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On the Erlenmeyer Reaction. II. Mechanism of DL-threo-N-Benzal-diphenylhydroxyethylamine Formation¹⁾

Kaoru Harada

Institute of Molecular Evolution and Department of Chemistry, University of Miami Coral Gables, Florida 33134 U.S.A.

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Erlenmeyer reported that glycine condensed easily with benzaldehyde in strongly alkaline aqueous ethanol.^{2,3)} The rapid condensation reaction at room temperature resulted in the formation of sodium salt of *threo-N*-benzalphenylserine.⁴⁾ The mechanism of the *threo-*phenylserine formation was explained in the earlier report⁵⁾ by a second order asymmetric transformation.

From the reaction mixture of the Erlenmeyer phenylserine formation, N-benzalisodiphenylhydroxyethylamine (threo-isomer) was isolated. The threo-diphenylhydroxyethylamine (threo-DHEA) was found to be the main product when three moles (instead of two moles) of benzaldehyde were used.⁶⁾ The presence of the more soluble erythro-N-benzal-DHEA isomer in the reaction mixture was identified.⁶⁾ It was found in the previous study⁵⁾ that the amount of DHEA in the Erlenmeyer reaction increased steadily with time. It was also found that with long reaction time, the final product was

crystalline *threo-N*-benzal-DHEA. From these results, it may be inferred that *erythro*-DHEA is converted into the *threo*-DHEA during the reaction.

In order to elucidate the stereochemical course of Erlenmeyer's DHEA formation, several sets of synthetic and conversion reactions were carried out. These reactions are: 1) glycine, benzaldehyde and alkali; 2) DL-threo-phenylserine, benzaldehyde and alkali; 3) DL-erythro-phenylserine, benzaldehyde and alkali; 4) DL-erythro-DHEA, benzaldehyde and alkali; 5) L-(+)-erythro-DHEA, benzaldehyde and alkali; 6) D-(+)-erythro-Nbenzal-DHEA and alkali. These reactions were carried out in alcoholic aqueous solution at room temperature in a manner similar to that of the Erlenmeyer reaction. It was found that final products of reactions 1)-6) were all DL-threo-Nbenzal-DHEA. Melting points, elemental analyses, and infrared absorption spectra all agreed with the authentic DL-threo-N-benzal-DHEA. Results are

Table 1. Formation of dl-threo-diphenylhydroxyethylamine

Starting material		PhCHO	кон	Solvent		N-Benzal-	$^{ m Mp^{*3}}_{^{\circ}{ m C}}$	Nitrogen analysis*4
	g(mol)	$ml \pmod{m}$	g	$_{\mathrm{m}l}^{\mathrm{EtOH}}$	$^{ m H_2O}_{ m m}l$	DHEA,*2g	$^{\circ}\mathbf{C}$	Found, %
1	Gly 1.50 (0.02)	6.4 (0.04)	3.5	10	20	2.70	132—133	4.57
2	threo-Ph-Ser H ₂ O 3.08 (0.02)	3.2 (0.02)	3.5	10	20	2.65	132—133	4.64
3	erythro-Ph-Ser, 1/2 dioxane 4.50 (0.02)	3.2 (0.02)	3.5	10	20	2.58	132—133	4.80
4	DL-erythro-DHEA* 4.26 (0.02)	$\begin{array}{cc} *1 & 3.2 \\ (0.02) \end{array}$	3.5	35	5	2.58	132—133	4.84
5	L-erythro-DHEA*1 2.13(0.01)	$\frac{1.6}{(0.01)}$	1.6	17	2.5	1.78	131—132	4.67
6	N-Benzal- D-erythro-DHEA*1		0.9	9	1.3	0.28	131—132	4.80

- *1 Reaction mixtures of 4) and 5) were heated at 60-65°C for 10 min to dissolve DHEA.
- *2 The yields show the weights of crystal after washing.
- *3 The melting points show after one recrystallization.
- *4 The nitrogen analyses were carried out by Micro-Tech. Laboratories, Skokie, Illinois, U. S. A. Calculated value of the nitrogen analysis is 4.65%.

- 2) E. Erlenmeyer, Jr., Ber., 25, 3455 (1892).
- 3) E. Erlenmeyer, Jr., and E. Frühstück, *Ann.*, **284**, 36 (1894).
- 4) K. Vogler, Helv. Chim. Acta, 33, 2111 (1950).
- 5) T. Kaneko and K. Harada, This Bulletin, 34, 1314 (1961).
 - 6) E. Erlenmeyer, Jr., Ann., 307, 70 (1899).

¹⁾ Contribution No. 113 of the Institute of Molecular Evolution, University of Miami.

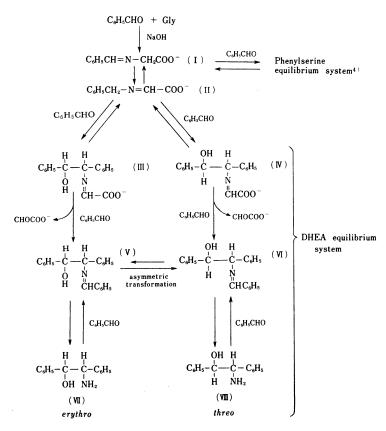


Fig. 1. Postulated mechanism of DL-threo-diphenylhydroxyethylamine formation in the Erlenmeyer reaction.

summarized in Table 1. These results suggest a possible mechanism for the formation of DL-threo-DHEA in the Erlenmeyer reaction. The postulated pathway of the reactions is shown in Fig. 1.

As described in the earlier study,⁵⁾ N-benzalglycine (I) was the starting material to form threophenylserine. The I could be tautomerized under strongly alkaline conditions into structure II, which was proven by isolation of benzylamine from a reaction mixture of the Erlenmeyer reaction.6,7) The II reacts with benzaldehyde forming two racemic isomers, erythro (III) and threo (IV) isomers. These III and IV could be converted to N-benzal isomers V and VI in the presence of benzaldehyde. The solubility of V in the reaction mixture (alkaline aqueous ethanol) was found to be very large and it does not crystallize. However, the solubility of the corresponding diastereomeric isomer (VI) is small and it crystallized easily from the reaction solvent. Therefore, if there is an equilibrium between V and VI under the reaction conditions, the erythro isomer V could be converted into *threo* isomer VI by crystallization (second order asymmetric transformation). It has been reported that the reaction of benzaldehyde with phenylalanine, tyrosine, leucine, and aspartic acid resulted in the formation of corresponding α -keto acids and DL-threo-DHEA with no isolable phenylserine analogs.^{6,8)}

This finding also supports the inference that the DHEA formation is not dependent on the amino acid used but on the intermediate (II) which is tautomerized from the *N*-benzal-amino acid. Under conditions which were employed in this study, optically active *erythro*-DHEA was converted to racemic *threo*-DHEA. Solubility of the optically active *erythro-N*-benzal-DHEA was found to be much smaller than that of the racemic *N*-benzal-

⁷⁾ Benzylamine was also isolated from the reaction mixture of glycine and benzaldehyde by heating at 130°C; T. Curtius and G. Lederer, *Ber.*, **19**, 2462 (1886).

⁸⁾ E. Erlenmeyer, Jr., Ann., **337**, 205 (1904); Ber., **30**, 2896 (1897).

DHEA in the reaction solvent. Therefore, the reaction mixture was kept at $60-65^{\circ}\mathrm{C}$ for 10 min at the beginning of the reaction. This might be a reason for the racemization of both asymmetric carbons of optically active *erythro*-DHEA. However, another explanation of the racemization is possible, *i. e.*, a cleavage of α - β carbon linkage. Such a mechanism is conceivable since the α,β -linkage is rather weak.⁹⁾ However, at the present time it is difficult to decide whether the conversion pathway is a) direct $(V \rightarrow VI)$ or b) indirect $(V \rightarrow IX \rightarrow VI)$.

$$\begin{array}{c|c} erythro (V) & \xrightarrow{} & threo (VI) \\ \hline -C_6H_5CHO & \begin{pmatrix} H_2C-C_6H_5 \\ N \\ HC-C_6H_5 \end{pmatrix} \\ & (IX) & \end{array}$$

The results obtained in this study and also in the previous study⁵⁾ show that there are two large equilibrium systems in the Erlenmeyer reaction (Fig. 1). The one is the phenylserine equilibrium system⁵⁾ and the other is the DHEA equilibrium system. These two systems are connected to each other at structure I in Fig. 1. In a short reaction time, the Erlenmeyer reaction resulted in the formation of crystalline sodium salt of DL-threophenylserine from glycine and benzaldehyde by the second order asymmetric transformation. However, in a prolonged reaction, threo-N-benzal-DHEA was crystallized out from the reaction mixture by the second order asymmetric transformation.

Experimental

Reaction (1): Formation of DL-threo-N-benzal-**DHEA from Glycine.** Glycine, 1.50 g (0.02 mol), was dissolved in a solution of 3.50 g of potassium hydroxide in 20 ml of water. The solution was mixed with a solution of 4.75 ml of benzaldehyde and 10 ml of ethanol under cooling. Nitrogen gas was introduced in the reaction flask and the mixture was shaken until it became clear. Crystallization of N-benzal-threophenylserine sodium salt began after 30 min. The mixture was kept at room temperature. After two days, the crystals of threo-phenylserine sodium salt decreased in amount. It seems that the conversion reaction of phenylserine to DHEA took place during this time. In order to complete the conversion reaction, the reaction mixture was kept at room temperature for two more weeks. After the reaction was over, the crystals were filtered and washed with a small amount of cold ethanol, yield 2.70 g, mp 132-133°C. This was recrystallized from 24 ml of ethanol, yield 2.33 g, mp 132—133°C. Nitrogen analysis, found: 4.57%. Infrared absorption spectrum: 3480, OH; 2700—3000 monosubstituted benzene; 1650, C=N; 1605, 1590, benzene CH; 754, 700, monosubstituted benzene. The infrared absorption spectrum was found to be identical with that of authentic DL-threo-N-benzal-DHEA.

Reactions (2) and (3) were carried out in the same way as Reaction (1). In both reactions, DL-threo-N-benzal-DHEA was isolated after 16 days of reaction.

Reaction (4): Conversion of DL-erythro-DHEA to DL-threo-DHEA. A mixture of DL-erythro-DHEA, 4.26 g (0.02 mol), and 3.20 ml of benzaldehyde in 35 ml of ethanol was mixed with a solution of 3.5 g of potassium hydroxide and 5.0 ml of water. Nitrogen gas was introduced in the reaction flask and the mixture was heated in a water bath at 65°C to dissolve the DHEA under shaking. After the reaction mixture became clear, the solution was cooled by water and was kept at room temperature for 16 days. Crystallization began after 3 hr. Crystals were separated by filtration and were washed with a small amount of cold ethanol. Yield, 2.58 g, mp 130-131°C. This was recrystallized once from ethanol, mp 132-133°C. Infrared absorption spectrum was found to be identical to the authentic DL-threo-N-benzal-DHEA. Nitrogen analysis, found: 4.84%.

Reaction (5): Conversion of L-(+)-erythro-**DHEA to DL-***threo-***DHEA.** D-(-)- and L-(+)-erythro-DHEA was resolved by the use of L- and D-glutamic acid. 10) D-(-)-erythro-DHEA, mp 142.5—143°C, $[\alpha]_D^{25}$ -6.0° in absolute ethanol; D-erythro-DHEA hydrochloride, mp 213—214°C, $[\alpha]_D^{25}$ —62.8° in H_2O ; Derythro-N-benzal-DHEA, mp 109°C, $[\alpha]_D^{25}$ +76.9° in absolute EtOH. L-(+)-erythro-DHEA, mp 142.5—143°C, $[\alpha]_D^{25} + 6.3^{\circ}$ in absolute ethanol; L-erythro-DHEA hydrochloride, mp 213—214°C, $[\alpha]_D^{25}$ +64.2° in H₂O; L-erythro-N-benzal-DHEA, mp 109°C, $[\alpha]_D^{25}$ -77.3° in absolute EtOH. Reaction (5) was carried out in the same way as reaction (4). Starting from 2.13 g of L-erythro-DHEA, 1.78 g of DL-threo-N-benzal-DHEA was obtained after 6 days of reaction, mp 130-132°C. After one recrystallization, the melting point rose to 131-132°C. No optical rotation was observed. Infrared absorption spectrum was identical to that of the authentic DL-threo-N-benzal-DHEA. Nitrogen analysis, found: 4.67%.

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⁹⁾ DL-three-DHEA resulted in benzylamine by heating at 130°C.

¹⁰⁾ J. Weiland, K. Pfister, III, E. F. Swanezy, C. A. Robinson and M. Tishler, J. Am. Chem. Soc., 73, 1217 (1951). The literature reported that the specific rotation of D- and L-erythro-DHEA were -10.1° and $+10.2^{\circ}$ respectively. Attempts to obtain D- and L-erythro-DHEA which have the specific rotations of -10.1° and $+10.2^{\circ}$ were unsuccessful. Recent literature [M. Nakazaki, This Bulletin, 36, 1204 (1963)] reported that the specific rotation of D-(-)-erythro-DHEA was -6.4° . However, other physical properties were found to be the same as in the literature by Weiland et al.