Synthesis of β,β'-(4,4'-Diphenyl ether)-dialanine*

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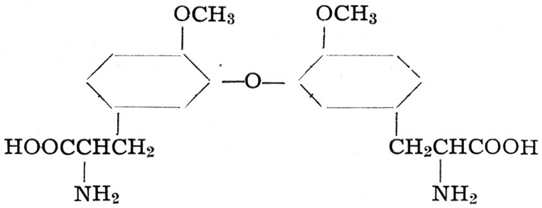
β,β'-(4,4'-Diphenyl ether)-dialanine has been prepared by the use of Erlenmeyer reaction starting from 4,4'-diformyldiphenylether.

Although a number of symmetrically built physiologically active substances of aromatic series has been reported, and some of them are in practical use (e. g. Propamidine, Stilbamidine etc.), no symmetrical aromatic bis-(α-amino acid) has been described hitherto. On the other hand, the physiological activity of a great number of diphenyl ether derivatives, both simple (e. g. thyroxine, tyrosine, tyramine etc.) and complicated (e. g. alkaloids of *Menispermaceae* and *Berberidaceae* groups) is well established. However, the amino acid derivatives of diphenyl ether have been prepared mainly in connection with investigations on thyroxine-like active substances [1, 2, 3, 4, 5]. By examining the chemical literature we found only one publication dealing with bis-(α-amino acids) of diphenyl ether series[6], where the intermediates for the preparation of



are described but neither this nor any other amino acid mentioned has been prepared. We considered, therefore, of interest to prepare a simpler analogue of the above amino acid, β,β'-(4,4'-diphenyl ether)-dialanine (VII). This was obtained by the following route:

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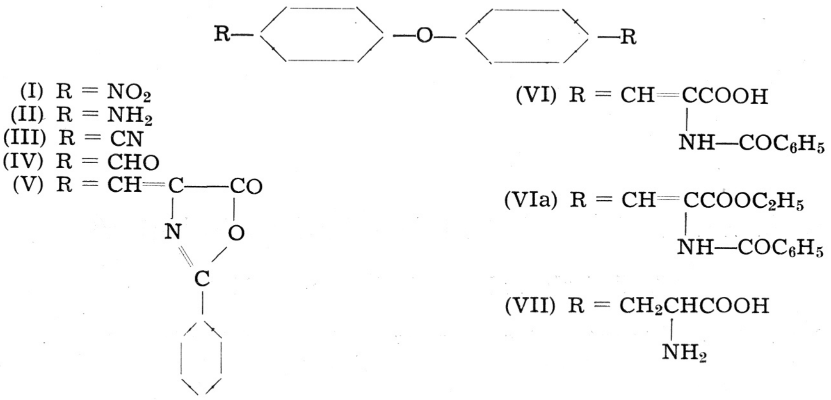

4,4′-Dicyanodiphenyl ether[7] (III) was converted by Stephen's reduction[8] to 4,4′-diformyldiphenyl ether (IV) which was condensed with hippuric acid to give the bisazlactone (V). This was converted to the bis-amino-acid (VII) either by hydrolyzing it to the corresponding bis-benzoylaminoacrylic acid (VI), resp. its ester (VI a), and then reducing (VI), resp. (VI a) with hydriodic acid and red phosphorus, or, performing both operations in one step by boiling (V) with hydriodic acid and red phosphorus in glacial acetic acid to obtain the bis-amino acid (VII) directly in good yield. The conditions for the preparation of the bis-amino acid (VII) via the bis-benzoylaminoacrylic acid (VI) were based on those described for the preparation of 4-phenoxy-β-phenylalanine[9].

Since our methods for the preparation of the intermediates used differ slightly from those previously described for 4,4′-dinitro-[10] (I), 4,4′-diamino-[10] (II) and 4,4′-dicyanodiphenyl ether[7] (III) and are in some points improved, we report them in detail.

The preparation of the dianil of 4,4′-diformyldiphenyl ether from the diamine (II) in a very poor yield has been reported in a recent publication on the interaction of diazonium salts and oximes[11], but no other data about the dialdehyde itself or its derivatives have been mentioned.

The microanalytical determinations were carried out in our microanalytical laboratory under the direction of Mr. N. Manger.

EXPERIMENTAL*

4,4′-Dinitrodiphenyl ether (I)

In a three-necked flask fitted with an air condenser, thermometer and mechanical stirrer 250 g. (1.59 mole) of p-chloronitrobenzene was placed. The flask was heated on a metal bath to 220°C and 2 g. of copper-catalyst[12] and 60 g. (0.338 mole) of dry potassium p-nitrophenoxyde were added in portions over a 30 minutes period with stirring. The stirring and heating was continued for 4 hours. The reaction mixture was then cooled to 160° and poured into 600 ml. of cold, vigorously stirred water. The separated solids were filtered off, washed several times with water, dried at room temperature and distilled *in vacuo* to remove the excess of p-chloronitrobenzene. The residue in the distillation flask was crude 4,4'-dinitrodiphenyl ether with m. p. 130—138° and weighed 82 g. (93%). After crystallization from 96% ethanol it melted at 138—140°.

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* The melting points of analytical samples are corrected.

4,4'-Diaminodiphenyl ether (II)

To 20 g. (0.077 mole) of crude 4,4'-dinitrodiphenyl ether, 70 g. (0.59 g.-atome) of metallic tin and 70 ml. of 96% ethanol, placed in a 1000 ml. round-bottomed flask, 500 ml. of conc. hydrochloric acid was added in portions, and the resulting mixture heated under reflux for three hours. After standing overnight in a refrigerator, the separated complex tin salt was filtered off and dissolved in 400 ml. of water. This solution was warmed to 90° and saturated with hydrogene sulphide. The precipitate of tin sulphides was filtered off and washed three times with water. Aqueous ammonia was added to the filtrates until alcaline to litmus to precipitate 12.7 g. (82.5%) of white, microcrystalline material, which melted at 179—181°.

4,4'-Dicyanodiphenyl ether (III)

To a solution of 25 g. (0.1 mole) of copper sulphate and 22.4 g. of rock salt in 160 ml. of water 15 ml. of a 30% sodium bisulphite solution was added and the resulting mixture heated to boil until the evolution of sulphur dioxide ceased. To the hot solution 20.2 g. (15.3 ml., 0.152 mole) of a 30% sodium hydroxyde solution was added and the resulting mixture cooled to 10°. A solution of 16.5 g. (0.336 mole) of sodium cyanide in water was then dropped in at a temperature below 15°. The mixture was neutralized with 8 ml. glacial acetic acid and 23 g. of sodium bicarbonate was added. After cooling with ice-water to 5°, a solution of tetrazotized 4,4'-diaminodiphenyl ether [prepared by addition of 6.9 g. (0.1 mole) of sodium nitrite dissolved in 20 ml. of water to 10 g. (0.05 mole) of the diamine (II), dissolved in a mixture of 40 ml. of water, 30 ml. of concentrated hydrochloric acid and 50 g. ice, at 0° and subsequent neutralization with sodium bicarbonate] was dropwise added with vigorous stirring at a temperature not exceeding 5°. A light brown precipitate formed immediately. The reaction mixture was stirred at room temperature for additional two hours, the precipitate filtered off, washed well with water and dried. The crude product was extracted with 250 ml. of hot benzene. The benzene solution was filtered and evaporated to dryness. The residue was dissolved in 300 ml. of 96% ethanol and decolorized with charcoal. This solution was concentrated to 50 ml. After cooling 6 g. (54.5%) of slightly tan-coloured 4,4'-dicyanodiphenylether separated, m. p. 175—177°. By several recrystallizations from benzene-petroleum ether fine, colourless needles with m. p. 182° were obtained. (Reported yield and m. p.[7] 50% resp. 180°).

4,4'-Diformyldiphenyl ether (IV)

A suspension of 50 g. (0.264 mole) of anhydrous stannous chloride in 200 ml. of anhydrous ether was saturated with dry hydrogene chloride under stirring and cooling. To the resulting clear solution a solution of 5 g. (0.0228 mole) of 4,4'-dicyanodiphenyl ether (III) in 25 ml. of chloroform was added. After standing overnight the supernatant liquid was decanted and the precipitate hydrolyzed by boiling it with 100 ml. of 5% hydrochloric acid during 10—15 minutes. A dark oil separated, which was extracted with three 50 ml. portions of chloroform. The chloroform solution was washed three times with water, then with sodium bicarbonate solution, dried over sodium sulphate and evaporated to leave 4.5 g. (87.6%) of a yellowish product, m. p. 54—56°C. Repeated crystallizations from benzene-petroleum ether (2 : 1) gave colourless plates, m. p. 65—66°.

Anal. 15.83 mg. subst.: 43.10 mg. CO_2, 6.05 mg. H_2O
$C_{14}H_{10}O_3$ (226.22) calc'd.: C 74.33; H 4.46%
found: C 74.30; H 4.28%

The bis-oxime, prepared in the usual manner, melted after three crystallizations from benzene at 156°.

Anal. 14.14 mg. subst.: 33.90 mg. CO_2, 5.68 mg. H_2O
2.482 mg. subst.: 0.232 ml. N_2 (20°, 756 mm)
$C_{14}H_{12}N_2O_3$ (256.25) calc'd.: C 65.62; H 4.72; N 10.93%
found: C 65.42; H 4.52; N 10.83%

The bis-(2,4-dinitrophenylhydrazone) was prepared in ordinary manner. It was crystallized from nitrobenzene and washed with ethanol. Red crystals with m. p. 280—282°.

Anal. 1.888 mg. subst.: 0.314 ml. N_2 (22°, 748 mm)
$C_{26}H_{18}N_8O_9$ (586.47) calc'd.: N 19.11%
found: N 18.94%

Bisazlactone of 4,4'-diformyldiphenyl ether (V)

A mixture of 2.9 g. (0.0128 mole) of 4,4'-diformyldiphenyl ether (IV), 4.8 g. (0.0274 mole) of hippuric acid, 2.2 g (0.0268 mole) of freshly fused sodium acetate and 20 ml. of acetic anhydride was heated for 15 minutes on a water bath. At the beginning of heating the reaction mass was dissolved completely, but separation of the yellow azlactone started soon. The reaction mixture was then cooled, 50 ml. of water was added and left to stand for one hour. The separated azlactone was filtered off, washed well with water, then with ethanol, and finally with ether. 4.8 g. of crude V was obtained (73%), which melted at 254—255°. For analysis it was crystallized from benzene, m. p. 265—266° (decomposition).

Anal. 12.69 mg. subst. 34.93 mg. CO_2, 4.25 mg. H_2O
8.88 mg. subst.: 0.412 ml. N_2 (21°, 759 mm)
$C_{32}H_{20}N_2O_5$ (512.50) calc'd.: C 74.99; H 3.93; N 5.47%
found: C 75.11; H 3.74; N 5.37%

Diphenyl ether-4,4'-bis-α-benzoylaminoacrylic acid (VI)

1.4 g. (0.00274 mole) of bisazlactone (V) was refluxed for 15 minutes with 0.22 g. (0.0055 mole) of sodium hydroxyde in 15 ml. of 70% ethanol. After neutralization with 5% hydrochloric acid and cooling 1.4 g. (93%) of crude (VI) was obtained, m. p. 243° (decomposition). For analysis it was crystallized three times from ethanol-water (3 : 1); m. p. 250—251° (decomposition).

Anal. 18.79 mg. subst.: 48.03 mg. CO_2, 6.92 mg. H_2O
6.58 mg. subst.: 0.294 ml. N_2 (22°, 772 mm)
$C_{32}H_{24}N_2O_7$ (548.53) calc'd.: C 70.06; H 4.41; N 5.11%
found: C 69.75; H 4.12; N 5.25%

Diphenyl ether-4,4'-bis-α-benzoylaminoacrylic acid diethyl ester (VI a)

A solution of 2 g. (0.0039 mole) of bisazlactone V in 150 ml. of absolute ethanol and 10 ml. of concentrated sulphuric acid was heated under reflux during 30 min., concentrated by distilling off 80 ml. of ethanol and poured into 500 ml. of cold water. The obtained mixture was extracted with four 100 ml. portions of ether. The ethereal solution was dried and evaporated to leave 1.6 g. (68%) of crude ester VIa. Crystallized from benzene it melted at 145—150°. For analysis it was recrystallized three times from benzene-ether; m. p. 153—154.5°.

Anal. 10.22 mg. subst.: 26.70 mg. CO_2, 4.85 mg. H_2O
$C_{36}H_{32}N_2O_7$ (604.63) calc'd.: C 71.51; H 5.33%
found: C 71.29; H 5.31%

β,β'-(4,4'-Diphenyl ether)-dialanine (VII)

a) From VIa:

0.75 g. (0.00124 mole) of diethylester VIa was mixed with 4.65 ml. (0.0358 mole) of hydriodic acid (d = 1.7) and 1 g. (0.0322 g. atom) of red phosphorus and heated under reflux for one and a half hour. The obtained solution was filtered hot and the filtrate evaporated *in vacuo* to dryness. To the residue 10 ml. of water was added and evaporated again *in vacuo* to dryness. This same procedure was repeated twice more. The residue was then dissolved in 10 ml. of water, extracted with ether, filtered and heated to boil. The hot aqueous solution was neutralized by addition of a hot sodium acetate solution. A crystalline product separated, which was filtered off after cooling and washed succesively with water, ethanol and ether. 0.200 g.

(47%) of β,β'-(4,4'-diphenyl ether)-dialanine was obtained. It did not melt up to 340°, and gave a positive ninhydrin reaction.

Anal. 7.97 mg. subst.: 18.25 mg. CO_2 3.94 mg. H_2O
$C_{18}H_{20}N_2O_5$ (344.36) calc'd.: C 62.78; H 5.85%
found: C 62.49; H 5.53%

b) From VI:

A mixture of 0.5 g. (0.00091 mole) of the diacid VI, 5 ml. (0.0385 mole) of hydriodic acid (d = 1.7), 1 g. of red phosphorus and 10 ml. of glacial acetic acid was heated under reflux for one and a half hour. The solution was filtered hot, the phosphorus washed three times with 5 ml. portions of hot acetic acid and the combined filtrates evaporated to dryness *in vacuo*. To the dark residue 10 ml. of water was added and evaporated again to dryness. The residue was dissolved in 20 ml. of water, extracted three times with 10 ml. portions of ether, aqueous layer evaporated to dryness *in vacuo* and the residue dissolved in 15 ml. of water. This solution was filtered, heated to boil and made to pH 5 by addition of aqueous ammonia. After standing overnight in an ice-box the separated aminoacid was filtered off and washed successively with water, ethanol and ether. 0.172 g. (54.5%) of white crystals were obtained, which did not melt up to 340° and behaved identically as the product obtained by procedure under a).

c) From V:

A mixture of 2 g. (0.0039 mole) of the bisazlactone V, 4 g. (0.129 g. atom) of red phosphorus, 10 ml (0.077 mole) of hydriodic acid (d = 1.7) and 20 ml. of glacial acetic acid was heated under reflux for one and a half hours. Phosphorus was filtered off while hot and washed with hot acetic acid. The filtrates were evaporated *in vacuo* to dryness, 25 ml. of water was added to the residue and evaporated *in vacuo* again. The residue was dissolved in 20 ml. of water and the obtained solution extracted three times with 20 ml. portions of ether. The aqueous layer was decolorized with charcoal and evaporated to dryness *in vacuo*. The residue was dissolved in 30 ml. of hot water and adjusted to pH 5 with aqueous ammonia. At this point 0.2 g. of the amino acid separated and was filtered off. This material contained some iodine. The hot filtrate was then adjusted to pH 6 and 5 ml. of ethanol was added. After standing overnight at 0°, the amino acid VII, precipitated as white crystals, was filtered off and washed with water, ethanol and ether. The total yield of VII was 0.8 g. (59.5%). It did not melt up to 340° and behaved the same as the prior products. For analysis it was purified by dissolution in hot 10% hydrochloric acid and reprecipitation with ammonia at pH 6.

Anal. 13.40 mg. subst.: 30.69 mg CO_2, 6.81 mg H_2O
$C_{18}H_{20}N_2O_5$ (344.36) calc'd: C 62.78; H 5.85%
found: C 62.50; H 5.69%

The dihydrochloride was obtained by dissolving the amino acid in 10% hydrochloric acid, evaporating to dryness in vacuo, dissolving the residue in absolute ethanol, and adding ether. The analytical sample was crystallized twice from absolute ethanol-ether (2:1). It decomposed at 300°

Anal. 14.59 mg. subst.: 27.60 mg. CO_2; 6.88 mg H_2O
5.30 mg. subst.: 0.304 ml. N_2 (17°, 759 mm)
$C_{18}H_{22}N_2O_5Cl_2$ (417.29) calc'd.: C 51.81; H 5.31; N 6.71%
found: C 51.62 H 5.27 N 6.73%

The dibenzoyl derivative was prepared by the Schotten-Baumann benzoylation of the amino acid. Crystallized three times from ethanol it melted at 232—233° with decomposition.

Anal. 14.82 mg. subst.: 37.81 mg. CO_2, 6.68 mg. H_2O
$C_{32}H_{28}N_2O_7$ (552.56) calc'd.: C 69.55; H 5.11; N 5.07%
found: C 69.62; H 5.04; N 4.79

(N estimated by micro Wagner-Parnass method).

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IZVOD

Sinteza β,β'-(4,4'-difenil eter)-dialanina

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β,β'-(4,'-Difenil eter)-dialanin pripremljen je primjenom Erlenmeyerove reakcije na 4,4'-diformildifenileter. Kondenzacijom hipurne kiseline s 4,4'-diformileterom dobiven je bisazlakton (V). Taj je bisazlakton hidrolizom i redukcijom jodovodičnom kiselinom i fosforom preveden izravno u bis-amino kiselinu (VII), ili je prethodno hidroliziran u bis-benzoilamino cimetnu kiselinu (VI), odnosno njen ester (VIa), koji su onda, obrađeni jodovodičnom kiselinom i fosforom, također dali bis-amino kiselinu (VII).

Prikazani su povoljniji uvjeti za pripremanje već opisanih intermedijera za ovu sintezu: 4,4'-dinitro-, 4,4'-diamino- i 4,4'-dinitrilodifeniletera.

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