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SYNTHESIS OF PROVITAMIN D_5 FROM PLANT RAW MATERIAL

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It has been shown previously [1] that on heating phytosterol with chloride salts of divalent metals, complex compounds of β-sitosterol are formed with the metal chlorides which then may be readily decomposed into the sterol and inorganic components. This affords a real basis for converting phytosterol obtained on treating wood [2, 3] or the resin of peat wax [4] into provitamin D_5 by the scheme: phytosterol→complex of β-sitosterol with metal chloride→β-sitosterol→β-sitosterol benzoate→7-bromo-β-sitost-5-en-3β-ol benzoate→β-sitosta-5,7-dien-3β-ol benzoate→β-sitosta-5,7-dien-3β-ol→provitamin D_5→vitamin D_5. The antirachitic activity of vitamin D_5 was studied previously in [5, 6]. In practice provitamin and vitamin D_5 may be obtained by this scheme from various samples of phytosterol with a β-sitosterol (I) content of 40% and more.

Data are given in the present work on methods of obtaining provitamin D_5 from phytosterol isolated from the byproducts of cellulose sulfate manufacture. Phytosterol from the Kekhrassk Paper Combine [3] was used in the work and had mp 80-125°C containing 65% (I) determined by the digitonin method [7].

The first and second stages of the synthesis, the preparation of a molecular complex of calcium chloride with (I) and decomposition of the molecular complex to sterol and inorganic portions and isolation of (I), were carried out under conditions close to those described previously [1]. With this aim phytosterol was mixed with an organic solvent with heating, the insoluble portion was filtered off, and calcium chloride, dissolved in 96% ethyl alcohol, was added to the solution heated to 40°C. After standing for a day the molecular complex of calcium chloride with (I) of composition $(C_{29}H_{50}O)_2 \cdot CaCl_2 \cdot 6H_2O$ was filtered off and boiled in alcohol. On cooling the alcohol solution (I) crystallized out. More pure (I) was obtained when decomposition of the addition product of (I) with calcium chloride was carried out in the presence of activated carbon.

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A series of esters has been synthesized from (I) with radicals of aromatic and aliphatic acids [8, 9]. The best yield of bromo derivative was obtained on using β-sitosterol benzoate. On the basis of this and also of literature data [10] β-sitosterol benzoate (II) was selected as starting material for further conversions. Allylic bromination of (II) and also dehydrobromination of 7-bromo-β-sitost-5-en-3β-ol benzoate (III) and subsequent saponification of (III) were carried out by known methods under conditions close to those described for cholesterol [10, 11]. The best yield of β-sitosta-5,7-dien-3β-ol benzoate in the dehydrobromination process was obtained under more mild conditions in comparison with cholesterol. Boiling point of the reaction mass was 140°C, dehydrobromination temperature was 1 h, the ratio of (III) and sodium bicarbonate was 1:4 (in moles), and 0.25 mole α-picoline was selected for each mole of (III). For cholesterol the highest yield of cholesta-5,7-dien-3β-ol benzoate was obtained at a temperature of 160°C, a dehydrobromination time of 30 min, and the quantity of α-picoline was 1 mole per mole of 7-bromocholest-5-en-3β-ol benzoate [11]. On dehydrobrominating (III) with sodium bicarbonate α-picoline seemingly fulfills the role not only of a catalyst in the dehydrobromination reaction but also acts as a stabilizer of the unstable β-sitosterol $\Delta^{5,7}$ diene which is able to oxidize and decompose thermally under the action of heat, light, and oxygen of the air.

With the aim of preventing oxidative decomposition of the unstable intermediate products, antioxidants of the phenolic type were used in the study. Pyrocatechol and 3,5-di-tert-butyl-4-hydroxybenzylidene-p-hydroxyaniline were used at 0.2-0.5% of the weight of the β-sitosterol derivative. The percentage content of β-sitosta-5,7-dien-3β-ol benzoate (IV) and the $\Delta^{5,7}$ diene of β-sitosterol (V) were determined by a spectrophotometric method at a wavelength of 282 nm [12]. The yield of provitamin D_5 calculated on (I) was 32.7%.

Chromatographically pure (V) of mp 142-143°C and $[\alpha]_D^{20}$ -114° (in $CHCl_3$) was obtained by recrystallizing (V) with a content of 91.6% (from alcohol) in the presence of 0.5% antioxidant.

The purity of compounds and a check on the course of reactions was effected by thin layer chromatography on Silufol plates in the system n-hexane–ethyl acetate (4:1) under conditions close to those described in [12]. In contrast to [12] chromatograms were visualized with dilute phosphoric and sulfuric acids (1:1) and subsequent heating in a thermostat for 1-2 min at 100-105°C. Provitamin D_5 appeared as a pinkish lilac-colored spot of R_f 0.19 under these conditions.

The possibility of synthesizing vitamin D_5 from an available domestic raw material, namely phytosterol, has therefore been demonstrated.

EXPERIMENTAL

β-Sitosterol·$CaCl_2 \cdot 6H_2O$. A solution of phytosterol (mp 80-125°C, 5 g) in acetone (100 ml) was stirred at 40°C for 30 min. The insoluble portion was filtered off and a solution of $CaCl_2 \cdot 6H_2O$ (2.5 g) in 96% ethyl alcohol (5 ml) was added to the acetone solution. The reaction mixture was stirred for 2 h at 40°C, cooled to room temperature, kept for a day, and before filtering was cooled to 0°C. The molecular complex which separated was filtered off, washed with cold acetone, and dried. A white crystalline powder (3.8 g) of composition $(C_{29}H_{50}O)_2CaCl_2 \cdot 6H_2O$ was obtained.

β-Sitosterol(I). Ethyl alcohol (96%, 100 ml) was added to the molecular complex (3.8 g) of sitosterol and calcium chloride and the mixture was boiled for 30 min with activated carbon (0.2 g). After filtration the solution was cooled to 0°C and the precipitate of (I) was filtered off giving 2.2 g (73.3%) of mp 132-134°C. According to literature data [5], mp 135-137°C.

β-Sitost-5-en-3β-ol Benzoate (II) was obtained by heating (I) (2.2 g), benzoyl chloride (3 ml), and pyridine (15 ml) at 100°C for 1.5-2 h. The crude product was recrystallized from n-propyl alcohol, white needle crystals (2 g, 72.7%) of (II) were isolated of mp 144-145°C, R_f 0.88. According to literature data [9], it had mp 145-146°C.

7-Bromo-β-sitost-5-en-3β-ol benzoate (III) was obtained by the known method [10] by brominating a solution of (II) (2 g) in carbon tetrachloride (15 ml) with 1,3-dibromo-5,5-dimethylhydantoin (0.8 g) in the presence of azoisobutyric acid dinitrile (100 mg). The reaction was conducted in a nitrogen atmosphere under illumination by two photolamps (300 W) for 3 min. At the end of the reaction the content of (III) in the carbon tetrachloride

solution was determined by an argentometric method [13]. The value found was 110 mg/ml. This solution was used for further conversion into β-sitost-5-en-3β-ol benzoate. The crystalline bromo derivative (III) was isolated from the reaction mass by distilling off the carbon tetrachloride under vacuum at 30-40°C. The residue was recrystallized from petroleum ether (40-60°C fraction) and white needle crystals were obtained having mp 134-135°C. Found, %: Br 13.43. $C_{36}H_{53}O_2Br$. Calculated, %: Br 13.40.

β-Sitost-5,7-dien-3β-ol Benzoate (IV) was synthesized from (III) [11] at a reaction mass temperature of 140°C and a dehydrobromination time of 1 h. The amount of α-picoline was 0.04 ml and of sodium bicarbonate 1.12 g. Crystalline (IV) was isolated from the reaction mass by complete distillation of the solvent under vacuum at 60°C in the presence of catechol (0.2%) as antioxidant and subsequent solution of the residue in acetone (6 ml). The acetone solution of (IV) was cooled to 0°C and after standing for 24 h compound (IV) was isolated with a 91.6% content of main product (spectrophotometric method). Yield was 55% calculated on benzoate (I). Analytically pure (IV) was isolated by recrystallization from alcohol with activated carbon in the presence of 0.2% antioxidant. White needle crystals of mp 146-148°C and R_f 0.6 were obtained. According to literature data [14] it had mp 149°C.

β-Sitosta-5,7-dien-3β-ol (V), provitamin D, was obtained by saponification of (IV) (1.2 g) by the method in [12] with 5% alcoholic alkali in a nitrogen atmosphere. After recrystallization from a mixture of methanol–toluene (2:1) in the presence of the antioxidant 3,5-di-tert-butyl-4-hydroxybenzylidene-p-hydroxyaniline (0.5%) a substance (0.85 g) was obtained containing 90% of the desired product. The yield of provitamin D_5 calculated on compound (I) was 32.7%, it had mp 141-143°C, $[\alpha]_D^{20}$ -114° (chloroform). According to literature data [14], (V) had mp 144-145°C, $[\alpha]_D^{20}$ -116° (chloroform). IR spectrum (ν, cm^{-1} in Nujol): 3450 (OH); UV spectrum (in alcohol), λ_{max} nm, 272, 282, 294.

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