SYNTHESIS OF VITAMIN E ACETATE

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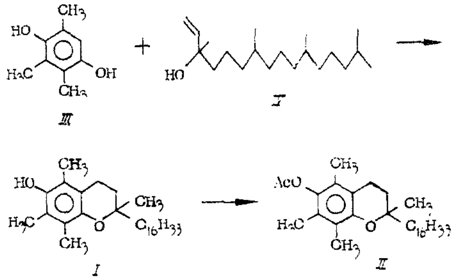
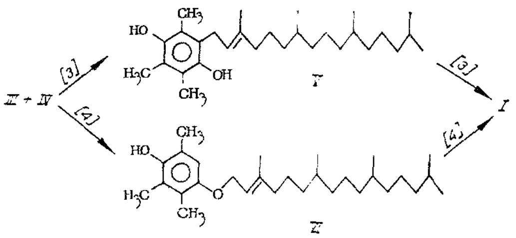
UDC 615.356:577.161.3].012.1

Vitamin E in the form of free α-tocopherol (I), and also in the esterified form, is widely used in medical practice, cosmetics, and in the veterinary and food industry. In the USSR, the Pharmacopoeia preparation of vitamin E is α-tocopherol acetate (II), obtained by acetylation of I, which in turn is prepared [1] from trimethylhydroquinone (III) and isophytol (IV).



In the existing methods, zinc chloride is usually used as the activator for the condensation reaction of III and IV. Under given conditions, when considerable amounts of this catalyst are consumed (0.8-1.1 mole per mole of IV), a high quality vitamin E can be obtained in satisfactory yield [2]. In a previous paper [3] we reported that in certain organic solvents (o-xylene, butyl acetate, acetic acid), in the presence of zinc chloride taken in an amount of 0.14 mole per mole of III, the preparation of I is preceded by the formation of trimethylphytylhydroquinone (V). At the same time, from the spectral data it was found [4] that in decane, zinc chloride used in equimolar amount with respect to III forms a molecular complex with the latter, which in reaction with IV converts into I via the intermediate phytyl trimethylhydroquinone ether (VI).

Thus, under the conditions studied, depending on the amount of zinc chloride and the nature of the solvent, the formation of I from III and IV can proceed via either the phytyl-substituted trimethylhydroquinone V or the phytyl trimethylhydroquinone ether VI.



It was interesting to study the influence of zinc chloride in amounts less than those previously used on the synthesis of I. In the present work we showed the possible condensation of III and IV in the presence of trace amounts (3.10^{-2} mole per mole of III) of zinc chloride in acetic acid. By means of GLC and TLC we found that under these conditions the main product of the reaction of III and IV is the intermediate compound V, with a lower mobility than I. Compound V was isolated by preparative TLC on silica gel (hexane—ether

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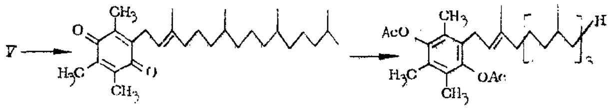
system, 3:1, R_f 0.47), and oxidized into trimethylphytylbenzoquinone (VII), which was identified by elemental analysis, IR, and UV spectra. During reductive acetylation of VII, trimethylphytylhydroquinone diacetate (VII), was obtained, identical to that previously described in [3].


VII VIII

In the study of the properties of V, we found that when additional amounts of zinc chloride or a strong protonic acid are introduced, it isomerizes into I. This observation, verified by GLC and TLC method, made it possible to work out a synthesis of I from II and IV in the presence of trace amounts of zinc chloride, followed by the addition of sulfuric acid in amounts of the order of magnitude of 10^{-2} mole of each reagent per mole of III. For the synthesis of III, the most suitable procedure is that in which IV is added in the course of 30 min to a boiling mixture of III and zinc chloride in acetic acid, and then sulfuric acid is added in the form of a 1% solution in the same solvent. According to GLC data, compound I thus obtained contains not more than 5% of II. Complete conversion of I into II occurs when the reaction mixture is treated with acetic anhydride; an aqueous solution of ammonia is added to neutralize sulfuric acid. The acetic acid and excess acetic anhydride are then distilled, and the residue dissolved in toluene and washed with an aqueous solution of Trilon B; after distillation of the solvent, the residue is subjected to fractional distillation. The main fraction of II is light yellow in color, and contains about 0.5% of I and 1-2% of unidentified compounds. Colorless II without these impurities is obtained by chromatography first on silica gel and neutral aluminum oxide, and then on Sephadex.

EXPERIMENTAL

Gas—liquid chromatography is carried out on "Chrom-4" (Czechoslovakia) with a flame ionization detector on a stainless steel column under the following conditions: length of column 1 m, internal diameter 0.3 cm, temperature of column thermostat 250°C, temperature of evaporator 300°C, flow rate of gas carrier (nitrogen) 30 ml/min, flow rate of hydrogen 40 ml/min, flow rate of air 300 ml/min. A 5% SE-30 on Chromaton N-AW-PMCS 0.16-0.28 mm was used as the stationary phase.

The IR spectra in thin layers were run on the UR-20 spectrophotometer (GDR). The UV spectra of the solutions in ethanol were recorded on the "Specord" spectrophotometer (GDR). The purity of the compounds obtained and the course of the reaction were controlled by TLC on Silufol UV-254 plates in the hexane—ether (3:1) system, with iodine vapors as developer; R_f of α-tocopherol 0.6.

2,5,7,8-Tetramethyl-2-(4',8',12'-trimethyltridecyl)-6-acetoxy-chromane (II). A mixture of 15.2 g (0.2 mole) of III and 0.4 g (0.003 mole) of zinc chloride in 60 ml of acetic acid is heated to boiling, with stirring, in a nitrogen atmosphere, and 28.6 g (0.1 mole) of IV is added in the course of 30 min. Water which forms during the process is distilled with acetic acid. A 0.49-g portion (0.006 mole) of sulfuric acid (d 1.83) in 50 ml of the solvent used is added to the reaction mixture, and then 12.2 g (0.12 mole) of acetic anhydride. Stirring is continued for 30 min at 125-130°C. The reaction mixture is cooled to 40°C, and 0.31 ml of a 0.25% solution of ammonia is added. Excess acetic anhydride and also the acetic acid formed in the course of the acetylation are distilled at 10-12 mm Hg. The residue is dissolved in 25 ml of toluene and washed with a 5% aqueous solution of Trilon B (2 × 100). The solvent is removed at a residual pressure of 10-20 mm Hg, and crude II is fractionated in a high vacuum, bp 224-226°C (0.03 mm Hg). The yield of II is 92%. With a content of the main compound of 98.7% (according to GLC).

Chromatographic Purification of II. A solution of 20 g of distilled II in 15 ml of hexane is placed on a column (3.5 × 110 cm) filled with 200 g of silica gel L 100/160. First, 0.5 liter of hexane is used as the eluent, and then a mixture of hexane and ether (100:3). Solvent is removed from the combined fractions not containing impurities having R_f 0.9, and the residue in the form of a solution in hexane is passed through a layer of aluminum oxide grade II of activity on a funnel with a No. 3 porous filter. The solvent is removed from filtrates not containing the impurity of I (R_f 0.6), and 4.2 g of II are obtained. A 2.5-g portion of II is dissolved in 2 ml of chloroform and the solution is placed on a column (1.5 × 30 cm) filled with Sephadex LH-20 (about 20 g). Chloroform is used as the eluent. Fractions of 5 ml are collected and analyzed by GLC. Yield, 0.5 g of colorless II. UV spectrum (C_2H_5OH), λ_{max}, nm: 285. $E^{1\%}_{1cm}$ 43. n_D^{20} 1.4975.

Trimethylphytylbenzoquinone (VII). n_D^{20} 1.5000. Found, %: C 81.16; H 11.38. $C_{29}H_{48}O$. Calculated, %: C 81.26; H 11.29. IR spectrum, ν, cm^{-1}: 1650 (C=O). UV spectrum (C_2H_5OH), λ_{max}, nm: 258, 266 (log ε 2.61; 2.60).

Diacetyltrimethylphytylhydroquinone VIII. n_D^{20} 1.4912. Found, %: C 76.91; H 10.65. $C_{33}H_{54}O_4$. Calculated, %: C 76.99; H 10.57. IR spectrum, ν, cm^{-1}: 1770, 1200 (—OAc).

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IMPROVED METHOD OF OXIDATIVE CLEAVAGE OF THE DIHYDROXYACETONE SIDE CHAIN IN CORTICOSTEROIDS

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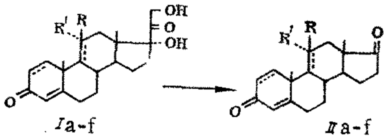
UDC 615.357:577.175.53].015.11

The oxidative cleavage of the side chain of corticosteroids (I) with the formation of 17-ketoandrostanes (II) is used to establish the structure of compounds I, and also as a path for the preparation of compounds II. However, the existing methods [1, 2] for carrying out this transformation are not always satisfactory as a preparative method: The yields of products II vary depending on the structure of the starting compounds I, and do not usually exceed 50%. The process is also accompanied by oxidation reactions at C^6, formation of a Δ^6 bond, etc.



Ia-f IIa-f

a: R = RI = H; b: R = H, $\Delta^{9(11)}$ bond; c: RRI = 0; d: R = OH, RI = H;
e: R = OH, RI = H, Δ^1 bond; f. RR^1 = 0, Δ^1 bond

The oxidation of compounds Ia, c, d by active MnO_2 [4] into 17-ketones IIa, c, d in yields of 34, 65, and 52%, respectively has been described in [3]. When studying this reaction by TLC, we noticed that in the course of prolonged (25 h) heating, 6-ketones are formed, and oxidation of the hydroxy group at C^{11} takes place, which hinders the isolation and purification of compounds II. We therefore increased the amount of MnO_2 so that the time of the reaction could be shortened and the formation of side products could be avoided. The proposed method consists in boiling compound I with a 20-fold excess of MnO_2 in chloroform for 3-4 h. At the end of the oxidation (TLC test), MnO_2 is filtered, and a solution of chromatographically almost pure compound II is obtained. The experimental results are listed in Table 1.

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