METHODS OF SYNTHESIS AND TECHNOLOGY OF THE MANUFACTURE OF NEW DRUGS

SYNTHESIS OF ESTERS OF d*l*-α-TOCOPHEROL WITH HIGHER FATTY ACIDS

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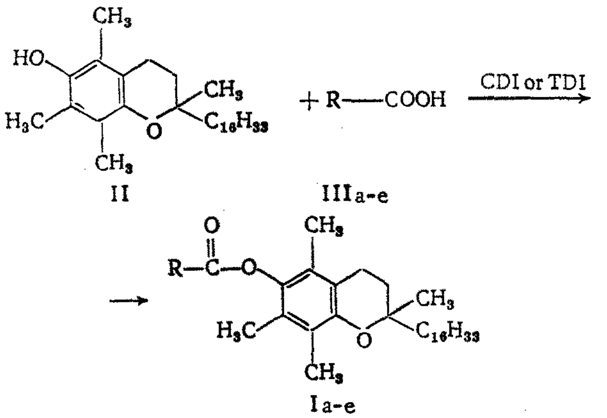
Noteworthy among vitamin E derivatives are esters of d*l*-α-tocopherol with higher fatty acids, individual representatives of which are of definite interest for medicine. Thus d*l*-α-tocopheryl linoleate (Ic), linolenate (Id), and arachidonate (Ie) and the ester of d*l*-α-tocopherol with 5,8,11,14,17-eicosapentaenoic acid, which have not only E-vitamin activity but also new biological properties, have been demonstrated for the treatment of atherosclerosis, inflammatory processes, and other diseases [2-5]. The development of simple (in an experimental respect) methods that make it possible to realize the synthesis of these compounds in preparative amounts is necessary for the detailed study of their therapeutic action.

Methods for the synthesis of d*l*-α-tocopherol esters I that consist in the acetylation of d*l*-α-tocopherol (II) by heating with the chlorides or anhydrides of the corresponding acids are known [2]. In addition, the direct esterification of d*l*-α-tocopherol (II) by fatty acids III in the presence of specially obtained pyrophosphate by heating [3], as well as under the influence of 2-chloro-1-methylpyridinium p-toluenesulfonate and other agents that tie up water [4], can also be carried out. Among the inadequacies of the indicated methods [2-4], one should include, first, the need to carry out additional steps for the preparation of the reagents used and, second, realization of the principal reaction at high temperature, which can cause structural changes in both the acidic components of the synthesis and in the reaction products [6, 7].

In this connection, in the case of the preparation of d*l*-α-tocopheryl palmitate (Ia), stearate (Ib), linoleate (Ic), linolenate (Id), and arachidonate (Ie) we used a convenient laboratory method based on the esterification of II by fatty acids IIIa-e in the presence of carbonyldiimidazole (CDI) or thionyldiimidazole (TDI) via the following scheme:



Ia and IIIa: $R = C_{15}H_{31}$; Ib and IIIb. $R = C_{17}H_{35}$; Ic and IIIc:
$R = CH_3(CH_2)_4CH{=}CH{-}CH_2{-}CH{=}CH(CH_2)_7$; Id and IIId:
$R = CH_3{-}CH_2{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2{-}CH{=}CH(CH_2)_7$; Ie and IIIe:
$R = CH_3(CH_2)_4{-}CH{=}CH{-}CH_2{-}CH{=}CH{-}CH_2CH{=}CH{-}CH_2{-}CH{=}CH(CH_2)_3$.

The formation of an ester bond proceeds through the imidazolides of the starting acids, the reaction of which with II in an organic solvent leads to the production of esters Ia-e and is accompanied by the precipitation of imidazole (IV), which can be reused in the work, particularly in the preparation of TDI. The latter, in contrast to crystalline CDI, is read-

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TABLE 1. Spectral Characteristics of the Synthesized Compounds

Compound	IR spectrum, ν, cm^{-1}		UV spectrum, (heptanel), λ_{max}, nm ($E^{1\%}_{1cm}$)	^1H NMR spectrum (deuterochloroform), δ, ppm
	C=O	C=C		
Ia	1750	—	284 (31,8)	0,95 m (18H, CH_3, 2-CH_3); 1,30 m (44H, CH_2); 1,75 q (2H, 3-CH_2, J=7Hz): 2,00 s (6H, 5,7-CH_3); 2,10 s (3H, 8-CH_3): 2,40 t (2H, —CH_2—COOR, J=7 Hz); 2,55 t (2H, 4-CH_2, J=7 Hz)
Ib	1750	—	284 (32,8)	0,90 m (18 H, CH_3, 2-CH_3); 1,25 m (48H, CH_2); 1,75 q (2H, 3-CH_2, J=7 Hz); 2,05 s (6H, 5,7-CH_3): 2,15 s (3H, 8-CH_3); 2,38 t (2H—CH_2—COOR, J==7 Hz); 2,50 t (2H,4-CH_2, J=7 Hz)
Ic	1750	1650	284 (30,3)	0,90 m (18H, CH_3, 2-CH_3); 1,30 m (34H, CH_2); 1,75 q (2H, 3-CH_2, J=7 Hz); 2,00 s (6H, 5, 7-CH_3); 2,05 s (3H, 8-CH_3); 2,10 m (4H—CH_2—CH=); 2,55 t (4H, 4-CH_2, —CH_2—COOR, J==7 Hz); 2,80 t (2H, =CH—CH_2—CH=, J=6 Hz); 5,40 m (4H, cis CH=CH—)
Id	1750	1650	284 (26,7)	0,85 m (18H, CH_3, 2-CH_3); 1,25 m (28H, CH_2); 1,78 q (2H, 3-CH_2, J=7 Hz); 2,00 s (6H, 5, 7-CH_3); 2,05 s (3H, 8-CH_3); 2,15 m (4H, —CH_2—CH=); 2,50 t (4H, 4-CH_2, —CH_2—COOR, J=7 Hz); 2,85 t (4H, =CH—CH_2—CH=, J=6 Hz); 5,35 m (6H, cis CH=CH—)
Ie	1750	1650	284 (26,2)	0,85 m (18H, CH_3, 2-CH_3); 1,20 m (24H, CH_2); 1,75 q (2H, 3-CH_2, J=7 Hz); 2,00 s (6H, 5, 7-CH_3); 2,05 s (3H, 8-CH_3); 2,10 m (4H, —CH_2—CH=); 2,55 t (4H, 4-CH_2, —CH_2—COOR, J=7 Hz); 2,80 t (6H, =CH—CH_2—CH=, J=6 Hz): 5,40 m (8H, cis CH=CH—)

TABLE 2. Physicochemical Properties of the Compounds Obtained

Compound	mp, °C	TLC, R_f (A)	Percentage from HPLC data, %	Found, %		Empirical formula	Calculated, %	
				C	H		C	H
Ia	42,4	0,75	99,4	80,54	11,95	$C_{45}H_{80}O_3$	80,84	11,98
Ib	39,4	0,75	99,5	81,44	12,01	$C_{47}H_{84}O_3$	81,03	12,07
Ic	—	0,75	98,9	81,44	11,63	$C_{47}H_{80}O_3$	81,50	11,56
Id	—	0,75	98,3	81,30	11,46	$C_{47}H_{78}O_3$	81,74	11,30
Ie	—	0,75	98,5	82,44	11,26	$C_{49}H_{89}O_3$	82,12	11,17

ily decomposed by moist air and is therefore prepared in the form of a solution in tetrahydrofuran (THF) from IV and thionyl chloride immediately prior to the reaction.

The course of the process was monitored chromatographically on Silufol UV-254 plates (Czechoslovakian SSR) in a petroleum ether—ether system (10:1; system A). Purification of Ia and Ib was achieved by recrystallization from acetone—isopropyl alcohol (1:1), whereas esters Ic-e were isolated by column chromatography on silica gel L40/100 (Czechoslovakian SSR).

The structures and individuality of the desired Ia-e were confirmed by IR, UV, and ^1H NMR spectroscopy (Table 1) and by the results of elementary analysis (Table 2).

EXPERIMENTAL

The IR spectra of mineral oil suspensions or films of the compounds were recorded with a Shimadzu IR435 spectrometer (Japan). The UV spectra at 240-350 nm were obtained with a Shimadzu UV240 spectrophotometer (Japan). The ^1H NMR spectra were recorded with a Brucker WM-250 spectrometer (West Germany) with an operating frequency of 250 MHz with deuterochloroform as the solvent and hexamethyldisiloxane (HMDS) as the internal standard. The purity of the reaction products was evaluated with an SP-8000 liquid chromatograph (West Germany) with the aid of an SP-8430 spectrophotometric detector and a 5-μm (25 cm by 16 mm) ServaSi-100-RP-8 column; the eluent was methanol (1 ml/min).

d*l*-α-Tocopheryl Palmitate (Ia). A solution of 1.3 g of II in 5 ml of dry chloroform was added in the course of 10 min to a mixture of 2.5 g (0.01 mole) of IIIa and 5.0 g (0.03 mole) of CDI in 10 ml of dry chloroform after it had been stirred for 15 min, after which the mixture was stirred for 6 h at 20°C and then evaporated to dryness in vacuo [at 10-15 mm (mercury column)]. A mixture of 20 ml of petroleum ether and 20 ml of 5% hydrochloric acid was added to the residue, and the ether layer was separated, washed with distilled water until the wash water had pH 6.0-7.0, and dried with sodium sulfate. The solvent was removed by distillation, and the residue was crystallized from acetone—isopropyl alcohol (1:1) to give Ia (see Tables 1 and 2).

d*l*-α-Tocopheryl Stearate (Ib), d*l*-α-Tocopheryl Linoleate (Ic), and d*l*-α-Tocopheryl Linolenate (Id). These compounds were similarly obtained from II and IIIb-d (see Tables 1 and 2). Esters Ic,d were isolated by column chromatography on silica gel (80 cm^3) by elution with system A.

d*l*-α-Tocopheryl Arachidonate (Ie). A solution of 0.273 g (0.002 mole) of thionyl chloride in 2 ml of THF was added to a cooled (to 0°C) solution of 0.625 g (0.009 mole) of IV in 12.5 ml of anhydrous THF, after which the mixture was stirred for 10 min at 20°C, and the resulting precipitate was removed by filtration. A solution of 0.035 g (0.001 mole) of IIIe in 3 ml of THF was added with stirring to the filtrate, the mixture was stirred for 15 min, and a solution of 0.43 g (0.001 mole) of II in 5 ml of THF was added in the course of 5 min. The reaction mixture was maintained in a desiccator for 20 h, after which it was evaporated, and a mixture of 10 ml of petroleum ether and 10 ml of 5% hydrochloric acid was added to the residue. The ether layer was separated, washed with distilled water until the wash water had pH 6.0-7.0, dried with sodium sulfate, and evaporated. The residue was chromatographed with a column packed with silica gel (40 cm^3) in system A to give Ie (see Tables 1 and 2).

In contrast to the IR spectra of starting acids IIIa-e, which have characteristic absorption bands of a carboxy group, the IR spectra of Ia-e do not contain a COO^- band (λ_{max}, cm^{-1}: 1610), and the C=O absorption (1720 cm^{-1}) is shifted to 1750 cm^{-1} due to the formation of an ester bond; in contrast to II, an OH absorption band (3400 cm^{-1}) is not observed (see Table 1).

Signals of II residues and acyl substituents are recorded in the ^1H NMR spectra of Ia-e (see Table 1).

A comparison of the UV spectra of esters Ia-e (see Table 1) and starting II ($\lambda_{max}^{CH_3OH}$ 292, $E_{1cm}^{1\%}$ 73.8 [1]) shows that a hypsochromic shift of the absorption maximum and a hypochromic effect are characteristic for them; this is also observed for other esters of II, such as the acetate of II: $\lambda_{max}^{CHCl_3}$ 287, $E_{1cm}^{1\%}$ 92.0 [1]).

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