ASYMMETRIC SYNTHESIS OF AMINO ACIDS BY THE CATALYTIC REDUCTION OF AZLACTONES OF SUBSTITUTED N-ACYLAMINOACRYLIC ACIDS. COMMUNICATION 16. INFLUENCE OF REACTION CONDITIONS ON THE SYNTHESIS OF 3,4-DIHYDROXYPHENYLALANINE

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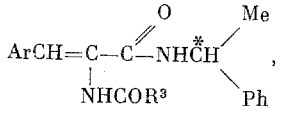
It has been shown [1] that it is possible in principle to prepare the drug S-3,4-dihydroxyphenylalanine (S-DOPA) by the asymmetric reductive aminolysis of m-methoxy-p-acetoxy-α-acetamidocinnamic acid azlactone (Ia). Catalytic reductive aminolysis (RA) of (Ia) in the presence of S-α-phenylethylamine (S-II)) and a palladium catalyst affords a 50% excess of the SS-diastereomer of m-methoxy-p-acetoxy-N-acetylphenylalanine α-phenylethylamide (IIIa). Crystallization and hydrolysis of SS-(IIIa) afforded optically pure S-DOPA. However, the overall yield of amides was no greater than 50%, and RA byproducts complicated the isolation of the readily oxidized S-DOPA.

This communication reports a study of the reaction conditions for the RA of DOPA precursors, with the aim of increasing the yields and purity of SS-(III).

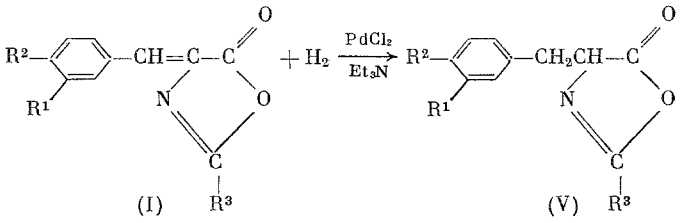
DISCUSSION OF RESULTS

The starting matterials for the synthesis of the amides (III) were the azlactones of aromatic ring-substituted N-acylaminocinnamic acids, viz., m-methoxy-p-acetoxy- (Ia), m-acetoxy-p-methoxy- (Ib) acetoaminocinnamic acids, and m-methoxy-p-acetoxy-N-benzoylaminocinnamic acid (Ic). Unlike the single-stage RA described in [1], we here separated the preparation of the amides into two stages (see Scheme 1), the first being hydrogenation of (I) in the presence of a palladium catalyst obtained in situ by reducing $PdCl_2$ with hydrogen in the presence of Et_3N, and the second being the subsequent aminolysis of the saturated azlactone obtained by hydrogenation with the amine S-(II) (SA reaction). The stereoselectivity of the reaction, expressed as the excess of diastereomer (ED), was determined from the ratio of diastereoisomers of (III) by PMR. In those cases in which the reaction products contained unsaturated α-phenylethylamides (IV)



formed by aminolysis of unreduced (I), quantitative analysis of (IV) was carried out by UV spectroscopy

Scheme 1



(1)

(I) (V)

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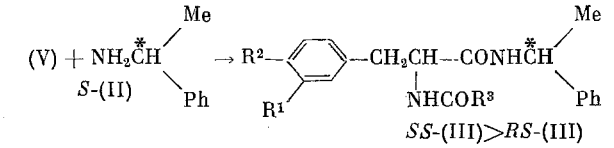
TABLE 1. Effect of Structures of N-Acylaminocinnamic Acid Azlactones (I) on the Yields of Amides (III) in the Single-Stage (RA) and Two-Stage (SA) Reactions [(I) — 1 mmole, Et_3N — 1.5, S-(II) — 1.5, $PdCl_2$ — 0.26 mmole, 15 ml dimethoxyethane, 10°C]

Azlactone	Reaction	$*\tau_{1/2}$, min	Yield of (III), %	ED SS-(III), %
(Ia)	RA	35	50	50
	SA	30	98	50
(Iб)	RA	36	53	46
	SA	100	61	48
(Iв)	RA	20	64	0
	SA	50	70	0

*$\tau_{1/2}$ is the half-conversion time.



SS-(III)>RS-(III)

$R^1 = MeO$; $R^2 = AcO$, $R^3 = Me$ (a); $R^1 = AcO$; $R^2 = MeO$, $R^3 = Me$ (b); $R^1 = MeO$, $R^2 = AcO$, $R^3 = Ph$ (c).

In order to increase the yield of the desired product, S-DOPA, the effects of solvent, temperature, and structure of the azlactone (I) on the yields of the amine (III) were studied. Table 1 shows comparative results for the single-stage RA and the two-stage (SA) reactions for the preparation of amides (III), the reduction of the azlactone being effected under the optimum conditions as determined previously for the RA of (Ia) [1].

As will be shown in Table 1, division of the reaction into two stages increases the yields of (III). When (Ia) is reduced in the presence of Et_3N, the rate remains unchanged in comparison with RA in the presence of S-(II), but the yield of (IIIa) increases by factor of two. In the cases of (Ib) and (Ic), the rate of reduction in the presence of Et_3N is lower than with RA, and the overall yield of (III) is increased by only 10%. The increase in the yield of (III) in the two-stage synthesis is explained by the reduced likelihood of the occurrence of side reactions (cleavage of (I) to give (IV), and condensation of saturated and unsaturated azlactones) which occur in the one-stage process. It is noteworthy that the position of the substituents in the aromatic rings in (Ia) and (Ib) has no noticeable effect on the stereoselectivity of the RA and SA reactions. However, replacement of Me by Ph (substituent R^3) in (Ic) results in the disappearance of stereoselectivity in both reactions. A considerable reduction in stereoselectivity in the RA of (I) has been observed previously in cases in which the substituent at C^2 of the oxazolone ring is pH, and has been interpreted as being due to a reduction in the strength of the Pd—C bond in the intermediate catalytic complex [2].

Since the greatest increase in the yields of amides (II) in the SA reaction was obtained with (Ia), subsequent studies on the selection of the optimum reaction conditions were carried out with this compound.

Table 2 shows data for the effects of the ratios of the reaction components (catalyst, substrate, Et_3N, and S-(II)) on the yields of the amides (IIIa). It will be seen that variations in all the components had little effect on the yields of (IIIa) (90-98%) or the stereoselectivity of the reaction (ED of SS-(III), 50-53%). Increasing the amount of $PdCl_2$ from 0.18 to 0.26 mmole increased the rate of reduction by a factor of 1.5, but further increases in the amount of $PdCl_2$ had no further effect on the rate. The effect of type of solvent and temperature in each stage of the two-stage synthesis of (IIIa) on the product yields and the stereoselectivity of the reaction are shown in Table 3. Examination of the results obtained when the temperature was varied in the first stage (hydrogenation of (Ia) with Et_3N) shows that in dimethoxyethane (DME), a reduction in temperature from 20°C to 10°C increases the rate of reduction by a factor of two (the yield of (IIIa) is 90-95%). A further reduction in the temperature to 5°C retards the reaction.

TABLE 2. Effect of Ratio of Components in the SA Reaction of m-Methoxy-p-acetoxy-α-acetamidocinnamic Acid Azlactone (Ia) [(Ia) — 1 mmole, dimethoxyethane — 15 ml, 10°C]

$PdCl_2$	Et_3N	S-(II)	$\tau_{1/2}$, min	Yield of (III), %	ED SS-(III), %
mmoles					
0,18	1,55	1,55	55	95	50
0,26	1,55	1,55	30	98	50
0,33	1,55	1,55	28	98	50
0,26	0,78	1,55	40	90	46
0,26	2,34	1,55	35	95	50
0,26	1,55	1,15	30	95	43
0,26	1,55	2,55	30	95	50
0,26	1,55	3,10	30	98	53

TABLE 3. Effect of Type of Solvent and Temperature in the SA Reaction of m-Methoxy-p-acetoxy-α-acetaminocinnamic Acid Azlactone (Ia) [$PdCl_2$ — 0.26 mmole, (Ia) — 1, Et_3N — 1.50, S-(II) — 1.50 mmole, solvent — 15 ml]

First stage of SA hydrogenation of (Ia) over Pd with Et_3N			Second stage of SA aminolysis of RS-(Va) with amine S-(II)		SA reaction products, %		ED SS-(IIIa), %
solvent	T., °C	$\tau_{1/2}$, min	solvent	T., °C	(IVa)	(IIIa)	
DME	20	60	DME	20	—	93	45
DME	10	30	DME	20	—	98	50
DME	10	30	DME	10	—	95	48
DME	5	50	DME	20	—	82	54
Dioxane	20	No reaction		—	—	—	—
THF	10	130	THF	20	19	63	46
THF	20	120	THF	20	21	60	32
AcOEt	20	135	AcOEt	20	17	68	32
AcOEt	10	140	AcOEt	20	14	65	40
DME	10	30	Toluene	20	—	85	27
DME	10	30	$CHCl_3$	20	—	78	28

The stereoselectivity of the subsequent aminolysis of (Va) with amine S-(II) (stage two) in DME is not affected when the aminolysis temperature is reduced to 10°C.

Hydrogenation of (Ia) in other ethereal solvents (dioxane and THF) at 20°C occurs much more slowly than in DME. There was hardly any reaction in dioxane, and only 60% hydrogenation of (Ia) was reached in THF at 10-20°C. At 10-20°C in ethyl acetate, hydrogenation of (Ia) took place as slowly as in THF, and yield of (IIIa) was only 65-68%. The stereoselectivity of the aminolysis of (Va) in THF and ethyl acetate was slightly less than in DME. The reaction mixture contained (IVa), which is the aminolysis product of unreduced (Ia). In DME, in which the reduction of (Ia) proceeded to completion, (IVa) was absent from the reaction products. It was therefore of interest to carry out the first stage of the reaction in DME, and the second in another solvent such as toluene or $CHCl_3$, which inhibit the racemization of saturated azlactones (V) [3]. As shown in Table 3, this approach resulted in reductions both in the yield of (IIIa), and the excess of the SS-(IIIa) diasteoisomer. The latter observation is explained by the fact that in the nonpolar solvents used, the reaction occurs largely by interaction of the saturated azlactone carbanion with the ammonium ion, which should result in an increase in the proportion of the RS-diastereomer [4].

Hence, the optimum conditions for the asymmetric synthesis of amides (IIIa) by the reduction of azlactones of substituted N-acylaminocinnamic acids followed by aminolysis of the saturated product with the chiral amine S-(II) are as follows: (Ia) — 1 mmole, Et_3N — 1.5, $PdCl_2$ — 0.26 mmole, DME — 15 ml, S-(II) — 1.5 mmole, hydrogenation temperature 10°C, aminolysis temperature 20°C. The yields of amides (IIIa) reach 98%, the excess of the diastereomer SS-(IIIa) being 50%. Recrystallization and hydrolysis of SS-(IIIa) afforded optically pure S-DOPA in a yield of 39.5% based on the original (Ia).

EXPERIMENTAL

The materials used were pure grade $PdCl_2$ and S-α-phenylethylamine, S-(II), with $[\alpha]_D^{20}$ —39°C (no solvent). m-Methoxy-p-acetoxy- (Ia) and m-acetoxy-p-methoxy-α-acetamidocinnamic

acid (Ib) azlactones were prepared as in [1], (Ia), mp 149-151°C (from dry benzene). m-Methoxy-p-acetoxy-α-benzoylaminocinnamic acid azlactone (Ic) was obtained as in [5], mp 191.5-192.5°C (from dry benzene). The method used for reductive aminolysis in the presence of S-(II) has been described [6].

Two-Stage Synthesis of Amides (III) (SA Reaction). In a magnetically stirred, thermostatted reactor were placed 0.05 g (0.26 mmole) of $PdCl_2$, 5 ml of DME, and 0.2 ml (1.50 mmole) of Et_3N. The system was flushed out with purified hydrogen, and the stirrer was then switched on. When the $PdCl_2$ had been reduced, the reactor was attached to a gas buret, and when stationary conditions had been established 0.3 g (1 mmole) of (Ia) in 10 ml of DME was added. When the theoretical amount of hydrogen had been taken up, 0.2 ml (1.50 mmole) of S-(II) was introduced by means of a syringe into the reactor, and the mixture was kept for one day at ∿20°C. The catalyst was then removed by centrifugation, the solvent removed in vacuo, and the residue dissolved in $CHCl_3$, washed with dilute HCl, then with water until neutral. The solvent was removed in vacuo, and the residue dried in a vacuum desiccator over KOH and analyzed by PMR and UV. The yield of amide (IIIa) was 98%, excess SS-(IIIa) 50%. The amide was recrystallized from absolute ethanol to give a 42% yield of pure SS-(IIIa). The latter was hydrolyzed with 48% HBr as described in [1], to give optically pure S-DOPA in 96% yield. The yield of S-DOPA based on the original (Ia) was 39%.

When the aminolysis stage was carried out in toluene or $CHCl_3$, the reaction mixture following hydrogenation was separated from the catalyst, washed with DME, and the combined extracts evaporated to dryness in vacuo. The residue was treated with 15 ml of toluene or $CHCl_3$ and 0.2 ml (1.5 mmole) of S-(II), and kept for one day at ∿20°C under nitrogen. The mixture was then worked up as described above.

CONCLUSIONS

1. Division of the reductive aminolysis of N-acylaminocinnamic acid azlactones into two stages (hydrogenation over a Pd catalyst in the presence of Et_3N, and the aminolysis of the saturated azlactone with S-α-phenylethylamine) improved yields of aromatic ring-substituted N-acetylphenylalanine amides by 40-45%.

2. The optimum conditions for the preparation of optically pure S-3,4-dihydroxyphenylalanine have been established.

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