SYNTHESIS OF THE SEX PHEROMONE OF THE GRAIN MOTH Ephestia Elutella

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A most convenient synthesis of tetradeca-9Z,12E-dien-1-ol and its acetate — components of the sex pheromone of the grain moth — has been carried out on the basis of a scheme for obtaining a cis-1,trans-4-dienic system.

The grain moth Ephestia elutella causes great damage to food reserves. Its caterpillar damages grain, grain products, sunflower seeds, cacao, nuts, dried fruits and vegetables, confectionary articles, and various seeds of garden, vegetable, and forest plants [1, 2].

A promising method for the flight against this pest may be the use of pheromone traps. The sex pheromone of the grain moth is a two-component system: tetradeca-2Z,12E-dien-1-ol (I) and tetradeca-9Z,12E-dien-1-yl acetate (II). Although compound (I) by itself does not possess a male-attracting action, its addition to (II) increases the efficacy of hormone traps in all cases [3].

We have considered a stereospecific synthesis of both components of the sex pheromone based on a scheme for obtaining a cis-1,trans-4-dienic system [4].

Compound (III) was obtained by two routes: by the reaction of dibromobutane with ethylene oxide [5], and by the reduction of diethyl suberate. The halohydrin was synthesized by the method of continuous extraction using various solvents. The best result was obtained with the use of the heptane—octane (1:1) system.

Compound (IX) is an intermediate in the synthesis of a number of pheromones. But-2-yn-1-ol was obtained from 3-chlorobut-2-en-1-ol by the action of sodium amide in liquid ammonia. However, working with sodium amide and liquid ammonia has a number of inconveniences, and therefore we studied dehydrohalogenation under the conditions of phase-transfer catalysis. As the splitting-out agent we used powdered caustic potash, and as catalyst tetrabutylammonium iodide (TBAI). 1-Bromobut-2E-ene was obtained by the bromination of (VIII) with phosphorus tribromide in pyridine with a 63% yield.

According to Jacobson [6], compound (V) was obtained by the coupling of (IV) with lithium acetylide in dimethyl sulfoxide with a yield of 74%. To obtain the same compound, Rossi [4] used a complex of lithium acetylide with ethylene diamine, but in this case the yield was only 40%. Methods of acetylation using lithium and sodium acetylides obtained via butyllithium [7] and sodium [8] have also been described. We tested all the methods of obtaining compound (V). The best proved to be [6], by which 10-(tetrahydropyranyloxy)dec-1-yne was always obtained in good yield and with only a small amount of by-products.

The key stage in the synthesis of tetradeca-cis-9,trans-12-dien-1-yl acetate is the linkage of the synthons obtained. We performed the linkage by two methods. The first method of synthesis consisted in the coupling of the lithium derivative of 2-(9-decyloxy)tetrahydropyran with 1-bromo-trans-2-butene. The reaction was performed in hexametapol at 40°C. The second route consisted in the coupling of an alkynl magnesium bromide with 1-bromobut-trans-2-ene in tetrahydrofuran catalyzed by a monovalent copper salt. In the absence of the monovalent copper salt the reaction takes place very poorly or does not proceed at all [9, 11]. Hydrogenation was carried out by two methods, using the catalyst P-2 Ni followed by the elimination of the pyranyl protection and hydrogenation of the tetradec-trans-12-en-9-yn-1-yl acetate (X).

The spectral characteristics of tetradeca-cis-9,trans-12-dien-1-ol and its acetate corresponded to the structure of these compounds. Gas-liquid chromatography showed that the products obtained had a purity of 98%.

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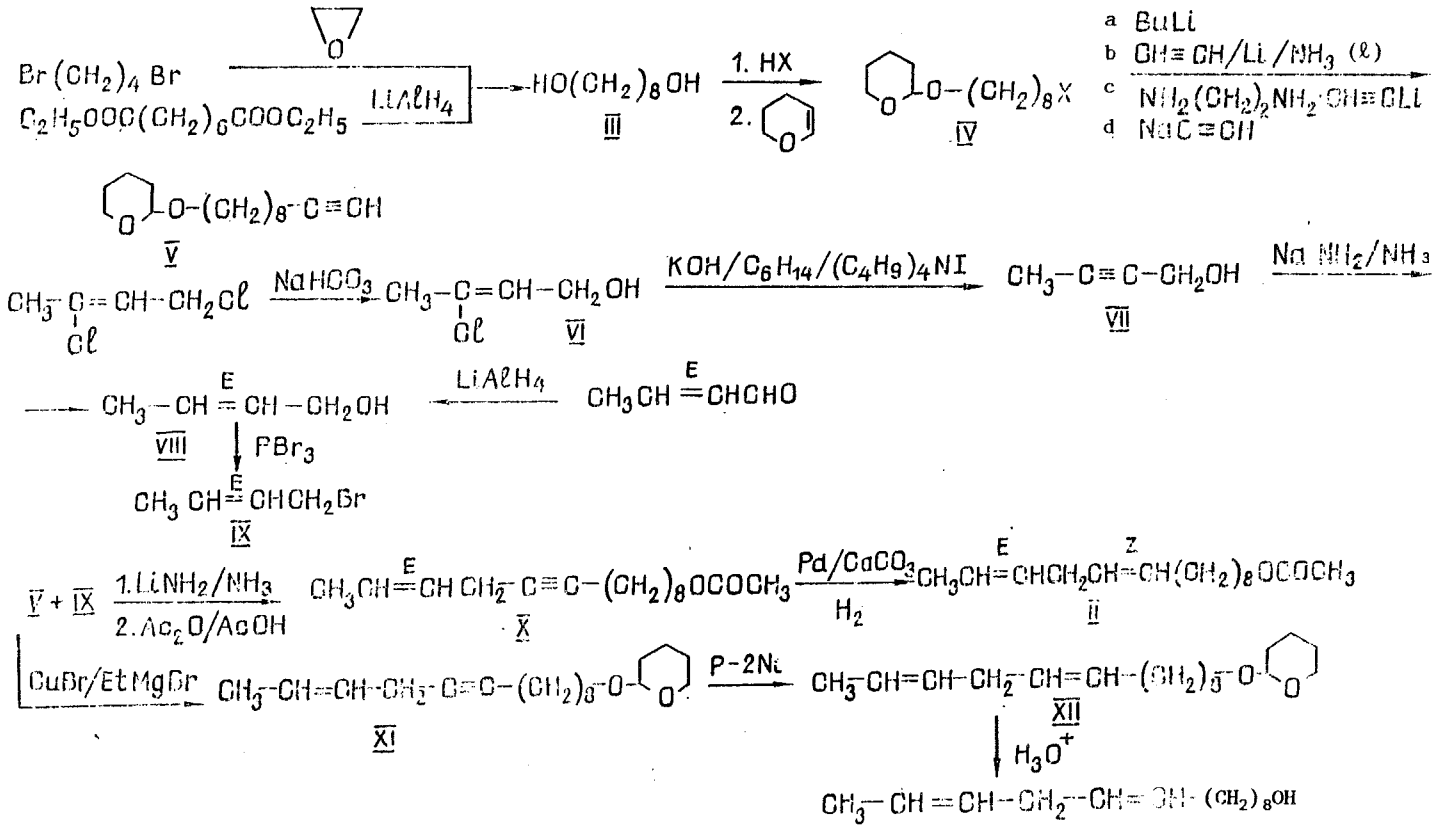

Synthesis of tetradeca-9Z,12E-dien-1-ol and its acetate – components of the pheromone of the grain moth.

EXPERIMENTAL

PMR spectra were obtained on a Varian XL-200 NMR spectrometer with a working frequency of 200 MHz. The samples used were solutions of the substances under investigation in CCl_4, with the signal of HMDS as internal standard. IR spectra were taken on a UR-20 instrument in carbon tetrachloride. Gas-liquid chromatography was performed on a Hewlett-Packard 5710A instrument using columns with OV-1 and DEGS. The results of the analyses of all the compounds corresponded to the calculated figures. All the reactions with organometallic compounds were performed in an atmosphere of nitrogen and helium.

Octane-1,8-diol (III). a) reduction with lithium tetrahydroaluminate of diethyl suberate. bp 101-105°C/4 mm. Yield 81%.

b) A flask fitted with a dropping funnel with cooling, a reflux condenser, and a mechanical stirrer was charged with 4.85 g (0.199 mole) of magnesium in the form of a powder, and 10 ml of tetrahydrofuran (THF) was added. To initiate the reaction, a small crystal of iodine and a few drops of dibromobutane were added to the reaction flask. After the beginning of the reaction, 21.6 g (0.1 mole) of dibromobutane in 30 ml of THF was added dropwise. Then the mixture was heated to the boiling point for one hour, after which the reaction flask was cooled with a mixture of ice and salt to −10°C, and 9 g (0.204 mole) of ethylene oxide in 25 ml of THF was added slowly. The mixture was stirred at room temperature for an hour, the solvent was driven off, and the residue was decomposed with concentrated HCl with stirring and cooling. The mixture obtained was extracted with ether and dried over K_2CO_3. The solvent wad driven off, and the residue was distilled in vacuum. The yield was 6 g (43%).

8-Chlorooctan-1-ol. A continuous extractor was charged with 8.7 g (0.069 mole) of octane-1,8-diol and 82 ml of 9 N NCl and with a mixture of the solvents heptane and octane (1:1) until it was full. Extraction was carried out for 20 h at the boiling point of the solvent. The extract was dried with potassium carbonate. The solvent was driven off and the residue was distilled in vacuum. This gave 7.25 g of a product with bp 105°C/4 mm; n_D^{20} 1.4585. Yield 73%.

1-Chloro-8-(2-tetrahydropyranyloxy)octane (IV). With ice-salt cooling, dihydropyran was added slowly dropwise to 5.1 g (0.031 mole) of chlorooctanol and 0.01 ml of HCl in an atmosphere of nitrogen. The reaction mixture was stirred at room temperature for 3 h. Then it was diluted with two volumes of absolute ether and was washed with a 2 N solution of NaOH and a saturated solution of NaCl. It was dried over calcined potassium carbonate, the solvent was driven off under reduced pressure, and the residue was distilled in vacuum. This gave 5.86 g of a product with bp 124-127°C/3 mm. Yield 67%. PMR (ppm): 4.44 (1H, O—CH—O, t), 3.2-3.8 (4H, O—CH_2, m), 3.29 (2H, t, J = 6 Hz, CH_2—Br), 1.1-1.9 (18H, CH_2, m).

10-(2-Tetrahydropyranyloxy)dec-1-yne (V). a) The reaction was performed in an atmosphere of helium. A four-necked flask was charged with 50 ml of dry hexane and 2 g of finely cut metallic lithium. The reaction mixture was heated at 40°C, and butyl chloride was added dropwise. Heating was continued for 40 min, and then the solution was filtered on a Schott funnel in an atmosphere of helium. The normality of the solution was 1.7 (titration with 0.1 N HCl).

A current of acetylene was passed into a three-necked flask containing 16 ml of absolute tetrahydrofuran until it was saturated. Then, slowly, with ice-salt cooling, the 1.7 N solution of butyllithium was added dropwise. The mixture was stirred for 30 min, and then a solution of 5.86 g (0.0235 mole) of the chlorooctanol tetrahydropyranyl ether(IV) in 20 ml of hexametapol was added. After the reaction mixture had been stirred for an hour, a small amount of ice water was added and the product was extracted with ether. The ethereal extract was washed with water and was dried over calcined potassium carbonate. The solvent was driven off and the residue was distilled in vacuum, giving 3 g of a product with bp 169-175°/5 mm, n_D^{20} 1.4615. Yield 54%.

b) A powerful current of acetylene was passed into a flask containing 150 ml of liquid ammonia for 10 min. Metallic lithum was cut into small pieces and a current of acetylene was passed [sic]. Then DMSO was added, followed by 4 g (0.016 mole) of 1-chloro-8-(2-tetrahydropyranyloxy)octane. The mixture was stirred at room temperature for two hours, and then 60 ml of a mixture of ether and pentane (1:1) was added, and, after treatment with ice water, the extract was dried over anhydrous $MgSO_4$. The solvent was distilled off and then residue was purified by column chromatography on Chemapol L 60/100 silica gel with ether—pentane (1:1) as eluent. The yield was 3 g (80%).

c) The complex $H_2NCH_2CH_2NH_2 \cdot CH{\equiv}CLi$ was obtained according to [10]. A mixture of 100 ml of dimethyl sulfoxide and 4.4 g (0.0478 mole) of the above-mentioned complex was stirred for 1 h. With cooling to 0-5°C, 4 g (0.016 mole) of the tetrahydropyranyl ether of chlorooctanol in 50 ml of dimethyl sulfoxide was added. The reaction mixture was stirred at room temperature for 15 h. Then it was extracted with ether and the extract was dried over anhydrous $NaHCO_3$. The solvent was driven off and the residue was distilled in vacuum. This gave 2 g of product with bp 168-173°C/5.5 mm; n_D^{20} 1.4595; yield 52%.

d) Metallic sodium (3.57 g; 0.148 mole) was suspended in absolute xylene (43 ml). A current of acetylene was passed into the flask with the suspended sodium at 105°C. The reaction mixture rapidly became dark brown. After 2 h, its color began to lighten. Acetylene was passed through for another 6 h. After the passage of acetylene had been stopped, the reaction mixture was cooled, absolute DMFA and, dropwise over 20 min, 12.42 g (0.05 mole) of 1-chloro-8-(2-tetrahydropyranyloxy)octane were added. The mixture was stirred at room temperature for about 10 h. Very carefully, 50 ml of water was added, the dark brown precipitate was filtered off and it was washed twice with water, and the organic layer was separated off and was dried over $MgSO_4$. The solvent was evaporated off and the residue was distilled in vacuum. This gave 7.5 g of a product with bp 164-172°C/5 mm, n_D^{20} 1.4620. Yield 67%. IR spectrum (cm^{-1}): 3300, 2100, 1195, 1130, 1115, 1070, 900, 860, 805, 715. PMR spectrum (ppm): 4.44 (1H, O—CH—O t); 3.2-3.8 (4H, OCH_2, m); 2.07 (2H, CH_2—C≡, m); 1.7 (1H, ≡CH, t); 1.1-1.8 (18H, CH_2, m).

But-2-yn-1-ol (VII). 3-Chlorobut-2-en-1-ol was obtained by saponifying 1,3-dichlorobut-2-ene [12]. A mixture of 10.65 (0.1 mole) of 3-chlorobut-2-en-1-ol, 12.2 g (0.2 mole) of powdered caustic potash, and 0.738 g (0.002 mole) of tetrabutylammonium iodide in 100 ml of hexane was boiled under reflux for 12 h and was then acidified with concentrated HCl and extracted with ether (2 × 40 ml). The ethereal extracts were combined, washed with water, and dried over anhydrous Na_2SO_4. The solvent was driven off and the residue was fractionated at atmospheric pressure. This gave 8.1 g of a product with bp 140-142°C, n_D^{25} 1.4514. Yield 50%.

But-trans-2-en-1-ol (VIII). a) To 650 ml of liquid ammonia was added 13.26 g (0.62 mole) of metallic sodium. After this mixture had been stirred at −30°C for 30 min, 12.63 g (0.18 mole) of but-2-yn-1-ol in 80 ml of absolute ether was added over one hour. Stirring was continued for 3 h and, after the addition of NH_4Cl, the reaction mixture was left overnight. Then 130 ml of ice water was added and extraction was carried out with ether. The etheral extract was washed with water and dried with anhydrous Na_2SO_4. The solvent was driven off and the residue was fractionated. This gave 5.04 g of a product with bp 113-117°C, n_D^{25} 1.4219. Yield 39%.

b) To 10.64 g of lithium tetrahydroaluminate in 700 ml of absolute ether was added 70 g of crotonaldehyde at a rate keeping the reaction mixture at the boil. Then, with ice-salt cooling, ice-water was added drowise to decompose the excess of hydride. The reaction mixture was poured into 100 ml of ice water, and 50 ml of 10% H_2SO_4 was added. After ethereal extracts had been dried, the solvent was driven off and the residue was fractionated. This gave 36 g of a product with bp 115°C, n_D^{25} 1.4254. Yield 52%.

1-Brombut-trans-2-ene (IX). To a reaction mixture containing 8.25 g (0.114 mole) of but-trans-2-en-1-ol and 0.2 ml of pyridine in 35 ml of absolute ether was added 11.6 g of PBr_3 dropwise at a rate keeping the ether at the boil. After the addition of all the PBr_3 the reaction mixture was stirred at the boiling point of the solvent for 2 h. Then it was poured into ice water and was extracted with ether. The ethereal extracts were washed with solutions of $NaHCO_3$ and NaCl and were dried over calcined potassium carbonate. After the solvent had been distilled off, the residue was fractioned, giving 10 g of a product with bp 98-102°C, n_D^{25} 1.4760. Yield 63%. PMR (ppm): 5.46-5.85 (2H, m, J = 15.0 Hz, CH=CH); 3.82 (2H, d, J = 4.8 Hz, CH_2Br); 1.93 (3H, d, J = 4.8 Hz, CH_3—C=C).

Tetradec-12E-en-9-yn-1-yl Acetate (X). A 500-ml three-necked flask was charged with 300 ml of liquid ammonia, and a small crystal of $Fe(NO_3)_3$ was added. Then finely cut lithium was added. The solution became colored blue, and after the color had disappeared, 25 ml of HMPTA was added dropwise, the mixture was stirred for 30 min, and then 9 g (0.0378 mole) of 10-(tetrahydropyran-2-yloxy)dec-1-yne in 15 ml of HMPTA was added. The resulting mixture was stirred for 30 min, and 5.105 g (0.0378 mole) of 1-bromobut-trans-2-ene in 10 ml of HMPTA was added. The new mixture was stirred at room temperature for 2 h and then at 40°C for 8 h. It was decomposed with a saturated solution of NH_4Cl, the products were extracted

with ether, and the ethereal extracts were dried over Na_2SO_4. The solvent was driven off. The residue, 12.1 g, was treated with 40 ml of glacial acetic acid, and 20 ml of acetic anhydride. The mixture was stirred at 80°C for about 10 h. After cooling, it was poured into ice water and extracted with ether. The ethereal extracts were washed with 5% $NaHCO_3$ and 5% NaCl and were dried over Na_2SO_4. The solvents were driven off and the residue was distilled in vacuum, giving 5.1 g of a product with bp 173-176°C/2 mm, n_D^{25} 1.4625. Yield 48.1%. IR spectrum (cm^{-1}): 3000, 1725, 1230, 1030, 960, 715. PMR (ppm): 5.2-5.7 (2H, m, CH=CH); 2.94 (2H, t, J = 5.8 Hz, CH_2COO); 2.72 (2H, m, $\equiv C-CH_2-C$); 2.08 (2H, m, $CH_2-C\equiv$); 1.93 (3H, s, CH_3COO); 1.63 (3H, dd, J = 6.0 Hz, 1.1 Hz, $CH_3-C=C$); 1.1-1.7 (12H, m, CH_2).

Tetradec-9Z,12E-dien-1-yl Acetate (II). Reaction was carried out over Lindlar catalyst obtained by a known procedure [13]. Compound (X) (2.5 g; 0.01 mole) was placed in a conical flask and was reduced at −10°C in hexane (40 ml) in the presence of quinoline (0.030 ml). After the completion of reduction, the catalyst was filtered off, the solvent was evaporated, and the residue was distilled in vacuum, giving 1.4 g of a product with bp 190-194°C/2 mm, n_D^{25} 1.4565. Yield 55.5%. Stereochemical purity 98% (GLC, capillary column 50 × 0.25 m [sic], stationary-phase 1,2,3-tris-(2-cyanoethoxy)propane; temperature 160°C; carrier gas helium. IR spectrum (cm^{-1}): 3010, 1730, 1230, 1030, 960, 720. PMR (ppm): 5.15-5.40 (4H, m, 2CH=CH); 3.92 (2H, t, J = 6.0 Hz, CH_2COAc); 2.60 (2H, m, $=C-CH_2-C=$), 1.93 (2H, m, $=C-CH_2$); 1.91 (3H, s, CH_3COO), 1.50 (3H, m, $CH_3-C=$); 1.1-1.4 (12H, m, CH_2).

1-(Tetrahydropyran-2-yloxy)tetradec-12E-en-9-yne. A 250-ml conical flask was charged with magnesium, absolute THF, and a small crystal of iodine. After the addition of 4.74 g (0.0436 mole) of ethyl bromide, the mixture was boiled for 30 min. Then 9.5 g (0.04 mole) of 10-(tetrahydropyran-2-oyloxy)dec-1-yne (V) in THF was added and the reaction mixture was boiled for 1 h. After cooling, 0.386 g of CuBr and 5.44 g (0.04 mole) of 1-bromobut-trans-2-ene in 20 ml of THF were added over 20 min. The mixture was boiled for 1 h and it was then stirred at room temperature for another 36 h. The resulting yellow mixture was decomposed with 10% NH_4Cl, the organic layer was separated off, the aqueous layer was extracted three times with ether, and the extracts were combined and were washed twice with 10% NH_4Cl. The solvent was driven off and the coupling product obtained was used in the next stage without further purification.

2-(Tetradeca-trans-12,cis-9-dienyloxy)pyran (XII). At room temperature, with stirring, a solution of 0.204 g (0.0054 mole) of $NaBH_4$ in 15 ml of ethanol was added to 0.89 g (0.0036 mole) of $Ni(OCOCH_3)_2 \cdot 4H_2O$ in 30 ml of ethanol in an atmosphere of hydrogen. Then 0.6 ml of ethylenediamine and 106 g (0.036 mole) of compound (XI) were added successively. After the absorption of the calculated amount of hydrogen, the reaction stopped. The catalyst was filtered off through a small amount of silica gel, the ethanol was distilled off, and the residue was diluted with 15 ml of water and was extracted with ether. The extracts were washed with water and were dried over Na_2SO_4. The solvent was driven off and the residue, 9.1 g, was used in the following stage without purification.

Tetradeca-cis-9,trans-12-dien-1-ol. The residue was dissolved in 40 ml of methanol containing p-TsOH, and the solution formed was boiled for 2 h and was concentrated in vacuum, diluted with water, and extracted with hexane. After drying and the elimination of the solvent, the residue was subjected to careful fractional distillation using Raschig packing in the form of glass rings. bp 98-99°C (0.1 mm), n_d^{20} 1.4705, yield 90%.

SUMMARY

A convenient method for the synthesis of tetradeca-9Z,12E-dien-1-oland its acetate — components of the sex pheromone of the grain moth — has been developed.

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DIFFERENCE-PERTURBATION SPECTRA OF IODOTYROSINES AND IODOTHYRONINES IN POLYETHYLENEGLYCOLS

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The difference-perturbation absorption spectra of monoiodotyrosine, diiodotyrosine, triiodothyronine, and thyroxine with low- and high-molecular-mass polyethyleneglycols as perturbants have been measured and characterized. The SDP spectra, and their intensity and the position of the main maximum depend on the number of iodine atoms and the state of ionization of the hydroxyl in accordance with their electron-accepting properties.

The spectrophotometric properties of iodotyrosines and iodothyronines, determined by their aromatic systems are used in the study of iodine derivatives of proteins containing residues of these iodinated amino acids [1]. The absorption spectra depend on the presence of the hydroxyl and of iodine atoms and can change with a variation in the solvent [2]. The technique of solvent-perturbation difference (SPD) spectrophotometry permits the recording of slight variations in the absorption spectra. Polyethyleneglycol (PEG), like ethylene glycol, has been proposed for the perturbation of the absorption spectra of aromatic amino acids [3, 4].
The possibility of using ethylene glycol for the perturbation of the absorption spectra of iodine derivatives of tyrosine and thyronine has been shown previously [5].

In spite of its molecular mass, which may reach several millions of daltons, PEG has a chemical nature similar to that of ethylene glycol which can explain the similarity of their specific interactions with a chromophor.

We have determined the SDP-spectrophotometric properties of 3-iodotyrosine (MIT), 3,5-diiodotyrosine (DIT), and 3,5,3',5'-tetraiodothyronine (thyroxine, T_4), and also of 3',3,5-triiodothyronine (T_3) with DPEGs having molecular masses of 400 (PEG-400) and 4000 (PEG-4000) as perturbants.

The SPD absorption spectra of the solutions of the iodinated amino acids with deprotonated hydroxyls are shown in Figs. 1 and 2 and their main parameters are given in Table 1. Like the absorption spectra of iodotyrosine [1] and the SPD spectra are shifted in the long-wave direction relative to the spectrum of tyrosine (λ_{max} 286 nm [3]), this being connected with the presence of iodine atoms as substituents in the aromatic system, expanding the region of delocalization of the π-electrons and, being good electron acceptors, leading to electron density to deformations.

Let us consider the SDP spectra in the presence of the low-molecular-mass PEG as perturbant. With an increase in the number of iodine atoms in the aromatic ring (deprotonated form) the difference molar extinction coefficient rises similarly to the change in the extinction coefficient [1], while the absorption of the long-wave band is practically identical with its

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