NEW SYNTHESIS OF PERILLENE AND SOME OTHER FURANOTERPENES BY CYCLOPROPYLCARBINYL REARRANGEMENT

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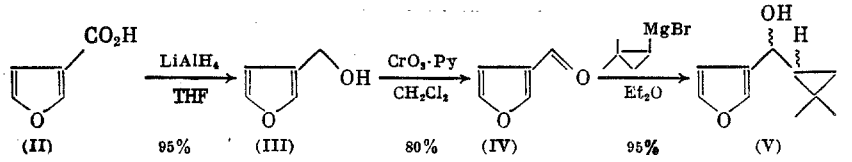
A whole series of furanoterpenes containing a prenyl substituent at C^3 have been found in natural sources [1]. At the present time there have been a considerable number of papers devoted to the production of such compounds, among which great attention has been paid to the synthesis of perillene (I) [2-5], which is the alarm pheromone of individual species of ants [6]; this substance is also found in certain plant sources [7].

In the present work we present the synthesis of (I) and also of certain unnatural furanoterpenes by means of the cyclopropylcarbinyl homoallylic rearrangement [8]. The starting compound was 3-formylfuran (IV), which was obtained by Collins oxidation of 3-hydroxymethylfuran (III) [9], and this is in turn formed with a good yield by the hydride reduction of the readily obtainable furan-3-carboxylic acid (II).

The reaction of the aldehyde (III) with 2,2-dimethylcyclopropylmagnesium bromide gives the furylcyclopropylcarbinol (V) quantitatively, and the product represents a mixtue ~1:1 of diastereomers, which are separated by flash chromatography on aluminum oxide. Here the less polar isomer, which also has a shorter retention time in GLC on a column with Carbowax 20M, can be assigned the threo configuration, and the second isomer can be assigned the erythro configuration (cf. [10, 11]). The differences between the diastereomers of the cyclopropylcarbinol (V) show up most clearly in the PMR spectra. Thus, the chemical shifts of the two singlets of the geminal CH_3 groups in the less polar threo isomer differ by 0.13 ppm, whereas these signals for the erythro isomer form a single six-proton singlet, which is moreover shifted upfield (cf. [11]).



Each of the diastereomers (V) or their mixture quickly isomerizes in the presence of a catalytic amount of 30% perchloric acid with the formation of the tertiary homoallylic alcohol (VI) and dehydroperillene (VII) in a ratio of ~3:2. Both these previously unknown furanoterpenes contain a trans disubstituted double bond in the side chain, and this follows reliably from the spin–spin coupling constant of the vicinal olefinic protons at this bond (J = 16 Hz) and also the characteristic absorption in the IR spectra at ~970 cm^{-1}.

The hydrogenation of the alcohol (VI) at a palladium catalyst leads to the previously described [12] carbinol (VIII), the characteristics of which (IR and PMR spectra) agreed with published data.

Thus, the carbinol (VIII) is obtained from the aldehyde (IV) in three stages, and its dehydration can lead to the required furanoterpene (I). However, it was this stage which proved deciding in the planned sequence of transformations. Thus, when (VIII) was boiled in benzene in the presence of catalytic amounts of p-toluenesulfonic acid, a mixture consisting of the desired perillene (I), its previously described [4] α isomer (IX), and the product from their electrophilic cyclization, i.e., the benzofuran derivative (X), slowly accumulated. After the addition of a further quantity of the acid the reaction soon terminated and was shifted completely toward the formation of the bicyclic product (X), which is a struc-

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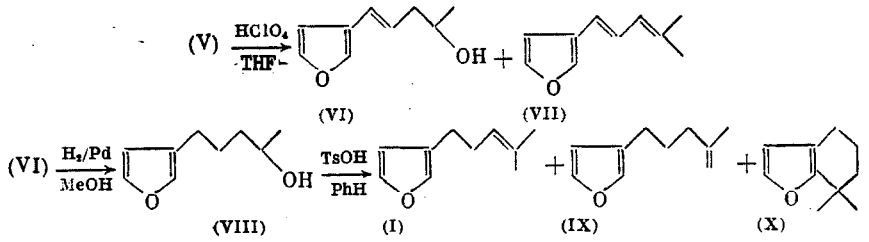
tural isomer of the menthofuran frequently encountered in nature. If the dehydration was conducted with constant distillation of the water–benzene azeotropic mixture, the initial (VIII) disappeared almost completely after ~5 h, and a mixture of (I), (IX), and (X) in ratios of (~7:1:2) was formed with a yield of ~70%. The content of the benzofuran derivative (X) in the mixture follows from the ratio of the integral intensities of the signals for the β-furan protons in the PMR spectrum [δ 5.99 ppm for (X) and 6.16 ppm for (I) and (IX)]; the ratio of the β- and α-perillenes (I) and (IX) was determined similarly by comparison of the integral intensities of the signals for the exomethylene protons of (IX) (δ 4.68 ppm) and the vinyl proton in the side chain of (I) (δ 5.12 ppm). The obtained ratios of (I), (IX), and (X) were confirmed by GLC data and chromato-mass spectrometry; the retention times of the structural isomers increase in the transition from (X) to (I).



The spectral characteristics (PMR and mass spectra) of the obtained perillene (I) [3] and its α isomer (IX) [4] are identical with the previously described values for these compounds.

Thus, the cyclopropylcarbinylhomoallylic rearrangement opens up a simple path to the synthesis of natural perillene and a series of other furanoterpenes from readily available starting compounds.

EXPERIMENTAL

The IR spectra were obtained in carbon tetrachloride solutions on a UR-20 instrument. The UV spectra of the alcohol solutions were obtained on a "Specord UV-VIS" spectrophotometer. The PMR spectra were measured with reference to TMS in carbon tetrachloride solution on Varian DA-60-IL or Tesla BS-497 spectrometers at 100 MHz. The mass spectra were obtained at 70 eV on a Varian MATCH-6 spectrometer or an LKB-2091 chromato-mass spectrometer (capillary column, 25 m × 0.25 mm, with SE-30). The GLC was conducted on an LKhM-8MD instrument (2 m × 3 mm column with 15% of Carbowax 20M on Chromaton N-AW-HMDS or a 50-m capillary column with OV-1).

3-Hydroxymethylfuran (III). To a stirred solution of 3 g (26.8 mmoles) of the acid (II) in 90 ml of ether at 10°C we added 1.48 g (39 mmoles) of lithium aluminum hydride in portions over 30 min. The reaction mass was stirred at 25°C for 1 h, treated with an excess of a mixture of $Na_2SO_4 \cdot 10H_2O$ and celite by the method in [13], and filtered. The filtrate was washed with a 2 M aqueous solution of sodium hydroxide and with water and dried with magnesium sulfate. After evaporation of the solvent the residue was distilled (~3 g). We obtained 2.5 g (95%) of the alcohol (III) [9]; bp 75°C (12 mm Hg), n_D^{20} 1.4850. IR spectrum (ν, cm^{-1}): 610, 880, 975, 1030, 1160, 1390, 1500, 3620. PMR spectrum (δ, ppm): 4.32 s (2H, CH_2O), 6.30 br.s (1H, HC^4), 7.26 br.s (2H, HC^2, HC^5).

3-Formylfuran (IV). From 1.95 g (20 mmoles) of the alcohol (III), 18.5 g (185 mmoles) of chromic anhydride, and 30 ml of pyridine in 400 ml of methylene chloride, according to the method described in [9], we obtained 1.53 g (80%) of the aldehyde (IV) [13]; bp 59°C (22 mm Hg), n_D^{20} 1.4932. IR spectrum (ν, cm^{-1}): 870, 1010, 1085, 1160, 1280, 1380, 1410, 1510, 1570, 1600, 1680, 1715, 3130, 3370. UV spectrum (λ_{max}, nm): 254 (ε 3955). PMR spectrum (δ, ppm): 6.74, 7.45 and 8.07 br.s (3H, HC^2, HC^4, HC^5), 9.92 s (1H, CHO).

(3-Furyl)-(2,2-dimethylcyclopropyl)methanol (V). To the Grignard reagent obtained from 5.5 g (37 mmoles) of 2,2-dimethylcyclopropyl bromide [14] and 0.94 g (39 mg·atom) of magnesium in 45 ml of ether over 10 min at −5°C we added with stirring a solution of 0.96 g (10 mmoles) of the aldehyde (IV) in 5 ml of ether. The reaction mass was stirred for 30 min, after which it was decomposed at 0°C with an excess of a saturated solution of ammonium chloride. The usual treatment of the ether layer gave 2.1 g of the product, which was chromatographed on 50 g of neutral aluminum oxide of II activity. By gradient elution from hexane

to ether (to 40% of the latter) we obtained (in order of elution) 0.90 g (54%) of threo-(V) and 0.75 g (45%) of erythro-(V).

Threo-(V), bp 63°C (1 mm Hg), n_D^{20} 1.4847. IR spectrum (ν, cm^{-1}): 880, 955, 1030, 1165, 1380, 1455, 1500, 3060, 3610. PMR spectrum (δ, ppm): 0.39-1.11 m (3H, cyclopropane H), 1.09 and 1.22 s (6H, CH_3), 4.09 br.d (1H, CHOH, J = 10 Hz), 6.35 and 7.29 br.s (3H, furan H). Mass spectrum, m/z (intensity, %): 166 (M^+, 3), 151(3), 148(8), 133(9), 110(76), 108(22), 105(16), 97(62), 95(38), 81(57), 69(49), 67(22), 59(54), 43(43), 41(100), Found %: C 72.09; H 8.55. $C_{10}H_{14}O_2$. Calculated %: C 72.26; H 8.49.

Erythro-(V), bp 65°C(1 mm Hg),, n_D^{20} 1.4856. IR spectrum (ν, cm^{-1}): 875, 965, 1030, 1165, 1220, 1380, 1455, 1500, 3060, 3610. PMR spectrum (δ, ppm): 0.42-1.14 m (3H, cyclopropane H), 1.06 br.s (6H, CH_3), 4.03 br.s (1H, CHOH, J = 10 Hz), 6.33 and 7.28 br.s (3H, furan H). Mass spectrum, m/z (intensity, %): 166 (M^+, 3), 148(9), 133(10), 123(13), 119(12), 110(58), 108(23), 105(19), 97(53), 95(35), 91(21), 81(56), 79(33), 77(28), 69(33), 59(65), 43(37), 41(100). Found %: C 72.16; H 8.52. $C_{10}H_{14}O_2$. Calculated %: C 72.26; H 8.49.

3-(4-Hydroxy-4-methyl-1E-pentenyl)furan(VI) and 3-(4-Methyl-1E,3-pentadienyl)furan (VII). A solution of 0.9 g of the mixture of alcohols (V) in 40 ml of THF containing 0.8 ml of 30% perchloric acid, was left at ~25°C until the initial (V) had disappeared (~2 h, TLC and GLC). It was then diluted with ether, washed with saturated solutions of sodium bicarbonate and sodium chloride, and dried with magnesium sulfate. The residue (~0.9 g) after concentration was chromatographed on 40 g of silica gel. By gradient elution from hexane to ether (to 40% of the latter) we obtained 0.55 g (61%) of (VI) and 0.31 g (39%) of (VII).

Compound (VI), bp 73°C (1 mm Hg), n_D^{22} 1.5081. IR spectrum (ν, cm^{-1}): 875, 910, 970, 1030, 1080, 1140, 1165, 1220, 1270, 1350, 1370, 1385, 1470, 1515, 1675, 1720, 3585, 3615. UV spectrum (λ_{max}, nm): 208 (ε 23318), 232 (ε 21611). PMR spectrum (δ, ppm, J, Hz): 1.22 s (6H, CH_3), 2.24 d (2H, CH_2, J = 7), 5.91 d.t (1H, $C\equiv C\underline{H}CH_2$, J = 16 and 7), 6.62 br.d (1H, $C\underline{H}=CCH_2$, J = 16), 6.44 br.s (1H, HC^4), 7.28 br.s (2H, HC^2, HC^5). Mass spectrum, m/z (intensity, %): 166 (M^+, 4), 151(4), 148(2), 108(53), 79(33), 77(18), 59(100), 43(41), 41(13). Found %: C 72.09; H 8.59. $C_{10}H_{14}O_2$. Calculated, %: C 72.26; H 8.49.

Compound (VII), bp 55°C (2 mm Hg), n_D^{20} 1.5559. IR spectrum (ν, cm^{-1}): 875, 955, 975, 1030, 1075, 1170, 1380, 1445, 1510, 1635, 1690, 1725. UV spectrum (λ_{max}, nm): 275 (ε 18377). PMR spectrum (δ, ppm, J, Hz): 1.79 br.s (6H, CH_3), 5.82 br.d (1H, $C\underline{H}=CMe_2$, J = 11), 6.15 br.s (1H, $C\underline{H}=CC=CMe_2$, J = 16), 6.45 br.s (1H, HC^4), 6.56 d.d (1H, $C\underline{H}C=CMe_2$, J = 16 and 11), 7.26 br.s (2H, HC^2, HC^5). Mass spectrum, m/z (intensity, %): 148 (M^+, 15), 133 (10), 119(11), 108(47), 105(16), 91(13), 79(37), 77(27), 71(16), 59(100), 43(44), 41(22). Found %: C 80.88; H 8.23. $C_{10}H_{12}O$. Calculated %: C 81.04; H 8.16.

3-(4-Hydroxy-4-methylpentyl)furan (VIII). Into a mixture of 0.4 g (2.4 mmoles) of the alcohol (VI) and 0.1 g of 1% $Pd/CaCO_3$ in 6 ml of methanol, while shaking, we passed hydrogen until the initial (VI) had disappeared and the absorption of hydrogen had stopped (~6 min, GLC). The mixture was filtered, the filtrate was evaporated, the residue was diluted with hexane, and the obtained solution was purified by chromatography on 20 g of silica gel with a 3:1 mixture of hexane and ether as eluant. We isolated 0.35 g (87%) of the alcohol (VIII) [12], bp 71°C (1 mm Hg), n_D^{25} 1.4712. IR spectrum (ν, cm^{-1}): 880, 915, 945, 1030, 1070, 1120, 1165, 1205, 1370, 1470, 1505, 1570, 3620. PMR spectrum (δ, ppm): 1.14 s (6H, CH_3), 1.46 m (4H, CH_2), 2.38 br.t (2H, $CH_2C=C$, J = 7 Hz), 6.16 br.s (1H, HC^4), 7.13 and 7.25 br.s (2H, HC^2, HC^5).

Dehydration of (VIII). 3-(4-Methyl-3-pentenyl)furan (I), 3-(4-Methyl-4-pentenyl)furan (IX), and 7,7-Dimethyl-4,5,6,7-tetrahydrobenzo[b]furan (X). a. A solution of 0.15 g (0.9 mmole of the alcohol (VIII) in 15 ml of benzene containing 15 mg of $TsOH\cdot H_2O$ was boiled under a reflux condenser for ~1 h, after which a further 20 mg of $TsOH\cdot H_2O$ was added to the reaction mixture and the boiling was continued for 30 min. The reaction mixture was cooled to ~20°C, neutralized with sodium bicarbonate solution, and dried with magnesium sulfate. The benzene was removed by azeotropic distillation with methanol, and the latter was removed by azeotropic distillation with pentane. The residue (~0.1 g) was purified by chromatography on 10 g of silica gel with pentane as eluant. We obtained 70 mg (52%) of (X). IR spectrum (ν, cm^{-1}): 700, 865, 895, 1040, 1080, 1110, 1160, 1250, 1290, 1360, 1455, 1505, 1625. PMR spectrum (δ, ppm, J, Hz): 1.21 s (6H, CH_3), 1.65 m (4H, H_2C^5, H_2C^6), 2.36 t (2H, H_2C^4, J = 6), 5.99 d (1H, HC^3, J = 1.5), 7.09 d (1H, HC^2, J = 1.5). Mass spectrum, m/z (intensity, %): 150 (M^+, 18), 136(18), 135(100), 122(5), 105(5), 91(10), 79(7), 77(10), 55(6), 51(6), 41(5).

b. A solution of 0.15 g (0.9 mmole) of the alcohol (VIII) in 25 ml of benzene, containing 10 mg of $TsOH \cdot H_2O$, was boiled with constant sampling of the distilling mixture and with the addition of fresh portions of benzene at the same rate until the initial (VIII) had disappeared (~5 h, GLC and TLC). After the usual treatment we obtained 90 mg (67%) of the product, which consisted (GLC, PMR) of 66% of perillene (I) [3], 12% of (IX) [14], and 22% of (X). PMR spectrum of (I) (δ, ppm): 1.58 and 1.68 br.s (6H, CH_3), 2.30 m (4H, CH_2), 5.12 br.t (1H, $C\underline{H}=CMe_2$, J = 6 Hz), 6.16 br.s (1H, HC^4), 7.11 and 7.23 br.s (2H, HC^2, HC^5). Mass spectrum, m/z (intensity, %): 150 (M^+, 50), 135(6), 94(15), 82(27), 81(70), 69(100), 53(16), 41(58).

PMR spectrum of (IX) (δ, ppm): 1.68 br.s (3H, CH_3), 1.9-2.4 m (6H, CH_2), 4.68 br.s (2H, $C=CH_2$), 6.16 br.s (1H, HC^4), 7.11 and 7.23 br.s (2H, HC^2, HC^5). Mass spectrum, m/z (intensity, %): 150 (M^+, 28), 135(3), 95(15), 94(100), 82(61), 81(40), 53(13), 41(23).

CONCLUSIONS

A simple synthesis of some furanomonoterpenes, including natural perillene, was realized on the basis of the cyclopropylcarbinyl homoallylic rearrangement.

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