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

4. PRODUCTION OF (S)-TYROSINE AND (S)-O-METHYLTYROSINE

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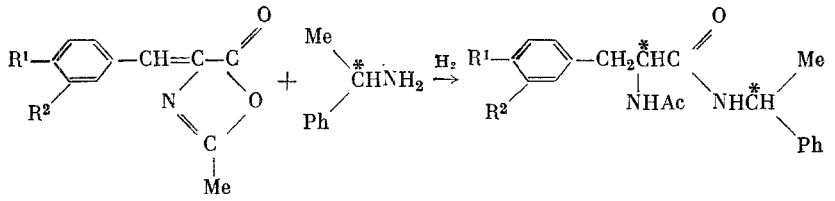
In the previous communications [1-3] we described the asymmetric synthesis of S-phenylalanine and S-3,4-dihydroxyphenylalanine (L-dopa) by reductive aminolysis of the corresponding azlactones by chiral S-α-phenylethylamine in the presence of palladium and rhodium catalysts. The present work is devoted to investigation of this reaction in ring-substituted azlactones in order to obtain S-tyrosine and S-O-methyltyrosine.

As starting compounds we used the azlactones of 4-acetoxy- and 4-methoxy-α-acetamidocinnamic acids (Ia) and (Ib). The main reaction took place according to the equation:



(I) (II) (III)

R^1=AcO, R^2=H (Ia); R^1=MeO, R^2=H (Ib)

The α-phenylethylamides of 4-acetoxy- and 4-methoxy-α-acetamidocinnamic acids (IVa) and (IVb), formed during the aminolysis of compounds (Ia) and (Ib), were side products. In addition, the acetoxy group in compound (IVa) is readily saponified, giving the α-phenylethylamide of 4-hydroxy-α-acetamidocinnamic acid (IVc). Analysis of the reaction products by the PMR method made it possible to determine the ratio of the diastereomers (III) and the content of (IV). Reductive aminolysis of (Ia) and (Ib) was realized at 20°C with 0.2-0.3 atm of hydrogen over palladium, obtained by reduction of palladium dichloride in situ. The results are given in Table 1.

TABLE 1. The Reductive Aminolysis of the Azlactones of 4-Acetoxy- and 4-Methoxy-α-acetamidocinnamic Acids (Ia) and (Ib) [0.18 mmole of $PdCl_2$, 1 mmole of (I), 1.55 mmole of amine, 15 ml of solvent]

Substrate	Solvent	Amine	Reaction rate $\tau_{1/2}$, min	Yield of (III), % of theoretical	Content of (IV), %	Preferred configuration (III)	E.d.,* %
(Ia)	DO	S(−)-(II)	30	63	11	*SS*	60
(Ia)	DME	S(−)-(II)	14	54	17	*SS*	46
(Ia)	THF	S(−)-(II)	18	41	12	*SS*	61
(Ib)	DO	S(−)-(II)	30	39	4	*SS*	36
(Ib)	DME	S(−)-(II)	20	51	6	*SS*	58
(Ib)	DME	S(−)-(II) TEA	35	42	–	*SS*	42
(Ib)	THF	S(−)-(II)	23	30	6	*SS*	60
(Ib)	THF	R(+)-(II)	–	18	7	*RR*	60
(Ib)	THF	R,S(∓)-(II)	–	15	13	*SS*, *RR*	56

*E.D. = excess of diastereomer; TEA = triethylamine.

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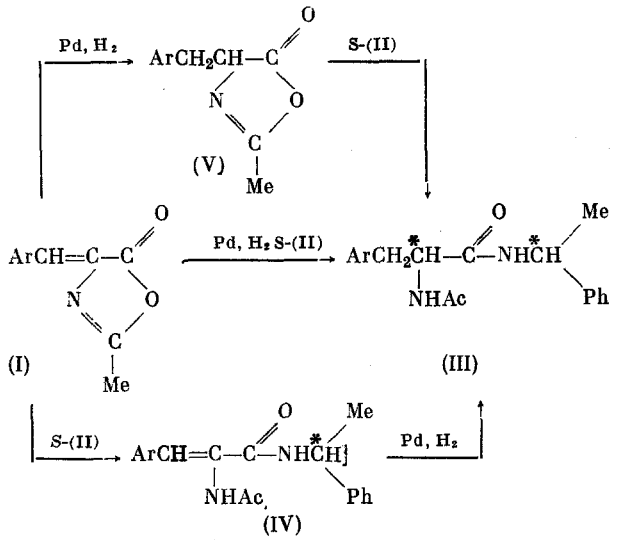
TABLE 2. Hydrogenation of S-α-Phenylethylamide of 4-Methoxy-α-acetamidocinnamic Acid (IVb) [0.18 mmole of $PdCl_2$, 1 mmole of (IVb), 1.5 mmole of amine, 15 ml of solvent]

No.	Solvent	Amine	Reaction rate $\tau_{1/2}$, min	Reaction time, min	Degree of conversion, %	Ratio of diastereomers, % SS : RS	Excess of RS diastereomer, %
1	DO	–	120	270	100	34 : 66	32
2	DO	*S,R*-(II)	–	330	54	50 : 50	0
3	DO	*S*-(II)	–	360	40	45 : 55	10
4	DME	–	210	350	74	36 : 64	28
5	THF	–	120	345	96	33 : 67	34
6	THF	*S,R*-(II)	–	390	43	50 : 50	0
7	C_2H_5OH	–	60	245	100	42 : 58	16
8	C_2H_5OH	*S,R*-(II)	–	470	57	39 : 61	22
9	C_2H_5OH	*S*-(II)	–	480	47	39 : 61	22
10	CH_3OH	–	25	160	100	41 : 59	18
11	CH_3OH	*S*-(II)	–	330	58	39 : 61	22

Hydrogenation of (Ia) and (Ib) in the presence of S-(II) in aprotic solvents [dimethoxyethane (DME), dioxane (DO), and THF] gives the amides (IIIa) and (IIIb) with the preferred SS configuration (Table 1). The best solvent for hydrogenation of compound (Ia) was dioxane, in which the reaction gives the highest yield of (IIIa) and is most stereospecific. In dimethoxyethane a decrease is observed in both values, and in THF with a high degree of stereospecificity the yield of the saturated amides (IIIa) is lower than in dioxane. The obtained compound (IIIa), with an excess of up to 60% of the SS diastereomer, gave the pure SS-(IIIa) after only one crystallization. By its hydrolysis in 6 N hydrochloric acid it was possible to obtain the optically pure S-tyrosine. Hydrogenation of compound (Ib) in DME has certain advantages. The product, obtained with a 57% yield, contains a 58% excess of the diastereomer SS-(IIIb). After crystallization once or twice from absolute alcohol it gave the pure SS-(IIIa), hydrolysis of which in 6 N hydrochloric acid led to the optically pure S-O-methyltyrosine. The use of the amine R-(II) in this reaction leads to the preferential formation of RR-(IIIa), and in the presence of racemic R,S-(II) the RR,SS-diastereomers are formed preferentially.

The possible paths for the transformation of the azlactones under the conditions of reductive aminolysis [1] are given in the following scheme:



(3)

(1)

(2)

In order to establish which of the paths is realized when substituents are introduced into the aromatic ring of the azlactones the behavior of the supposed intermediate products (IV) and (V) under the conditions of reductive aminolysis was studied.

Investigation of the hydrogenation of (IVa) in dioxane, dimethoxyethane, and tetrahydrofuran showed that the reaction in the absence of the amine occurs at a rate an order of magnitude lower than the rate of reductive aminolysis of compound (Ia) (28-32% conversion after 320 min). Similar amounts of SS-(IIIa) and RS-(IIIa) with a small excess of the RS diastereomer were found in the reaction products. It was difficult to determine the excess by

TABLE 3. The Aminolysis of the Saturated Azlactones of N,O-Diacetyltyrosine (Va) and O-Me-N-Acetyltyrosine (Vb) by S-(—)-α-phenylethylamine S-(II) [0.18 mmole of $PdCl_2$, 1 mmole of (Vb), 1.5 mmole of amine, and 15 ml of solvent]

Substrate	Solvent	Catalyst	Yield of (III), % of theoretical	Ratio of diastereomers, % SS : RS	Excess of SS, %
S-(Va)	DO	–	79	69,7 : 30,3	39,4
S-(Va)	DO	Pd	72	72,6 : 27,4	45,2
S,R-(Va)*	DME	–	69	82,0 : 18,0	64,0
S,R-(Vb)*	DME	–	49	69,0 : 31,0	38,0
S,R-(Vb)*	DME	TEA	80	66,0 : 34,0	32,0

*The racemic saturated azlactones were obtained by the hydrogenation of (Ia) and (Ib) in DME in the presence of TEA.

the PMR method. In absolute alcohol the reaction rate is rather higher, the degree of conversion amounts to 78% after 320 min, and the product (IIIa) contains a small excess of the RS-diastereomer (6%). In methanol the hydrogenation of compound (IVa) takes place at an even higher rate, and the compounds (IIIa) (obtained with a yield of ∿100%) have a 5% excess of the RS isomer.

From data on the hydrogenation of compound (IVb) (Table 2) it is seen that in aprotic solvents in the absence of the amine the hydrogenation rate of compound (IVb) is 4-10 times lower than the rate of reductive aminolysis of compound (Ib). Here, as in the hydrogenation of compound (IVa), the compound (III) with the other configuration is formed preferentially. Realization of the reaction in the presence of the racemic amine R,S-(II) reduces the hydrogenation rate, and the stereospecificity is lost. The formation of the other configuration during the hydrogenation of (IVa) and (IVb) and also the substantially lower reaction rate compared with the reductive aminolysis of (Ia) and (Ib) make it possible to state that the unsaturated amides (IV) are not intermediate products of this process. The use of the chiral amine S-(II) in the reaction also reduces the hydrogenation rate, but the reaction is stereospecific with the formation of a 10% excess of the RS isomer (Table 2). During the hydrogenation of (IVb) in the absence of the amine diastereoselective hydrogenation occurs, leading to the production of an excess of RS-(IIIb). In the presence of the chiral amine enantioselective hydrogenation is realized in addition to the diastereoselective process, and this shows up as a change in the excess of the RS-diastereomer (IIIb) during hydrogenation with the racemic amine and with the S-amine. In contrast to this, the hydrogenation of (IVb) in alcohols, although retarded in the presence of R,S- and S-amines, leads to practically the same ratio of diastereomers (IIIb) as in the absence of amines.

In order to investigate the possibility of realizing path (3) (see the scheme) we investigated the aminolysis of the saturated azlactones (Va) and (Vb) (Table 3). It is known that optically active saturated azlactones readily racemize, particularly in the presence of alcohols and benzylamine [4]. Aminolysis of racemic saturated azlactones in the presence of chiral agents can occur stereospecifically as a result of the difference in the reaction rates of the enantiomers, which are in equilibrium [5]. The investigation showed that the aminolysis of S-(Va) by benzylamine occurs at a high rate and leads to racemic 4-acetoxy-N-acetylphenylalanine benzylamide. To compare the rates of racemization and formation of the amide in the aminolysis of S-(—)-(Va) with racemic α-phenylethylamine we simultaneously ob-

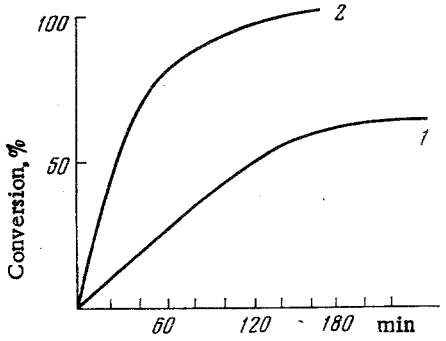
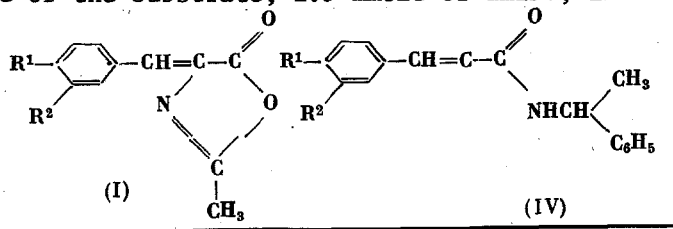


Fig. 1. The dependence of the degree of conversion (1) and the degree of racemization (2) on time in the aminolysis of the saturated azlactone (Va) by racemic S,R-phenylethylamine in dioxane [$C_{(Va)} = 0.0193$, $C_{S,R-(II)} = 0.0193$ M].

TABLE 4. The Rates ($\tau_{1/2}$) of Reductive Aminolysis and Hydrogenation of the Azlactones (I) and α-Phenylethylamides (IV) of Substituted Acetamidocinnamic Acids (0.18 mmole of $PdCl_2$, 1 mmole of the substrate, 1.5 mmole of amine, 15 ml of solvent)



(I) (IV)

R¹	R²	Reductive aminolysis of (I) with S-(II)			Hydrogenation of (I) with TEA			Hydrogenation of (IV) without amine		
		DME	DO	THF	DME	DO	THF	DME	DO	THF
		$\tau_{1/2}$ min								
H	H	22	45	15	36	70	290 †	9	19	14
AcO	H	14	30	18	21	No react.	–	††	††	††
MeO	H	20	30	23	65	–	120	210	120	120
AcO	MeO	34	38	48 *	45	–	130	No react.		

*Reaction temperature 10°C.

†The reaction hardly goes any further.

††The degree of transformation after 330 min is 26-32%.

served the variation of the optical rotation and the IR absorption at 1815 cm^{-1} [$\nu_{C=O}$ in (Va)] for solution containing equimolar amounts of S-(Va) and S,R-(II). It was shown (Fig. 1) that the racemization rate of S-(Va) is higher than the aminolysis rate. Racemization is almost complete after 120 min, but the amount of unreacted (Va) here is ∿50%.

On the basis of the suggestion that the reductive aminolysis of (Ia) and (Ib) can take place through the intermediate formation of saturated azlactones it was important to investigate the aminolysis of (Va) and (Vb) and to determine the role of the catalyst in this process (Table 4). Aminolysis of the optically active S-(Va) in dioxane leads to a 40% excess of SS-(IIIa) (see Table 4). Realization of the reaction in the presence of the palladium catalyst has practically no effect on the stereospecificity of the opening of the azlactone ring. It was not possible to establish the effect of the palladium catalyst on the transformation rate of S-(Va) since (according to the IR spectra) compound (Va) is practically absent only 4 min after the beginning of the reaction. Reductive aminolysis of compound (Ia) under the same conditions leads to a 60% excess of SS-(IIIa) (Table 1). In dimethoxyethane aminolysis of the racemic S,R-(Va) gives a 64% excess of SS-(IIIa), whereas reductive aminolysis gives a 46% excess of SS-(IIIa). Table 4 also gives data on the aminolysis of racemic S,R-(Vb) in the presence of triethylamine (TEA), which is a catalyst for racemization and for opening of the azlactone ring [6]. Aminolysis of S,R-(Vb) in dimethoxyethane gives a 38% excess of SS-(IIIb) (in the presence of triethylamine this value is slightly reduced), whereas the reductive aminolysis of (Ib) in dimethoxyethane leads to a 58% excess of SS-(IIIb) (Table 1). Realization of the reductive aminolysis of (Ib) in the presence of S-(II) and triethylamine leads to a 42% excess of SS-(IIIb). Aminolysis of the saturated azlactones (Va) and (Vb) by the optically active amine takes place stereospecifically with the preferred formation of the SS-diastereomers (III) (Table 4). Reductive aminolysis of the azlactones (I) has the same stereoselectivity. However, the ratio of the diastereomers obtained in these two reactions differs, and this is evidently due to the unsymmetrical character of the palladium catalyst, on which aminolysis occurs without reaction in the volume.

The results make it possible to suppose that the saturated azlactones can be intermediate products in reductive aminolysis. However, the high rate of their aminolysis and the effect of the surface of the modified catalyst on the stereospecificity of the hydrogenation of the azlactones indicates reaction of the azlactone (I), hydrogen, and amine under the influence of the catalyst in a single stage. The last suggestion is confirmed by the realization on the enantioselective hydrogenation of the azlactone (Ib) in methanol, which led to the production of R-N-acetyl-O-methyltyrosine methyl ester with an optical yield of 35%. The realization of an asymmetric synthesis is this case can only occur with stereospecific methanolysis of the saturated azlactone (Vb) at the surface of the unsymmetrical catalyst.

Comparison of the rates of reductive aminolysis for a series of 2-methyl-4-arylidene-5-oxazolones and the rates of hydrogenation of (I) and (IV), given in the present work and in [1-3] (Table 4), leads to the conclusion that substitution in the aromatic ring has little effect on the rate of reductive aminolysis in all the employed solvents, where the rate varies little with variation of the solvent. However, during hydrogenation of the azlactones in the presence of triethylamine both the substituent and the solvent have an effect on the reaction rate. In dioxane and tetrahydrofuran substitution has an effect on the hydrogenation rate. The effect of substituents is particularly strong during the hydrogenation of the open molecule (IV), where the rate decreases sharply with the substituents in the order H > MeO > AcO > 4-AcO-3-MeO, and in the latter case the reaction does not occur. These facts together with others indicate the generality of the mechanism of reductive aminolysis of 2-methyl-4-arylidene-5-oxazolones and confirm the suggestion that the azlactone reacts with the nucleophile and hydrogen in the presence of the catalyst in one stage.

EXPERIMENTAL

The PMR spectra were recorded on a Varian-60 radiospectrometer with TMS as internal standard. The azlactone of 4-acetoxy-α-acetamidocinnamic acid (Ia) was obtained according to the data in [7]; mp 135-137°C (from absolute ethanol or chloroform). The azlactone of 4-methoxy-α-acetamidocinnamic acid (Ib) was obtained similarly [8]; mp 110-111°C (from absolute ethanol). S-(—)-α-Phenylethylamine [S-(II)]. $[\alpha]_D^{20}$ —40.4° (without solvent). R-(+)-α-Phenylethylamine [R-(II)]. $[\alpha]_D^{20}$ +40.0° (without solvent).

S-(+)-α-Phenylethylamide of 4-Acetoxy-α-acetamidocinnamic Acid (IVa). Compound (IVa) was obtained according to data in [1, 3]; mp 173-176°C (from chloroform). $[\alpha]_\lambda^{17}$(λ, nm): +41.6° (589), +44.8° (578), +52.9° (546), +124.8° (436), +338° (365), +470° (350) (C = 1.02, methanol). UV spectrum (1:5 methanol—chloroform): λ_{max} 285 nm (ε 18,500). IR spectrum (potassium bromide, ν, cm^{-1}): 3230 (NH stretch), 1765 (C=O ester), 1655, 1630 (amide I), 1540, 1510 (amide II), 1280, 1210 (C—O). PMR spectrum (deuteromethanol + deuterochloroform, δ, ppm): 1.50 d ($J_{CH_3,H}$ = 7 Hz), 2.01 s, 2.28 s, 5.08 m, 6.70-7.40 m.

SR-(±)-α-Phenylethylamide of 4-Hydroxy-α-acetamidocinnamic Acid (IVc). The compound was obtained similarly from (Ia) and R,S-(II) in absolute ethanol; mp 81-91°C (from heptane—ethyl acetate). UV spectrum (in chloroform): λ_{max} 293 nm (ε 15,100). IR spectrum (chloroform, ν, cm^{-1}): 3430, 3230 (NH stretch), 1610, 1680 (amide I), 1520 (amide II), 1210, 1280 (C—O). PMR spectrum (deuteromethanol, δ, ppm): 1.47 ($J_{CH_3,H}$ = 7 Hz), 2.11 s, 7.05-7.51 m.

S-(+)-α-Phenylethylamide of 4-Methoxy-α-acetamidocinnamic Acid (IVb). The compound was obtained like compound (IVa): mp 208-210°C (from chloroform). $[\alpha]_\lambda^{17}$ (λ, nm): +57° (589), +60° (578), +73° (546), +185° (436), +584° (365), (C = 1.0, methanol). UV spectrum (1:5 methanol—chloroform): λ_{max} 302 nm (ε 19,000). IR spectrum (potassium bromide, ν, cm^{-1}): 3230 (NH stretch), 1610, 1650 (amide I), 1510-1550 (amide II), 1260 (C—O). PMR spectrum (deuterochloroform + deuteromethanol, δ, ppm): 1.50 d ($J_{CH_3,H}$ = 7 Hz), 2.03 s, 3.79 s, 5.14 m, 6.46-7.67 m.

The procedure for the reductive aminolysis was described in [1]. At the end of the reaction the precipitate was dissolved by heating in a mixture of methanol and chloroform. The catalyst was filtered off, and the filtrate was evaporated to 8-10 ml under vacuum. The precipitate was filtered off, washed with ether and with water, and dried under vacuum over concentrated sulfuric acid. The filtrate was diluted with water, acidified with 6 N hydrochloric acid, and passed through a column of Dowex 50 × 8 (in the H^+ form), the column was eluted with aqueous methanol, and the eluate was evaporated under vacuum.

During the reduction of (Ia) the isolated precipitate represented the pure S-(—)-α-phenylethylamide of N,O-diacetyl-2-tyrosine [SS-(IIIa)]; mp 234-238°C (from chloroform). $[\alpha]_\lambda^{17}$ (λ, nm): —25.2° (589), —25.9° (578), —26.7° (546), —47.4° (436), —74.6° (365), —86.0° (350), —149° (300), —201° (280) (C = 0.27, methanol). UV spectrum [chloroform, λ_{max}, nm (ε)]: 258 (315) 265 (324), 273 (260). IR spectrum (potassium bromide, ν, cm^{-1}): 3450, 3310, 3280 (NH stretch), 1765 (C=O ester), 1630 (amide I), 1420-1480 (amide II). PMR spectrum (deuterochloroform + deuteromethanol, δ, ppm):1.41 d ($J_{CH_3,H}$ = 7 Hz), 1.97 s, 2.28 s, 2.93 q, 4.5 m, 6.78-7.30 m.

RS-(IIIa). PMR spectrum (δ, ppm): 1.26 d ($J_{CH_3,H}$ = 7 Hz), 1.92 s, 2.28 s, 2.93 q, 4.5 m, 6.78-7.30 m.

During the reduction of (Ib) the catalysis product was passed through a cation-exchange resin to remove the excess of S-(II). The eluate was evaporated under vacuum, and the residue was transferred to a filter and washed with water. The dried precipitate [a mixture of (IVb) and (IIIb)] gave the pure S-(—)-α-phenylethylamide of N-acetyl-O-methyl-S-tyrosine [SS-(IIIb)] after one recrystallization; mp 218-220°C (from absolute ethanol). $[\alpha]_\lambda^{17}$ (λ, nm): —36.0° (589), —38.6° (578), —42.4° (546), —81.4° (436), —141.2° (365), —163° (350) (C = 0.3, methanol). UV spectrum [chloroform + methanol, λ_{max}, nm (ε)]: 278 (2420), 285 (2120), 300 (1530). IR spectrum (potassium bromide, ν, cm^{-1}): 3450, 3295, 3265 (NH stretch), 1630 (amide I), 1550, 1520 (amide II), 1255 (C—O). PMR spectrum (deuterochloroform + deuteromethanol, δ, ppm): 1.38 d ($J_{CH_3,H}$ = 7 Hz), 1.94 s, 2.87 q, 3.70 s, 4.59 m, 6.59-7.42 m.

R-(IIIb). PMR spectrum (δ, ppm): 1.24 d ($J_{CH_3,H}$ = 7 Hz), 1.88 s, 2.87 q, 3.73 s, 4.59 m, 6.59-7.42 m.

Hydrolysis of SS-(IIIa). A mixture of 1.64 g of SS-(IIIa) and 17.6 ml of 6 N hydrochloric acid was heated in a stream of argon at 110°C for 11 h. At the end of the reaction the mixture was cooled, and a solution of sodium hydroxide was added to pH 4. The white precipitate which separated on cooling was removed, washed with water, alcohol, and ether, and dried. The optically pure S-tyrosine was obtained; $[\alpha]_{589}^{20}$ —11.2° (C = 8.0, 1 N hydrochloric acid). The optical rotatory dispersion coincided with that of the authentic S-tyrosine.

Hydrolysis of S,S-(IIIb) according to [1]. S-O-Methyltyrosine was obtained; mp 264-265°C. $[\alpha]_\lambda^{17}$ (λ, nm): —6.66° (589), —7.02° (578), —7.72° (546), —8.85° (436), —0.71° (365), 0° (362), +5.17° (350), +101.2° (300), +57.0° (290) (C = 2.97, 1 N hydrochloric acid). Published data [9]: mp 265-264°, $[\alpha]_{546}^{29}$ —5.9° (C = 2.1 N hydrochloric acid).

N-Acetyl-O-methyltyrosine Methyl Ester. The reaction was carried out similarly to the production of the amides (IIIb) with absolute methanol as solvent. The catalyst was removed, the reaction mixture was acidified and passed through a column of cation-exchange resin to remove the amine, and the eluate was evaporated to dryness. The residue was crystallized from a mixture of benzene and cyclohexane. According to PMR data, it consisted of 12% of (IVb), 8% of (IIIb), and 24% of N-acetyl-O-methyltyrosine methyl ester. The precipitate was a mixture of the unsaturated ester and amide (IVb). The mother solution was separated by preparative TLC on silica gel (10:0.5 chloroform—methanol). From the fraction with Rf 0.54-0.68 we isolated a compound melting at 80-87°C. According to the IR and PMR spectra, it was identical with N-acetyl-O-methyltyrosine methyl ester $[\alpha]_{589}^{20}$ —9.3° (C = 0.3, methanol). Published data: N-acetyl-O-methyl-S-tyrosine methyl ester, mp 104-105°C, $[\alpha]_{589}^{25}$ 25.3° (C = 0.35, methanol).

Thus, a sample with the R configuration and 35% optical purity was obtained.

2-Methyl-4-(4-acetoxybenzyl)-5-oxazolone (Va). Compound (Va) [the saturated azlactone of (—)-N,O-diacetyl-S-tyrosine] was obtained according to data in [11]. IR spectrum (dioxane, ν, cm^{-1}): 1815 (C=O lactone), 1765 (C=O ester), 1765 (C=N). $[\alpha]_\lambda^{17}$ (λ, nm): —82.5° (589), —85.4° (578), —91.2° (546), —151.0° (436), —239.0° (365), —268° (350) (C = 1.405, dioxane, l = 0.1). PMR spectrum (carbon tetrachloride, δ, ppm): 1.95 d ($J_{CH_3,H}$ = 2 Hz), 2.15 s, 3.04 q, 4.21 m, 7.10 d [$J_{H,H(2,6)}$ = 8.5 Hz], 6.87 d [$J_{H,H(3,5)}$ = 8.5 Hz].

CONCLUSIONS

1. The reaction of the azlactones of 4-acetoxy- and 4-methoxy-α-acetamidocinnamic acids with S-(—)-α-phenylethylamine and hydrogen in the presence of a palladium catalyst in aprotic solvents gives the α-phenylethylamides of 4-acetoxy- and 4-methoxyacetylphenylalanine with the preferred SS configuration.

2. Conditions were found for the production of the pure SS-diastereomers, which give the optically pure S-tyrosine and S-O-methyltyrosine on hydrolysis.

3. During the reduction of the azlactone of 4-methoxyacetamidocinnamic acid in methanol in the presence of S-(—)-α-phenylethylamine and a palladium catalyst R-(—)-N-acetyl-O-methyltyrosine methyl ester was obtained with an optical yield of 35%.

4. Aminolysis of the saturated azlactones of N,O-diacetyltyrosine and N-acetyl-O-methyltyrosine by optically active S-phenylethylamine leads to α-phenylethylamides of N,O-diacetyltyrosine and N-acetyl-O-methyltyrosine with the preferred SS configuration.

5. Aminolysis of the optically active azlactone of S-(—)-N,O-diacetyltyrosine by the racemic α-phenylethylamine is accompanied by racemization, the rate of which is higher than the rate of aminolysis.

6. The reductive aminolysis of the azlactones occurs mainly as reaction of the azlactone with the amine and hydrogen at the surface of the catalyst.

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ASYMMETRIC SYNTHESIS OF AMINO ACIDS BY CATALYTIC REDUCTION OF AZLACTONES OF SUBSTITUTED ACYLAMINOACRYLIC ACIDS.

5. HYDROGENATION OF AZLACTONES IN ALCOHOLS

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In previous communications [1-4] we described the asymmetric reductive aminolysis of a series of ring-substituted 2-methyl-4-arylidene-5-oxazolones (I) by S-(—)-α-phenylethylamine (II) in the presence of Pd and Rh catalysts in aprotic solvents, leading to α-phenylethylamides of N-acetylamino acids (III) with the preferential SS configuration. The realization of this reaction in methanol led to the asymmetric reductive alcoholysis with the formation of methyl esters of the R-N-acetylamino acids with optical yields of 24-35%.

In the present work we investigated the hydrogenation of 2-methyl-4-arylidene-5-oxazolones in various alcohols in order to determine the mechanism of the reductive alcoholysis of the azlactones.

DISCUSSION OF RESULTS

As subjects for investigation we used the azlactones of α-acetamidocinnamic (Ia), 4-acetoxy-α-acetamidocinnamic (Ib), and 4-methoxy-α-acetamidocinnamic (Ic) acids. Hydrogenation was realized at 20°C at a hydrogen pressure of 0.2-0.3 atm in absolute alcohols (methyl, ethyl, and isopropyl) with additions of triethylamine (TEA) and (S)-(—)-α-phenylethylamine S-(II). As catalyst we used palladium, obtained by the reduction of palladium dichloride in situ.

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