SYNTHESIS OF E-C_5-HOMOLOG OF SQUALENE

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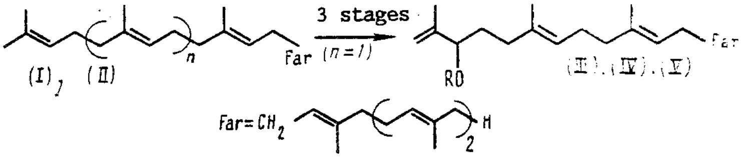
A stereospecific synthesis has been carried out for a monoisoprenolog of squalene by a cross-combination according to the Wurtz reaction of prenylmagnesium chloride with 3-hydroxyisosqualene tosylate.

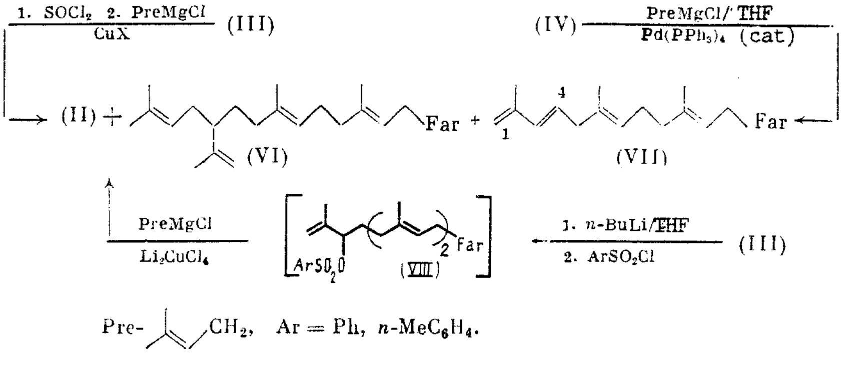
As a result of the need to prepare samples of isoprenologs of squalene (I) for biochemical investigations, the present article deals with the synthesis of its E-C_5-homolog (II). The approach adopted is based on 2,3-epoxysqualene [1], which readily isomerizes by the action of $(i\text{-PrO})_3Al$ according to the method in [2] into the known 2-hydroxyisosqualene (III) [3]. Taking into consideration the results we obtained for the transformation of 9-ubiquinone into 10-ubiquinone [4], it was proposed to convert (III) in the form of acyl (IV), (V) and certain other derivatives according to the Wurtz reaction scheme into the desired heptaene (II).



$n = 1$ (I), 2 (III); R = H (III), Ac (IV), Bz (V).

It was initially proposed to achieve the intended object by a transition metals catalyzed cross-combination of a Grignard reagent with a primary allyl chloride, prepared from prenyl chloride and secondary alcohol (III), respectively. Treatment of the secondary alcohol (III) with $SOCl_2$ in hexane leads to the desired E-Δ^2-C^1-chloro derivative of squalene, which, however, in contrast to the product of this reaction in the series of ubiquinones [5, 6], contains $\sim$20% of the secondary 3-chloro-Δ^1-isomer, as has been established by measuring the integral intensity in the PMR spectrum of this mixture of broadened single signals with δ 4.88 and 5.00 (2H, $H_2C{=}C$) and 4.01 ppm (2H, CH_2Cl).

The low-temperature condensation of an excess of prenylmagnesium chloride with a freshly prepared mixture ($\sim$4:1) of squaleneallyl chlorides, catalyzed by CuI in a THF medium, gives in >80% yield a difficultly separable mixture of hydrocarbons (II):(VI):(VII) ≃ 10:6:1 (PMR data). When this reaction was carried out in the presence of catalytic amounts of CuCl, a (II):(VI):(VII) ≃ 3:4:2 mixture was obtained in high yield.



Pre- CH_2, Ar = Ph, n-MeC_6H_4.

The latter ratio indicates a considerable contribution of a CuCl catalyzed competing S_N2'-type reaction, which leads to the branched hydrocarbon (VI) and is accompanied by dehydrochlorination of one or two initial allyl chlorides into the 1,3-diene (VII).

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The structure of the new compounds (II), (VI), and (VII) was established from the PMR spectral data. In particular, for the irregular terpenoid (VI), the proton signals of the isopropenyl residue at δ 4.65 and 4.69 br. s ($H_2C{=}C$) and 1.73 ppm br. s (CH_3) are characteristic, while in the spectrum of 1,3-E-diene (VII), the proton signals of the C^3—C^4 fragment at δ 6.16 br. d (HC^3, J = 15.2 Hz) and 5.64 ppm br. d. t (HC^4, J = 15.2 and 6.7 Hz) are readily identifiable [4, 7].

Replacement of the squaleneallyl chlorides by acyl derivatives (IV), (V) resulted in a relatively high reactivity of acetate (IV), the best result with which was achieved in its $Pd(PPh_3)_4$ catalyzed reaction with prenylmagnesium chloride, leading, however, to a (II):(VI): (VII) ≃ 1:1:1 mixture in a ∿35% yield (PMR data).

The loss of the regioselectivity of the cross-combination of prenylmagnesium chloride, observed in all the above-discussed cases, could be overcome by carrying out the reaction with unstable O-phenyl- or O-p-tolylsulfonyl derivatives (VIII), which cannot be subjected to chromatographic purification, and therefore are prepared in situ from the secondary alcohol (III). It was found that the Kochi reagent-catalyzed [8] low-temperature condensation of the latter leads to the desired hydrocarbon (II) in a good yield, which contains, according to its PMR spectrum data, an admixture of the regioisomer (VI) and 1,3-diene (VII), the overall amount of which does not exceed 5% on using tosylate (VIII). Thus, as in the series of ubiquinones [4], the combination of the secondary O-sulfonates with prenylmagnesium chloride using the Wurtz reaction serves as a convenient method of lengthening the regular isoprenoid chain by one E-C_5 unit.

EXPERIMENTAL

The R_f values are given for a stationary SiO_2 layer (Silufol) in a hexane—ether (1:1) mixture.* The IR spectra of the solutions in $CHCl_3$ were recorded on a Specord M-80 spectrophotometer. The PMR spectra were measured in $CDCl_3$ solutions relative to TMS on Bruker WP-200 and Bruker WM-250 spectrometers. Prenyl chloride was purified by passing through an Al_2O_3 layer (neutral), followed by distillation in vacuo, bp 53°C (95 mm). The solution of Li_2CuCl_4 in THF was prepared according to [8].

3-Hydroxyisosqualene (III). A solution of 7.45 g (17.45 mmoles) of 2,3-epoxysqualene [2] and 3.62 g (18 mmoles) of $(i\text{-}PrO)_3Al$ [3] in 40 ml of toluene was boiled (Ar) for 8 h. The reaction mixture was diluted with ether, neutralized with 1 N HCl, washed with water, dried over $MgSO_4$, and the residue (8.4 g) after the evaporation of solvents under vacuum was chromatographed on 100 g of SiO_2. Gradient elution from hexane to ether (up to 10% of the latter) gave 7.3 g (98%) of (III) in the form of a colorless oil, R_f 0.45, the PMR spectrum of which was identical to that described in [3].

Acetate (IV) — colorless oil, R_f 0.55. IR spectrum (ν, cm^{-1}): 440, 610, 900, 930, 1020, 1200, 1250, 1340, 1370, 1400, 1450, 1540, 1650, 1680, 1730, 2340, 2360, 2850, 2870, 2920. PMR spectrum (δ, ppm): 1.61 br. s (15H, CH_3), 1.69 br. s (3H, trans-CH_3), 1.79 br. s (3H, CH_3—C^2), 1.9-2.2 m (20H, CH_2), 2.06 s (3H, CH_3CO), 4.72 br. t (1H, J = 7 Hz, HC^3), 4.89 m (J = 1.2 Hz), and 4.94 m (2H, $H_2C{=}C$); 5.0-5.2 m (5H, HC=C). Found: C 81.75; H 11.75%. M^+ 469. $C_{32}H_{52}O_2$. Calculated: C 81.99; H 11.18%, mol. wt. 469.

Benzoate (V) — colorless oil, R_f 0.75. IR spectrum (ν, cm^{-1}): 370, 540, 680, 690, 700, 710, 930, 950, 960, 980, 1010, 1030, 1080, 1160, 1200, 1350, 1410, 1490, 1530, 1590, 1600, 1620, 1680, 2360, 2870, 2920. PMR spectrum (δ, ppm, J, Hz): 1.61 br. s (12H, CH_3) 1.63 br. s (3H, CH_3—C^6), 1.69 d (3H, J = 1, trans-CH_3), 1.81 d. d (3H, J = 1.5 and 0.8, CH_3—C^2), 1.9-2.2 m (20H, CH_2) 4.94 br. q (1H, J = 1.5, trans-HC^1), 5.05 m (1H, cis-HC^1), 5.0-5.2 m (5H, HC=C and HCO), 5.37 t (1H, J = 6.7, HC^7), 7.4-8.0 m (5H, C_6H_5). Found: C 83.80; H 10.35%. M^+ 531. $C_{37}H_{54}O_2$. Calculated: C 83.72; H 10.25%, mol. wt. 531.

2,6,10,14,19,23,27-Heptamethyl-2,6E,10E,14E,18E,22E,26-octacosaheptaene (II), 5-isopropenyl-2,8,12,17,21,25-hexamethyl-2,8E,12E,16E,20E,24-hexacosahexaene (VI) and 2,6,10,15,19,23-hexamethyl-1,3E,6E,10E,14E,18E,22-tetracosaheptaene (VII). A solution of 0.21 g (0.5 mmole) of (III) and 0.12 g (1 mmole) of $SOCl_2$ in 5 ml of hexane was allowed to stand (Ar) for 4 h at ∿25°C, was then diluted with ether, washed with water, neutralized with $NaHCO_3$, dried over $MgSO_4$, and the residue (0.24 g), after the evaporation of solvents under vacuum, was chromatographed on 10 g of SiO_2. Gradient elution from hexane to ether (up to 5% of the latter) gave 0.16 g (77%) of a mixture of chlorides in the form of a colorless oil, R_f 0.80 (pentane).

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*Unless otherwise noted.

A 10 mg portion (0.5 mmole) of CuI was added to a stirred (—30°C, Ar) Grignard reagent, prepared from 0.26 g (2.5 mmoles) of prenyl chloride and 70 mg (3 mg·atom) of Mg in 4 ml of THF (Ar). The reaction mixture was held for 10 min at —30°C, and then was treated at —60°C, over a period of 3 min with a solution of 0.22 g (0.5 mmole) of the above-obtained mixture of chlorides in 2 ml of THF. The reaction mixture was allowed to stand at —60°C for 10 min and was heated in the course of 30 min to —20°C, deocmposed with NH_4Cl, diluted with ether, neutralized with 1N HCl, washed with water, dried over $MgSO_4$, and the residue (0.31 g) after the evaporation of solvents under vacuum was chromatographed on 10 g of SiO_2. Gradient elution from hexane to ether (up to 5% of the latter) gave 0.2 g (83%) of a mixture of (II):(VI):(VII) ≈ 10:6:1 (PMR data) in the form of a colorless oil with R_f 0.80 (pentane).

PMR spectrum of (II) (δ, ppm): 1.60 br. s (21H, CH_3), 1.69 br. s (6H, trans-CH_3), 2.0-2.2 m (24H, CH_2), 5.0-5.2 m (7H, HC=C). PMR spectrum of (VI) (δ, ppm): 1.60 br. s (18H, CH_3), 1.4-1.7 m (2H, H_2C^6), 1.70 br. s (6H, trans-CH_3), 1.73 br. s (3H, $CH_3C{=}CH_2$), 1.9-2.2 m (21H, CH_2, HC^5), 4.65 and 4.69 br. s (2H, $H_2C{=}C$), 5.0-5.2 m (6H, HC=C). PMR spectrum of (VII) (δ, ppm, J, Hz): 1.62 br. s (12H, CH_3), 1.70 br. s (3H, trans-CH_3), 1.72 br. s (3H, $CH_3{-}C^6$), 1.86 br. s (3H, $CH_3{-}C^2$), 1.9-2.1 m (16H, CH_2), 2.77 br. d (2H, J = 6.7, H_2C^5), 4.90 br. s (2H, $H_2C{=}C$), 5.1-5.3 m (5H, HC=C), 5.64 br. d. t (1H, J = 15.2 and 6.7, HC^4), 6.16 br. d (1H, J = 15.2, HC^3).

In a similar way, from 0.12 g (0.25 mmole) of the above mixture of chlorides, 0.13 g (1.25 mmoles) of prenyl chloride, 36 mg (1.5 mg·atom) of Mg and 25 mg (0.25 mmole) of CuCl in 3 ml of THF, 90 mg (70%) of a mixture of (II):(VI):(VII) ≈ 3:4:2 was obtained (PMR data).

A Grignard reagent, prepared from 0.26 g (2.5 mmoles) of prenyl chloride and 70 mg (3 mg·atom) of Mg in 2 ml of THF, was added to a stirred (—10°C, Ar) solution of 0.47 g (1 mmole) of acetate (IV) and 0.1 g (0.1 mmole) of $Pd(PPh_3)_4$ in 3 ml of THF. The reaction mixture was heated over a period of 10 min to ∿25°C, held at this temperature for 30 min, was then decomposed with NH_4Cl, diluted with ether, washed with water, dried over $MgSO_4$, and the residue (0.39 g), after the evaporation of solvents under vacuum, was chromatographed on 10 g of SiO_2. Gradient elution from hexane to ether (up to 20% of the latter) gave 0.2 g (42%) of alcohol (III) and 0.17 g (35%) of a mixture of (II):(VI):(VII) ≈ 1:1:1 (PMR data).

A 0.95 M solution of n-BuLi in hexane was added to a stirred (—70°C, Ar) solution of 0.25 g (0.58 mmole) of (III) and 10 mg of Ph_3CH in 3 ml of THF and 0.1 ml of HMPA up to the appearance of a pink color (∿0.7 ml, 0.67 mmole), and then 106 mg (0.6 mmole) of $PhSO_2Cl$ was added. The reaction mixture was allowed to stand for 45 min at —40°C and then was successively treated at —70°C with 1 ml of a 0.1 M solution of Li_2CuCl_4 in THF (0.1 mmole) and a Grignard reagent, freshly prepared from 0.26 g (2.5 mmoles) of prenyl chloride and 70 mg (3 mg·atom) of Mg in 2 ml of THF. The reaction mixture was heated over the period of 30 min at 0°C, was then diluted with ether, neutralized with 1 N HCl, washed with water, dried over $MgSO_4$, and the residue (0.4 g) after the evaporation of solvents under vacuum was chromatographed on 10 g of SiO_2. Gradient elution from hexane to ether (up to 20% of the latter) gave 70 mg of (III) (a 72% conversion) and 0.2 g (99%) of a mixture of (II):(VI):(VII) ≈ 8:1:1 (PMR data) in the form of a colorless oil with R_f 0.80 (pentane).

In a similar way, the reaction of 0.21 g (0.5 mmole) of (III), 0.11 g (0.6 mmole) of TsCl in 3 ml of THF and 0.3 ml of HMPA, a Grignard reagent prepared from 0.26 g (2.5 mmoles) of prenyl chloride and 70 mg (3 mg·atom) of Mg in 2 ml of THF, and 0.5 ml of a 0.1 M solution of Li_2CuCl_2 in THF (0.05 mmole) gave 0.13 of (III) (a 38% conversion) and 60 mg (67%) of heptaene (II) containing ∿5% of an admixture of the regioisomer (VI) (PMR data). IR spectrum of (VI) (ν, cm^{-1}): 740, 830, 890, 980, 1030, 1110, 1150, 1330, 1380, 1450, 1660, 2860, 2920, 2960. Found: C 87.54; H 11.99%. M^+ 479. $C_{35}H_{58}$. Calculated: C 87.80; H 12.20%, mol. wt. 479.

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SYNTHESIS OF TRIDECAPRENOL WT$_3$C$_7$SCOH AND TETRAKISNOROCTAHYDRO ANALOGS OF PENTA- AND HEXAPRENOL

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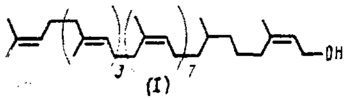
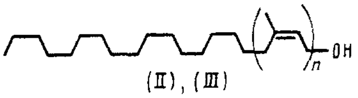
Tridecaprenol WT$_3$C$_7$SCOH and two modified prenols, having a saturated hydrocarbon residue bound to one or two isoprenoid units, were synthesized by a stepwise scheme using a C$_5$-saturated and cis-C$_5$-blocks.

The development of a stepwise scheme of a stereospecific synthesis of polyprenols enabled preparation of also their modified representatives [1]. The two series of compounds were found to be materials for studying the mechanism of the biosynthesis of carbon-containing biopolymers of cellular wall membranes of certain organisms [2, 3]. In continuation of this investigation, we discuss in the present article a stepwise synthesis of the modified prenols (I)-(III) indicated in the title. The first of these is distinguished from natural prenols by the presence of a (±)-S-unit inside the 1,5-polyene chain, while the cetyl residue of the other two were used to simulate a completely demethylated and reduced block of four WT/C units



(I)

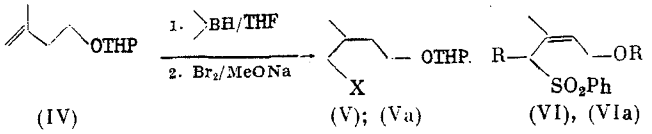


(II), (III)

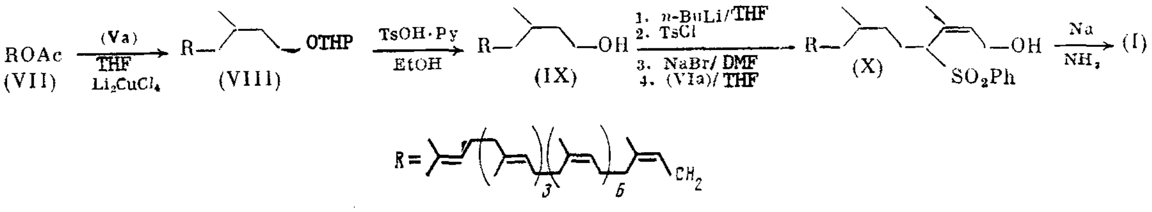
$= 1$ (II); 2 (III).

The tetrahydropyranyl (THP) ether (IV) of isobutenylcarbinol served as a precursor of a saturated C$_5$-syntone required for constructing the molecule of (I). Hydrobromination—bromination [4] of olefin (IV) led in 53% yield to bromide (V), recently obtained in a four-stage reaction from the same ether [5]. The known Z-hydroxy-sulfone (VI) [6] was used as another building block in the above-designated sequence of transformations, leading to compounds (I)-(III).

The Li$_2$CuCl$_4$-catalyzed condensation of the available [7] undecaprenol WT$_3$C$_7$OH in the form of its acetate (VII) with the Grignard reagent (Va), prepared from bromide (V), followed by TsOH·Py-catalyzed removal of the THP protective function in the intermediate (VIII), readily results in (cf. [8]) the dolichol-like prenol, WT$_3$C$_7$SOH (IX).



$X = Br$ (V), MgBr (Va); $R = H$ (VI), Li (VIa).



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