying chirality (Table 3) show that in all cases the hydrogenation of IV results in the preferential synthesis of RS-III, rather than SS-III, which is obtained in the case of the reductive aminolysis of I. In the absence of an amine the rate of the hydrogenation of IV exceeds the rate of reductive aminolysis.

TABLE 4. Hydrogenation of the Azlactone of Acetamidocinnamic Acid (I)* (0.18 mmole of $PdCl_2$, 1.0 mole of I, 15 ml of solvent)

Solvent	Amine	$\tau_{1/2}$, min	Reaction products, %		
			AACA	AcPhe	(V)
DO	–	*	45	45	–
"	TEA	70	–	53	47
"	(II)	45	–	–	–
DME	–	†	44	47	–
"	TEA	37	–	69	31
"	(II)	22	–	–	–

*The reaction time was 150 min.
†The reaction time was 160 min.

The introduction of achiral triethylamine (TEA) results in a decrease in the rate of hydrogenation and has no influence on the stereospecificity of the process. The hydrogenation of IV in the presence of racemic II also takes place with a decrease in the reaction rate; however, the stereospecificity then also decreases. A similar effect is produced by R(+)-II. In the presence of S(—)-II the reaction proceeds with the same rate as in the absence of an amine and with a higher stereospecificity. We note that an increase in the amount of amine causes the activity of the catalyst to decrease down to complete deactivation when there are 2 moles of II for every mole of IV. The reductive aminolysis takes place with a considerable rate under similar conditions (see Table 1). The changes in the rate and stereospecificity as a function of the chirality of II (experiments 8 and 10) suggest that a dissymmetric catalyst makes a contribution to the asymmetric synthesis (diastereo- and enantioselective hydrogenation).

The formation of III during the hydrogenation of IV with a configuration which differs from that in the case of the reductive aminolysis suggests that the second path, i.e., through unsaturated amide IV, is not the main path for the reductive aminolysis reaction, despite the presence of IV in the reaction mixture and the high rates of its hydrogenation. The presence of azlactone I in the reaction mixture apparently prevents the adsorption and hydrogenation of the IV which forms.

The hydrogenation of azlactone I (Table 4) in the absence of a base proceeds to only about a 50% extent of conversion. This is attributed, on the one hand, to the stability of the system of double bonds and, on the other hand, to the reactivity of the azlactone ring with respect to reactions involving the opening of the ring followed by polymerization, which results in deactivation of the catalyst. The original azlactone is not found in the case of practically all catalysts of incomplete hydrogenation. The reaction mixture consists of acetylphenylalanine (AcPhe) and acetamidocinnamic acid (AACA), the hydrolysis products of I, and V. In the presence of TEA, which is not capable of forming an amide, the hydrogenation process is facilitated, but the rate of the reaction is somewhat lower than in the case of reductive aminolysis. The reaction yields a mixture of AcPhe and its azlactone (V), which was identified according to its PMR spectrum [δ, ppm, 1.98 (d, CH_3, $J_{CH_3,H}$ = 2 Ha)] and its IR spectrum ($\nu_{C=O}$ 1820 cm^{-1}) [10]. It seemed of interest to establish whether azlactone V is present in the reaction mixture as a possible intermediate product of the reductive aminolysis in the initial steps of this reaction. For this purpose, samples of the reaction mixture were analyzed by IR spectroscopy. The presence of azlactone V was evaluated from the change in the ratio of the optical density of the reaction product at $\nu_{C=O}$ = 1805 cm^{-1} (I in DME) to the optical density at $\nu_{C=O}$ = 1820 cm^{-1} (V in DME). The reaction is accompanied by a decrease in this ratio (Table 5), which indicates the presence of V in the reaction mixture, since none of the products of the reductive aminolysis has an absorption band in that region. It was still necessary to ascertain the stereospecificity with which the aminolysis of V by S(—)-α-phenylethylamine takes place and the role of the catalyst in this process. Table 6 presents the results of two series of investigations on the aminolysis of V. The reaction rate was evaluated from the change in the optical density at ν = 1820 cm^{-1}. According to Table 6, the aminolysis process is stereospecific and results in the predominant formation of SS-III, and the catalyst increases both the rate of aminolysis and the stereospecificity of the reaction. This again points to the dissymmetric nature of the catalyst. Thus, path 3 is a very likely mechanism for the reductive aminolysis of azlactones, although these data do not rule out the first path, viz., the synchronous interaction of the azlactone with hydrogen and a nucleophile on the surface of the catalyst.

The dissymetric nature of the catalyst was displayed especially clearly in the case of the reduction of azlactone I in the presence of S(—)-II in methanol. In this case the main reaction product was optically active methyl R-α-acetamidohydrocinnamate with an optical purity of 24.2%.

TABLE 5. Investigation of the Initial Step in the Reductive Aminolysis of the Azlactone of Acetamidocinnamic Acid (I) in DME under Standard Conditions by IR Spectroscopy

Object of investigation	Optical density D (l = 0.183)* at		D_{1805}/D_{1820}
	1805 cm^{-1}	1820 cm^{-1}	
I, C_0 = 0.07 mole/liter	0,35	0,065	5,4
I, C_0 = 0.024 mole/liter	0,17	0,031	5,3
Reaction mixture after 10 min	0,32	0,097	3,3
Same after 30 min	0,20	0,068	2,9

*Here l is the optical path.

TABLE 6. Investigation of the Aminolysis of the Azlactone of Racemic Acetylphenylalanine (V) by S(—)-α-Phenylethylamine in DME by IR Spectroscopy ([V] = 0.07 mole/liter, 0.18 mmole of $PdCl_2$, 15 ml of DME)

Reaction time, min	Optical density at 1820 cm^{-1} (l = 0.183 cm)	
	without a catalyst	with a catalyst
0,0	0,33	0,33
20	0,27	0,13
30	0,25	0,097
90	0,0	0,0

Note. In the experiment without a catalyst III was obtained with a 30% excess of the diastereomer with the SS configuration, and in the experiment with the catalyst the excess was 44%.

EXPERIMENTAL

The PMR spectra were recorded on a Varian 60 radiospectrometer, and the internal reference was TMS. The IR spectra were recorded on a UR-20 spectrometer, and the spectropolarimetric measurements were carried out on a Spectropol-1 spectropolarimeter.

The $PdCl_2$ was pure-grade, the azlactone of acetamidocinnamic acid (I) had mp 150°C (from acetone), and the S(—)-α-phenylethylamine (II) had $[\alpha]_D = -40.4°$.

S(+)-N-(α'-Phenylethyl)-α-acetamidocinnamamide (IV). A 1.5-g portion of I and 0.8 ml of II in 35 ml of DME were left to stand for several hours, and the precipitate formed was filtered and washed with DME. This provided IV with a 50% yield. An additional amount of IV was obtained upon evaporation of the mother liquid, mp 195-197°C (from abs. ethanol). UV spectrum [ethanol, λ_{max}, nm (ε)]: 217 sh (21,100), 276 sh (20,800). IR spectrum (KBr, ν, cm^{-1}): 3430 (val. free NH), 3230 (val. bound NH), 1650, 1630 (first amide bond), 1530 (second amide bond). PMR spectrum (CD_3OD δ, ppm): 1.49 (d, $C\underline{H}_3CH$), 2.08 (s, $C\underline{H}_3CO$), 7.01 (s, CH=C), 7.15-7.40 (m, C_6H_5). $[\alpha]_D$ +43°, +51° (546 nm), +115° (436 nm), +302° (365 nm) (c 1.39, ethanol).

Azlactone of RS-Acetylphenylalanine (V). Compound V was obtained according to [11] in the form of an oil. IR spectrum (in a thin layer, ν, cm^{-1}); $\nu_{C=O}$ 1820, $\nu_{C=N}$ 1680. PMR spectrum ($CDCl_3$, δ, ppm): 1.98 (d, $C\underline{H}_3$, $J_{C\underline{H}_3H}$ = 2 Hz), 3.07 (q, CH_2), 4.33 (m, CH), 7.18 (C_6H_5).

Experimental Procedure. The reductive aminolysis was carried out in a thermostated reactor with magnetic stirring under an excess hydrogen pressure of 0.2-0.3 atm, which was maintained with the aid of a cylinder filled with purified H_2. A reactor with 0.035 g of $PdCl_2$, 5 ml of DME, and 0.2 ml of S(—)-II was blown through with H_2, and then the stirring was switched on. After the catalyst was reduced, the reactor was connected to a gasometric burette. After the establishment of a steady state in the reactor, a solution of 0.2 g of I in 10 ml of DME was introduced from a syringe. The rate of the hydrogenation of azlactone I was evaluated from the rate of the absorption of H_2. At the conclusion of the reaction the catalyst was removed by centrifugation, 1-2 ml of water were added to the catalysate, and the latter was acidified with 6 N HCl to pH 1-2 and passed through a column with the cation exchanger Dowex 50 × 8 (in the H^+ form) in order to remove the excess of amine II. The column was washed with aqueous methanol, and the solution obtained was evaporated in a vacuum to dryness. According to the data from the PMR spectrum, the product was a mixture of the diastereomers of N-(α'-phenylethyl)-α-acetamidohydrocinnamamide (III) with a 40% excess of the SS diastereomer and IV (5-10%). This product was crystallized from ethyl acetate with hexane. This yielded pure SS-III, mp 216°C. PMR spectrum (CD_3OD, δ, ppm): 1.39 (d, $C\underline{H}_3CH$), 1.91 (s, $C\underline{H}_3CO$), 2.90 (q, $C\underline{H}_2$), 7.13 (m, C_6H_5). $[\alpha]_D$ −46.8°, −52.7° (546 nm), −100° (436 nm), −177° (365 nm) (c 1.06, ethanol). The IR and UV spectra were identical to the spectra of the mixture of the diastereomers of III obtained by the back synthesis from racemic acetylphenylalanine and α-phenylethylamine under the action of dicyclohexylcarbodiimide

[12]. UV spectrum [ethanol, λ_{max}, nm (ε)]: 208 (19,800), 217 (9300), 257 (370). IR spectrum (KBr, ν, cm^{-1}): 3310, 3270 (NH), 1650 (first amide bond), 1560 (second amide bond). PMR spectrum (CD_3OD, δ, ppm): 1.22 (d), 1.39 (d), 1.88 (s), 1.91 (s).

Hydrolysis of SS-III. A mixture of 0.28 g of SS-III and 3 ml of 6 N HCl was boiled on an oil bath in a current of N_2 for 7 h. The hydrolysate was evaporated to dryness in a vacuum, 2 N NaOH was added, and S-II·HCl was extracted with ether, mp 171°, $[\alpha]_{350}$ −28.4°, $[\alpha]_{320}$ −39.0° (c 2, ethanol). The solution was acidified to a clearly acidic reaction and introduced into a column with Dowex 50 × 8 (in the H^+ form), the column was washed with water, and S(−)-phenylalanine was eluted by 2 N NH_4OH. The eluate was evaporated to dryness. Optically pure S(−)-phenylalanine was obtained with a 76% yield and $[\alpha]_D$ −33.4° (c 1.33, H_2O).

Synthesis of Methyl R-Acetamidohydrocinnamate. The reaction was carried out in an analogous manner in abs. CH_3OH. The product obtained following the removal of II and evaporation was an oil containing 70% methyl acetamidohydrocinnamate, 20% III and IV, and 10% acetylphenylalanine. The oil was treated with aqueous methanol, amides III (RS : SS = 1 : 1) and IV were separated, and the remaining product was crystallized form isopropyl ether. Methyl acetamidohydrocinnamate was obtained with mp 62-64°C. The IR spectrum was identical to the spectrum of a known sample; $[\alpha]_D$ −4.6°, −5.4° (546 nm), −10.4° (436 nm), −17.8° (365 nm) (c 2, CH_3OH); p = 24.2%, $[\alpha]_D$ +19° (c 2, CH_3OH) [13].

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CONCLUSIONS

1. The reaction of the azlactone of acetamidocinnamic acid with S(−)-α-phenylethylamine and hydrogen on the surface of a Pd catalyst in aprotonic solvents results in the formation of N-(α'-phenylethyl)-α-acetamidohydrocinnamamide predominantly of the SS configuration, whose hydrolysis yields optically pure S(−)-phenylalanine and S(−)-α-phenylethylamine.

2. The reduction of S(+)-N-(α'-phenylethyl)-α-acetamidocinnamamide on the Pd catalyst is stereospecific and results in the formation of N-(α'-phenylethyl)-α-acetamidohydrocinnamamide predominantly of the RS configuration.

3. The aminolysis of the azlactone of RS-acetylphenylalanine by S(−)-α-phenylethylamine yields N-(α'-phenylethyl)-α-acetamidohydrocinnamamide predominantly of the SS configuration.

4. The reduction of the azlactone of acetamidocinnamic acid in the presence of S(−)-α-phenylethylamine on the Pd catalyst in methanol yields methyl R-acetylphenylalanine with an optical purity of 24.2%.

5. The reduction of $PdCl_2$ in the presence of S(−)-α-phenylethylamine results in the formation of a dissymmetric catalyst for the hydrogenation of unsaturated perchiral precursors of amino acids.

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