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M. E. Maurit, G. V. Smirnova, E. A. Parfenov, I. K. Sarycheva

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Abstract

Full Text

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M. E. Maurit, G. V. Smirnova, E. A. Parfenov, I. K. Sarycheva and N. A. Preobrazhenskii

Complete Synthesis of 2,5,7,8-Tetramethyl-2-(4′,8′,12′-trimethyltridecyl)-6-hydroxychroman (Vitamin E, α-Tocopherol) and Its Derivatives

(Presented by Academician A. N. Nesmeyanov, 27 IV 1961)

Vitamin E, which performs various functions in the organism, is used in hormonal therapy, in cardiovascular disorders, and in the treatment of a number of other diseases; in addition, it is an active stabilizer of vegetable oils and is used as an antioxidant. Together with natural higher aliphatic acids—linoleic, linolenic, and arachidonic—α-tocopherol is known as vitamin F.

At the basis of vitamin E (I) lies the tocol molecule, which is 2-methyl-2-(4′,8′,12′-trimethyltridecyl)-6-hydroxychroman, substituted in positions 5,7,8 by methyl groups.

(I)

The low content of α-tocopherol in plant sources, and the presence of a number of isomers of dimethyl- and methyltocols and the corresponding vitamins accompanying α-tocopherol, which complicate the process of isolating it in pure form, stimulated numerous investigations aimed at finding synthetic methods for obtaining this compound.

Known routes for the synthesis of vitamin E (I) are based on the interaction of 2,3,5-trimethylhydroquinone (II) with phytol (III).

$$\text{(II)} + \text{HO}{-}\text{CH}_2{-}\text{CH} = \text{C}(\text{CH}_3){-}(-\text{CH}_2{-}\text{CH}_2{-}\text{CH}_2{-}\text{CH}(\text{CH}_3){-})_3{-}\text{CH}_3 \longrightarrow \text{(I)}$$

(III)

Zinc chloride, formic and acetic acids, phosphorus anhydride, and boron trifluoride etherate are used as catalysts for this reaction; however, the condensation may also proceed without special activators. In addition, it has been found

that, in the synthesis of α-tocopherol (I), the aliphatic component can also be phytadiene, phytyl bromide, phytal and isophytyl chloride, isophytol (IV), 2,6,10,14-tetramethylhexadecanediol-14,16, and other compounds close in structure to phytol (III) and isophytol (IV). The literature also describes syntheses of α-tocopherol and its analogs in which the hydropyran ring and the phytyl residue are formed stepwise. In most of the methods described so far for the synthetic preparation of 2,6,10,14-tetramethylhexadecen-14-ol-16, phytol (III), 2,6,10,14-tetramethylhexadecen-15-ol-14, isophytol (IV), and their derivatives, the starting materials are natural raw materials: citral, pseudoionone, linalool (^1).

In the present communication a total synthesis of isophytol, starting from acetone and acetylene, is presented.

Scheme 1

$$CH_3-CO-CH_3 \rightarrow CH_3-\underset{OH}{\overset{CH_3}{C}}-C\equiv CH \rightarrow CH_3-\overset{CH_3}{C}=CH-CH=CH-\overset{CH_3}{CO} \rightarrow$$

(V) (VI)

$$CH_3-\overset{CH_3}{CH}-CH_2-CH_2-CH_2-\overset{CH_3}{CO} \rightarrow CH_3-\overset{CH_3}{CH}-CH_2-CH_2-CH_2-\underset{OH}{\overset{CH_3}{C}}-C\equiv CH \rightarrow$$

(VII) (VIII)

$$CH_3-\overset{CH_3}{CH}-CH_2-CH_2-CH_2-\overset{CH_3}{C}=CH-CH=CH-\overset{CH_3}{CO} \rightarrow$$

(IX)

$$CH_3-\left(-\overset{CH_3}{CH}-CH_2-CH_2-CH_2-\right)_2-\overset{CH_3}{CO} \rightarrow CH_3-\left(-\overset{CH_3}{CH}-CH_2-CH_2-CH_2-\right)_2 \rightarrow$$

(X) (XI)

$$-\underset{OH}{\overset{CH_3}{C}}-C\equiv CH \rightarrow$$

$$CH_3-\left(-\overset{CH_3}{C}H-CH_2-CH_2-CH_2-\right)_2-\overset{CH_3}{C}=CH-CH=CH-\overset{CH_3}{C}O\rightarrow$$

(XII)

$$CH_3-\left(-\overset{CH_3}{C}H-CH_2-CH_2-CH_2-\right)_3-\overset{CH_3}{C}O\rightarrow$$

(XIII)

$$CH_3-\left(-\overset{CH_3}{C}H-CH_2-CH_2-CH_2-\right)_3-\overset{CH_3}{\underset{OH}{C}}-C\equiv CH\rightarrow$$

(XIV)

$$CH_3-\left(-\overset{CH_3}{C}H-CH_2-CH_2-CH_2-\right)_3-\overset{CH_3}{\underset{OH}{C}}-CH=CH_2.$$

(IV)

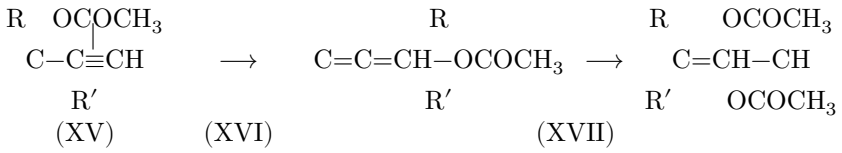
As is evident from Scheme 1, the synthesis is based on two consecutively repeated reactions: extension of each intermediate isoprene unit of the isophytol molecule by two, and then by three, carbon atoms.

For elongation of the chain by two carbon atoms, condensation of ketones with acetylene was used in organic solvents–xylene, toluene, dibutyl acetals of formaldehyde (b.p. 63-65°/7 mm; d_4^{20} 0.8473; n_D^{20} 1.4081; MR_D found 46.68, calculated for $C_9H_{20}O_2$ 47.04) or acetaldehyde (b.p. 64-64.5°/7 mm; d_4^{20} 0.8330; n_D^{20} 1.4086; MR_D found 51.68, calculated for $C_{10}H_{22}O_2$ 51.67) in the presence of caustic potash ([2]), or in liquid ammonia in the presence of sodium, leading to the formation of ethynylcarbinols. By these methods were obtained 2-methylbutyn-3-ol-2 (V), 2,6-dimethyloctyn-7-ol-6 (VIII), 2,6,10-trimethyldodecyn-11-ol-10 (XI), and 2,6,10,14-tetramethylhexadecyn-15-ol-14 (XIV), the physicochemical constants of which are given in Table 1.

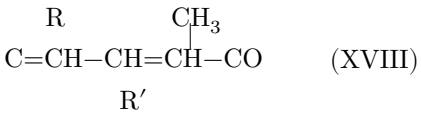
For elongation of the chain by three carbon atoms, the method of ob-

tion of α,β-unsaturated aldehydes and α,β; γ,δ-unsaturated ketones [(3)] (XVIII) from acetates of alcohols of the acetylene series (XV) by isomerizing them into

acetates of the allene structure (XVI) and acetal diacetates (XVII), followed by their condensation with acetone according to the scheme:



(XV) (XVI) (XVII)



(XVIII)

The 2-methylheptadien-2,4-one-6 (VI), 2,6-dimethylundecadien-6,8-one-10 (IX), and 2,6,10-trimethylpentadecadien-10,12-one-14 (XII) obtained by this method differ strongly in boiling point from the starting ethynylcarbinols and have a higher molecular refraction than that calculated, which is explained by conjugation of the double bonds and the carbonyl group (see Table 1).

For the conversion of the unsaturated ketones VI, IX, and XII into 2-methylheptanone-6 (VII), 2,6-dimethylundecanone-10 (X), and 2,6,10-trimethylpentadecanone-14 (XIII), a method of catalytic reduction in the presence of palladium chloride and activated carbon in methanol was used (see Table 1).

Table 1

Substance	Empirical formula	Yield, %	b.p., °C (mm)	d_4^{20}	n_D^{20}	Found MR_D	Found C, %	Found H, %	Calculated MR_D	Calculated C, %	Calculated H, %
Ethynylcarbinols											
2-Methylbutyn-3-ol-2 (V)	C_5H_8O	89.5	98–102° (752)	0.8658	1.4212	24.65			24.75		
2,6-Dimethyloctyn-7-ol-6 (VIII)	$C_{10}H_{18}O$	96.0	79–81° (10)	0.8521	1.4420	47.89			47.84		

Substance	Empirical formula	Yield, %	b.p., °C (mm)	d_4^{20}	n_D^{20}	Found MR_D	Found C, %	Found H, %	Calculated MR_D	Calculated C, %	Calculated H, %
2,6,10-Trimethyldodecyn-11-ol-10 (XI)	$C_{15}H_{28}O$	87.3	131–134° (9)	0.8542	1.4532	71.02	80.33	12.28	70.93	80.29	12.58
2,6,10,14-Tetramethylhexadecyn-15-ol-14 (XIV)	$C_{20}H_{38}O$	68.3	127–130° (0.25)	0.8517	1.4562	94.04	81.63	12.73	94.02	81.56	13.00
Unsaturated ketones											
2-Methylheptadien-2,4-one-6 (VI)	$C_8H_{12}O$	44.6	79–80° (9)	0.9006	1.5293	42.53	77.63	9.80	38.22	77.38	9.74
2,6-Dimethylundecadien-6,8-one-10 (IX)	$C_{13}H_{22}O$	72.8	132–135° (8)	0.8768	1.5097	66.26	80.29	11.14	61.31	80.35	11.41
2,6,10-Trimethylpentadecadien-10,12-one-14 (XII)	$C_{18}H_{32}O$	69.5	152–154° (4)	0.8684	1.4971	89.12	81.58	12.20	84.4	81.75	12.20
Saturated ketones											
2-Methylheptanone-6 (VII)	$C_8H_{16}O$	84.2	159–163° (752)	0.8203	1.4171	39.30	74.82	12.46	39.16	74.94	12.58

Substance	Empirical formula	Yield, %	b.p., °C (mm)	d_4^{20}	n_D^{20}	Found MR_D	Found C, %	Found H, %	Calculated MR_D	Calculated C, %	Calculated H, %
2,6-Dimethylundecanone-10 (X)	$C_{13}H_{26}O$	86.2	115–117° (8)	0.8300	1.4376	62.66	78.58	12.93	62.24	78.72	13.21
2,6,10-Trimethylpentadecanone-14 (XIII)	$C_{18}H_{36}O$	90.1	159–161° (5)	0.8368	1.4482	85.62	80.82	13.54	85.33	80.52	13.52

On reduction of 2,6,10,14-tetramethylhexadecyn-15-ol-14 (XIV) in the presence of Lindlar catalyst [4], or on hydrogenation in the presence of a palladium catalyst on calcium carbonate or a skeletal nickel catalyst in anhydrous methanol until 1 mole of hydrogen per 1 mole of substance is absorbed, 2,6,10,14-tetramethylhexadecen-15-ol-14, isophytol (IV). Yield 90.6%. B.p. 146–147°/5 mm; d_4^{20} 0.8454; n_D^{20} 1.4576; MR_D 95.64. $C_{20}H_{40}O$ F. Calculated 95.62.

Found, %: C 81.35; H 13.48
$C_{20}H_{40}O$. Calculated, %: C 81.35; H 13.60

The synthetic isophytol (IV) obtained in this way is one of the components for the preparation of α-tocopherol (I).

As the second component, 2,3,5-trimethylhydroquinone (II) is used; it was obtained from nitromesitylene (XIX) [5] by selective reduction to mesitylhydroxylamine (XX) and its conversion into 2,3,5-trimethylhydroquinone on the basis of the quinol rearrangement reaction into the corresponding hydroquinones according to E. Bamberger [6].

$$(\text{XIX}) \longrightarrow (\text{XX}) \longrightarrow (\text{II}); \quad (\text{IV}) \xrightarrow{(\text{II})} (\text{XXI})$$

In the condensation of isophytol (IV) with 2,3,5-trimethylhydroquinone (II) in acetic acid medium in the presence of boron trifluoride etherate and zinc chloride, vitamin E acetate (XXI) is obtained. Yield 69.5%.

Vitamin E acetate is a thick, viscous, light-yellow oil, soluble in organic solvents. B.p. 183–185°/0.07 mm; 205–208°/0.3 mm; d_4^{20} 0.9773; n_D^{20} 1.5021; MR_D 142.76. $C_{31}H_{52}O_3$ F_3. Calculated 142.85. $E_{1\text{ cm}}^{1\%}$ 43.35 ± 1 at 285 mμ.

Found, %: C 78.47; H 10.81
$C_{31}H_{52}O_3$. Calculated, %: C 78.76; H 11.09

By saponification of α-tocopherol acetate (XXI) with an alcoholic solution of caustic potassium, α-tocopherol (I) was obtained, which, on reaction with

palmitic acid chloride (XXII, b.p. 190–192°/14 mm), forms vitamin E palmitate (XXIII). Yield 37.5%. M.p. 36–37°.

$$\text{(I)} \xrightarrow[\text{(XXII)}]{C_{15}H_{31}COCl} \text{(XXIII)}$$

Found, %: C 80.91; H 11.88
$C_{45}H_{80}O_3$. Calculated, %: C 80.78; H 12.05.

Moscow Institute of Fine Chemical Technology
named after M. V. Lomonosov

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Note: Figure translations are in progress. See original paper for figures.