*The β-Phenylserine Series. Part III.**

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Condensation of benzaldehyde with glycine gives almost exclusively *erythro*-phenylserine at $\not>$ −5°, but only the *threo*-form at 30°.

Condensation of glycine ethyl ester with aromatic aldehydes gives, according to the conditions employed, either *threo*- or *erythro*-phenylserine ethyl ester.* Contrary to this experience, it is generally assumed that condensation of benzaldehyde and glycine (Erlenmeyer, *Annalen*, 1899, **307**, 84; 1904, **337**, 222; Erlenmeyer and Fruestueck, *ibid.*, 1895, **289**, 36) gives practically exclusively *threo*-phenylserine, m. p. 196° (decomp.). However, Erlenmeyer has already reported that a second substance, m. p. 187—188°, is also formed, in unspecified yield; it was recently shown by Viscontini and Fuchs (*Helv. Chim. Acta*, 1953, **36**, 660) to be the *erythro*-phenylserine: it was converted by an unambiguous procedure into the *threo*-isomer, and was identical with the product obtained by Chang and Hartung (*J. Amer. Chem. Soc.*, 1953, **75**, 89, 238) from ethyl hydroxyiminobenzoylacetate Ph·CO·C(:N·OH)·CO_2Et by catalytic reduction and subsequent hydrolysis (see Fones, *J. Org. Chem.*, 1952, **17**, 1534; Shaw and Fox, *J. Amer. Chem. Soc.*, 1953, **75**, 3417, 3421; Bolhofer, *ibid.*, 1952, **74**, 5459). The report that *erythro*-phenylserine melts at 260° (Elphimoff-Felkin and Felkin, *Compt. rend.*, 1951, **232**, 241; Elphimoff-Felkin, Felkin, and Tchoubar, and Welvart, *Bull. Soc. chim.*, 1952, 252) is erroneous.

It appeared interesting to study more accurately the stereochemical course of the Erlenmeyer condensation reaction. The Table shows that the reaction is slow at temperatures of 0° and below, but that between 5° and 30° a total yield of phenylserine of 75—90% can be obtained. The composition of this phenylserine depends markedly on the temperature of condensation: at −5° the *erythro*-form is produced almost exclusively; its relative quantity decreases with increasing condensation temperature, until it disappears completely at 30°.

Relative yields (%) of the isomeric phenylserines.

Temp.:	−10°	−5°	0°	+5°	+10°	+15°	+20°	+25°	+30°
Crude phenylserine	0	11	28	74	76	81	76	77	90
Ester hydrochlorides (total) *	—	64	60	77	83	84	71	83	82
threo-Salt *	—	2	18	55	54	69	67	78	82
erythro-Salt *	—	62	42	22	29	15	4	5	0

* Calc. on crude phenylserine.

The determination of the relative amounts of the two isomers in the crude phenylserine was based on the observation that the ethyl ester hydrochloride of the *erythro*-form is insoluble in ethyl alcohol, whilst the isomer has a very considerable solubility in this solvent. In the Table the yield of the total ethyl ester hydrochloride is indicated; it is of the order of magnitude of 75%. No attempt has been made to identify the balance of the product obtained in the esterification step.

These observations are of importance in view of the possible synthesis of chloramphenicol from *threo*-phenylserine (Carrara and Weitnauer, *Gazzetta*, 1949, **79**, 854; Vogler, *Helv. Chim. Acta*, 1950, **33**, 2111; Bendas and Bergmann, *Bull. Res. Council Israel*, 1951, **1**, No. 1/2, 131; *J.*, 1951, 2673); for this purpose the condensation of benzaldehyde and glycine is best carried out at 30°. For the preparation of the *erythro*-isomer, the most practical reaction temperature is 5°.

The *threo*-form of phenylserine has also been characterised by a number of derivatives, which are described below.

After this paper had been completed, Shaw and Fox (*locc. cit.*) reported that in the synthesis of phenylserine at 15° (the temperature rising spontaneously to 25—26°) within 1 hr. practically equal quantities of the two isomers were formed but that, when the solution was kept, the quantity of the *erythro*-isomer decreased sharply.

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Experimental

General Procedure.—To the solution of glycine (50 g.) in water (175 ml.) containing sodium hydroxide (41 g.), benzaldehyde (133 g.) was added with vigorous agitation and within a temperature range of ±1°. The temperature was kept constant for 48 hr.; then acetic acid (50 ml.) and water (34 ml.) were added, the temperature being kept at 0—2°. After 12 hr. at 0° the product was filtered off, dissolved in the minimum of boiling water, and precipitated by addition of twice the volume of alcohol and cooling.

This crude phenylserine was dissolved in alcohol, which had been saturated with gaseous hydrogen chloride, and gaseous hydrogen chloride was passed through the solution. On cooling, the *erythro*-ethyl ester hydrochloride crystallised; on concentration, the *threo*-form was obtained. M. p.s were 174° and 138°, respectively. The *erythro*-compound was analysed (Found: C, 53·6; H, 6·6; N, 5·8. Calc. for $C_{11}H_{16}O_3NCl$: C, 53·9; H, 6·5; N, 5·7%).

For the preparation of *erythro*-phenylserine, the following method proved superior to that of Bolhofer (*loc. cit.*) and Elphimoff-Felkin, Tchoubar, and Welvart (*loc. cit.*): the ethyl ester hydrochloride (24·5 g.) was dissolved in 2N-sodium hydroxide (100 ml.). After 30 min. at room temperature, N-hydrochloric acid (100 ml.) was added and the solution was kept for 12 hr. at 0°. Thus, 10 g. (56%) of the desired amino-acid, m. p. 202° (decomp.), were obtained.

For further identification, the following known derivatives were prepared: *ON*-dibenzoylphenylserine ethyl ester, m. p. 167° (from alcohol; *erythro*); *ON*-diacetylphenylserine ethyl ester, m. p. 124° (from *cyclo*hexane; *erythro*), 169—170° (from aqueous alcohol; *threo*); ethyl 2 : 5-diphenyloxazoline-4-carboxylate, m. p. 120° (*erythro*), 86—87° (*threo*). The *threo*-acetyl derivative is obtained only by acetylation at 100°. At the b. p. a compound, m. p. 83°, is formed, which contains one molecule of water less than expected. As this is also obtained from the *erythro*-isomer, it was assumed that it is *ethyl α-diacetylaminocinnamate* (Found: C, 65·8; H, 6·4; N, 5·1; OEt, 16·0. $C_{15}H_{17}O_4N$ requires C, 65·5; H, 6·2; N, 5·1; OEt, 16·3%). The ultra-violet and infra-red absorptions are in accord with this formula. In the latter, the following band assignments can be made: 1700 (Ac_2N and ester-CO); 1460 (Ph); 1380 cm.$^{-1}$ (Me of Ac); owing to conjugation effects, all values are shifted slightly to higher wave-numbers. In the ultra-violet region the compound absorbs at 2780 Å, compared with 2730 Å for cinnamic acid (Landolt-Börnstein, "Tabellen," Vol. II, p. 901, Springer, Berlin, 1923). In order to confirm the assumed formula, the compound was prepared by acetylation of the ethyl ester, prepared from the known (Erlenmeyer and Fruestueck, *loc. cit.*; Bergmann and Delis, *Annalen*, 1927, **458**, 76; Carrara, *Gazzetta*, 1949, **79**, 857) α-acetamidocinnamic acid by alcohol and concentrated sulphuric acid; the *ester* had m. p. 95° (from *cyclo*hexane) (Found: C, 67·1; H, 6·1. $C_{13}H_{15}O_3N$ requires C, 67·0; H, 6·4%).

A mixture of this substance (1 g.), sodium acetate (1 g.), and acetic anhydride (4 ml.), refluxed for 1 hr., gave the diacetyl derivative, m. p. 83° (from 50% alcohol), which did not depress the m. p. of the above compound and showed the identical ultra-violet spectrum (Found: C, 65·4; H, 6·2%).

Similar β-eliminations in α-amino-β-hydroxy-acid derivatives have recently been reported by Riley, Turnbull, and Wilson (*Chem. and Ind.*, 1953, 1180).

threo-ON-*Dibenzoylphenylserine ethyl ester* has been prepared (7 g. from 10 g.) as described for the *erythro*-isomer (Elphimoff-Felkin *et al.*, *loc. cit.*) and had m. p. 156° (from alcohol) (Found: C, 71·9; H, 5·5; N, 3·3. $C_{25}H_{23}O_5N$ requires C, 71·9; H, 5·5; N, 3·3%).

erythro-N-*Dichloroacetylphenylserine.*—Prepared by a Schotten–Baumann reaction at −5° (10 g. from 9 g.), this *compound* melted at 93° after recrystallisation from ether–ligroin (Found: C, 45·0; H, 3·9. $C_{11}H_{11}O_4NCl_2$ requires C, 45·2; H, 4·0%).

threo-N-*Chloroacetylphenylserine*, m. p. 164° (from water) (Found: C, 51·3; H, 4·6. $C_{11}H_{12}O_4NCl$ requires C, 51·3; H, 4·7%), and threo-N-*benzoylphenylserine*, m. p. 159° (from water) (Found: C, 67·3; H, 5·2. $C_{16}H_{15}O_4N$ requires C, 67·4; H, 5·3%), were similarly prepared.

erythro-N-*Chloroacetylphenylserine methyl ester* was prepared by means of boiling methyl chloroacetate (5 min.) and had m. p. 183° (from ethyl alcohol) (Found: C, 52·8; H, 5·5. $C_{12}H_{14}O_4NCl$ requires C, 53·0; H, 5·2%).

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