OXIDATIVE TRANSFORMATIONS OF POLYPRENOLS

E. V. Salimova,[1] O. S. Kukovinets,[1] V. G. Kasradze,[1] F. Z. Galin,[1] A. V. Kuchin,[2] and A. A. Koroleva[2]

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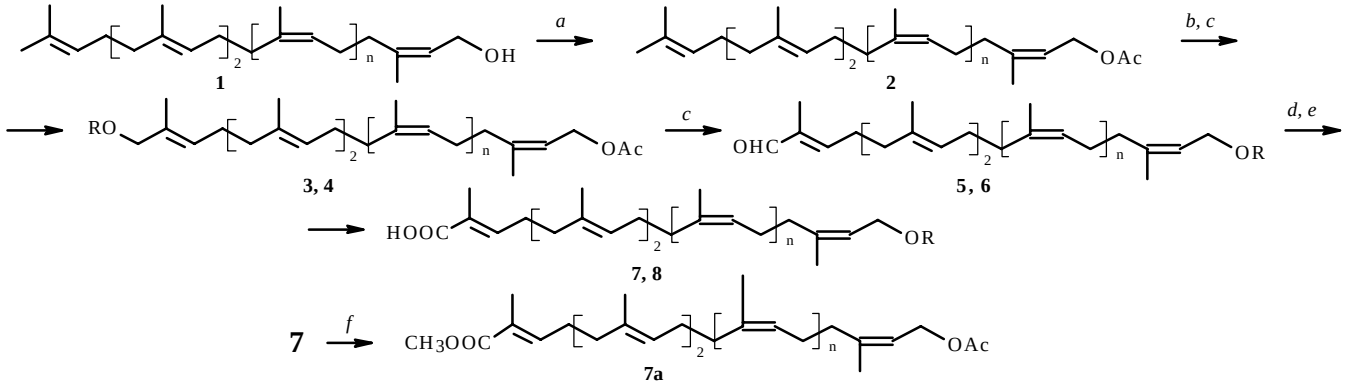
Oxidative transformations involving the hydroxyls and ω-methyls of polyprenols isolated from birch greenery (7-9 isoprene units in the chain) were used to produce α,ω-diols, diesters, aldehydoalcohols, and hydroxyacids. The products are of interest as potential anti-inflammatory, antiulcer, hepatoprotective, and cardio-active preparations.

Key words: polyprenols, birch greenery, oxidative transformations.

Polyprenols are readily available compounds that accumulate in large quantities during certain vegetative periods in the greenery of coniferous and broad-leaf trees. As a result, their physiological activity is well studied. In particular, it was shown that polyprenols isolated from greenery of broad-leaf trees (birch, alder, aspen) exhibit antiulcer activity [1], facilitate the dissolution of gall-bladder stones, lower the cholesterol content in vascular walls, and activate the immune system [2-4]. Furthermore, α,ω-oxidized polyprenols possess a variety of biological activities [5]. The pharmacological activity has been determined for pure compounds. It would be interesting to use transformation products of total polyprenols because preparing and isolating pure stereo- and regioisomers is a complicated task. Therefore, we used oxidative transformations of C_{35}-C_{45} polyprenols isolated from birch greenery to produce ω-hydroxy-, formyl-, and carboxypolyprenols and their derivatives for further study of the biological activity.

We previously established using geraniol and farnesol as examples [6] that the terminal methyl in isoprenoids was readily oxidized to an allyl alcohol by perselenic acid in CH_2Cl_2 (-5 to 0°C). The *trans*-methyl was stereospecifically oxidized. The hydroxyl in the molecule must be transformed to an acetate in order to synthesize α,ω-dihydroxy derivatives of polyprenols. Otherwise more complicated and unforeseen transformations in the polyprenols would occur. The prenylacetates were converted in good yield by *t*-BuOOH/SeO_2 in CH_2Cl_2 into α-acetoxy-ω-hydroxy derivatives (**3**).



n = 3 - 5

R = Ac (**4**, **5**, **7**); OH (**3**, **6**, **8**)

a. Ac_2O/Py; *b*. *t*-BuOOH/SeO_2-CH_2Cl_2; *c*. MnO_2; *d*. $AgNO_3$/NaOH; *e*. H_2O/HCl; *f*. CH_2N_2/Et_2O

1) Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, 450054, Ufa 54, pr. Oktyabrya, 71, fax (3472) 35 60 66; 2) Institute of Chemisry, Komi Scientific Center, Urals Division, Russian Academy of Sciences, 167982, Syktyvkar, Komi Republic, ul. Perevomaiskaya, 48. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 238-241, May-June, 2003. Original article submitted June 23, 2003.

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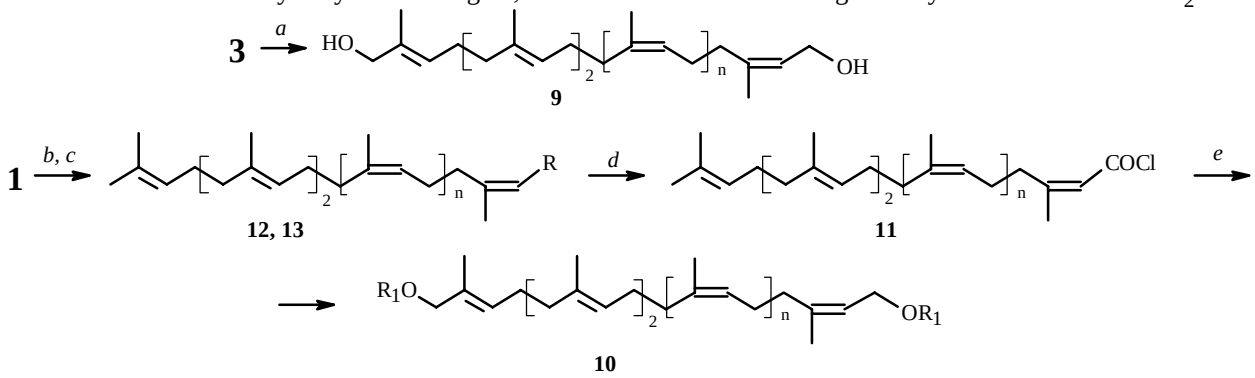
The appearance in the IR spectrum of alcohol **3** of a broad band of medium strength at 3250-3550 cm^{-1} that was missing in the spectrum of the starting material indicated that the transformations occurred.

Furthermore, alcohol **3** was identified as the diacetate **4**. Oxidation of a mixture of allyl alcohols **3** by MnO_2 with subsequent further oxidation of the resulting formyl derivatives **5** produced acetoxyacids **7**, which were identified as their methyl esters **7a**.

The similar analogs **6** and **8** exhibited gastro-protective properties [7]. Homologs often exhibit not only similar chemical but also biological properties. Therefore, the aforementioned method is promising for synthesizing such medicinal preparations. The desired compounds **6** and **8** were isolated by chromatography after removing the acetate protection.

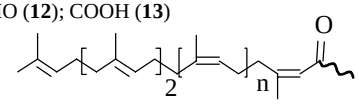
The acetates of prenols **2** can be transformed to acetoxyaldehydes **5** if the oxidation by *t*-BuOOH/SeO_2 is carried out in C_2H_5OH.

The α,ω-diols **9** were prepared by hydrolysis of acetoxyalcohols **3** and were used to synthesize diesters **10**, which are of interest as potential antiulcer and wound-healing compounds. The second component that is necessary for synthesizing diesters **10**, the mixture of acid chlorides **11**, was prepared from polyprenols **1** as usual, by oxidation with MnO_2, subsequent further oxidation of the aldehyde by Tolens reagent, and treatment of the resulting carboxylic acids **13** with $SOCl_2$.



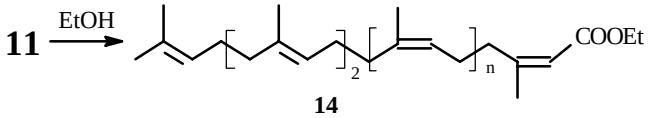
n = 3 - 5

R = CHO (**12**); COOH (**13**)

R_1 =  (**10**)

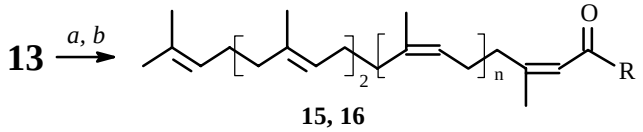
a. EtOH/H_3O^+; *b*. MnO_2; *c*. $AgNO_3/OH^-$; *d*. $SOCl_2$/Py; *e*. **9**

Prenylcarboxylic acids **13**, which are precursors to acid chlorides **11**, are independently valuable. Esters of these carboxylic acids have been recommended as blood-pressure stabilizers [8]. The ethyl esters **14** were prepared by treatment of **11** with ethanol.



n = 3 - 5

Acids **13** were also used as synthons for prenylacetic amides **15** and **16**, potential hepatoprotectors. These were prepared by reacting acids **13** with diisopropylamine or morpholine in the presence of $POCl_3$.



n = 3 - 5

R = *i* - Pr_2N (**15**), morpholine (**16**)

a. *i* - Pr_2NH, morpholine; *b*. $POCl_3$

EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument as thin layers or in nujol. PMR spectra were obtained on a Bruker spectrometer (300 MHz) at working frequency 75 MHz, $CDCl_3$ solvent, and TMS internal standard. TLC was performed on Silufol (Chemapol, Czech Rep.) plates using petroleum ether:ethylacetate (4:1) solvent. Compounds were developed by anisaldehyde:EtOH:H_2SO_4 (1:18:1) followed by heating at 100-120°C for 1-2 min.

Synthesis of Acetates 2. A mixture of polyprenols (**1**, 2.9 g) [1] was treated with Ac_2O (3.7 g) and absolute pyridine (3.9 mL). The reaction mixture was stirred for 24 h at room temperature; diluted with CH_2Cl_2 (70 mL); washed successviely with saturated NaCl, $NaHCO_3$, and NaCl solutions; and dried over $MgSO_4$. The solvent was removed. The solid was chromatographed (SiO_2, petroleum ether:ethylacetate, 4:1). Yield 3.01 g of acetate mixture **2**. IR spectrum (KBr, ν, cm^{-1}): 870 m, 980 m, 1655 m (C=C), 1745 s ($OCOCH_3$).

PMR spectrum (δ, ppm, J/Hz): 1.61, 1.70, 1.72 (all s, CH_3), 2.05 (m, CH_2), 2.10 (s, CH_3CO), 4.41 (d, J = 7.0, H-1), 5.14 (br.s, C=CH), 5.44 (t, J = 7.0, H-2).

***α*-Acetoxy-*ω*-hydroxy Derivatives 3.** A solution of SeO_2 (0.03 g) in absolute CH_2Cl_2 (1.5 mL) was treated with *t*-BuOOH (1.4 mL) in CH_2Cl_2 (4.89 mmol per mL, determined by iodometric titration), stirred for 0.5 h at room temperature, cooled to 0°C, and treated with the acetate mixture (**2**, 0.24 g) in CH_2Cl_2 (1.5 mL). Stirring was continued at 0° C for 3 h. The reaction mixture was diluted with diethylether, washed successively with KOH (10%) and saturated NaCl solutions, and dried over $MgSO_4$. The solvent was removed. The solid was chromatographed (SiO_2, petroleum ether:ethylacetate, 3:2). Yield 0.21 g of acetoxyalcohols **3**. IR spectrum (KBr, ν, cm^{-1}): 870 m, 980 m, 1660 m (C=C), 1750 s ($OCOCH_3$), 3250-3550 br.m (OH).

PMR spectrum (δ, ppm, J/Hz): 1.62, 1.68, 1.78 (all s, CH_3), 2.05 (m, CH_2), 2.10 (s, CH_3CO), 4.20 (s, OCH_2), 4.42 (d, J = 7.0, H-1), 5.13 (br.s, HC=C), 5.46 (t, J = 7.0, H-2).

***α*-Acetoxy-*ω*-formyl Derivatives 5.** The mixture of hydroxyacetates (**3**, 0.3 g) and freshly prepared MnO_2 (0.82 g) in dry CCl_4 (5 mL) was stirred at room temperature for 30 min and filtered. The filtrate was evaporated. The solid was purified by chromatography (SiO_2, petroleum ether:ethylacetate, 3:1). Yield 0.18 g of the mixture **5**. IR spectrum (KBr, ν, cm^{-1}): 865 w, 980 w, 1645 m (C=C), 1680 (CHO), 1740 ($OCOCH_3$).

PMR spectrum (δ, ppm, J/Hz): 1.62, 1.68, 1.98 (all s, CH_3), 2.06 (m, CH_2), 2.10 (s, CH_3CO), 4.42 (d, J = 7.0, H-1), 5.14 (br.s, C=CH), 5.22 (t, J = 7.5, H-*ω*-2), 5.42 (t, J = 7.0, H-2), 9.66 (s, CHO).

***α*-Acetoxy-*ω*-carboxylic Derivatives 7.** A solution of aldehydoacetate (**5**, 0.1 g) in absolute MeOH (0.5 mL) was added dropwise at room temperature to $AgNO_3$ (0.07 g) in H_2O (0.3 mL). The mixture was stirred for 5 min, treated dropwise with NaOH solution (5 mL, 1 N), stirred another 3 h at room temperature, left for 12 h, and filtered. The filtrate was acidified with HCl (10%) to pH 3. The product was extracted with diethylether, washed with saturated NaCl solution, dried over $MgSO_4$, and evaporated. The solid contained carboxyacetates **7** (0.09 g). The methyl ester **7a** was synthesized by treatment of **7** with diazomethane in ether.

For Acids 7. IR spectrum (KBr, ν, cm^1): 860 w, 975 m, 1640 m (C=C), 1680 s (COOH), 1745 s ($OCOCH_3$).

For Diesters 7a. IR spectrum (KBr, ν, cm^{-1}): 860 w, 980 m, 1640 m (C=C), 1715, 1745 (C=O).

PMR spectrum (δ, ppm, J/Hz): 1.62, 1.68, 1.78 (all s, CH_3), 2.06 (m, CH_2), 2.05 (s, CH_3CO), 3.80 (s, OCH_3), 4.42 (d, J = 7.0, H-1), 5.10 (br.s, C=CH), 5.20 (t, J = 7.5, H-*ω*-2), 5.45 (t, J = 7.0, H-2).

Hydrolysis of Acetates 3, 5, or 7. A solution of **3**, **5**, or **7** (0.2 g) in acetone (12 mL) was treated with HCl (4 mL, 5%) and stirred at room temperature until the starting compound disappeared (TLC monitoring). The acetone was distilled off. The solid was dissolved in CH_2Cl_2; washed successively with saturated NaCl, $NaHCO_3$, and NaCl (again) solutions; dried; and filtered. The solvent was evaporated. The solid yielded 0.12, 0.09, or 0.11 g of alcohols **9**, **6**, or **8**. IR spectrum (KBr, ν, cm^{-1}): 3200-3550 br.m (OH).

Mixture of Polyprenals 12. Total polyprenols (**1**, 1.0 g) and freshly prepared MnO_2 (2.82 g) in dry CCl_4 (5 mL) was stirred at room temperature for 30 min. The reaction mixture was filtered. The filtrate was evaporated. The solid was chromatographed (SiO_2, petroleum ether:ethylacetate, 3:1). Yield 0.94 g of mixture **12**. IR spectrum (KBr, ν, cm^{-1}): 860 w, 1640 m (C=C), 1680 s (CHO).

PMR spectrum (δ, ppm): 1.63, 1.70, 1.98 (all s, CH_3), 2.05 (m, CH_2), 5.14 (br.s, C=CH), 6.04 (s, H-2), 9.60 (s, CHO).

Polyprenylcarboxylic Acid Chlorides (11). Prenals **12** (0.95 g) and $AgNO_3$ (0.67 g) in H_2O (3 mL) and NaOH solution (4.5 mL, 1 N) were oxidized as described for compound **7**. Yield 0.63 g of acid **13**. IR spectrum (KBr, ν, cm^{-1}): 2400-3600 br.m (OH), 1690 s (C=O).

Acid **13** (0.6 g) in absolute benzene (2 mL) was added with stirring to freshly distilled $SOCl_2$ (0.3 g). The mixture was heated at 60-80°C until evolution of HCl ceased. Solvent and the excess of $SOCl_2$ were distilled off. Yield 0.6 g of acid chlorides mixture **11**, which were used without further purification to synthesize **10**.

Mixture of Diesters 10. A solution of diols **9** (0.15 g) in absolute benzene (10 mL) was treated dropwise at 0°C with acid chlorides **11** (0.34 g). Stirring was continued for another hour at 0°C. The temperature was slowly increased to 20°C and left there for 12 h. The solvent was removed. The solid was chromatographed (SiO_2, petroleum ether:ethylacetate, 4:1). Yield 0.28 g of diesters **10**. IR spectrum (KBr, ν, cm^{-1}): 870 w, 960 m, 1205 m, 1660 m (C=C), 1735 m ($COOCH_3$).

PMR spectrum (δ, ppm, J/Hz): 1.61, 1.68, 1.72 (all s, CH_3), 2.05 (m, CH_2), 4.43 (d, J = 7.5, H-1), 4.78 (s, H-ω), 5.10 (m, HC=C), 5.92 (t, J = 7.5, H-2), 6.94 (s, HC–CO).

Ethyl Esters of Polyprenylacetic Acids 14. A solution of acid chlorides **11** (0.15 g) in absolute benzene (20 mL) at 0°C was treated dropwise with stirring with EtOH (0.2 mL) and stirred at 0°C for 30 min. The temperature was slowly increased to room temperature. The mixture was left for 12 h. The solvent was removed. The solid was chromatographed (SiO_2, petroleum ether:ethylacetate, 17:3). Yield 0.17 g of a mixture of esters **14**. IR spectrum (KBr, ν, cm^{-1}): 870 w, 960 m, 1250 m, 1660 m (C=C), 1720 m (COOEt).

PMR spectrum (δ, ppm, J/Hz): 1.15 (t, J = 7.0, $\underline{CH_3}CH_2O$), 1.64, 1.72, 1.94 (all s, CH_3), 2.1 (m, CH_2), 4.28 (q, J = 7.0, OCH_2), 5.14 (br.s, C=CH), 5.87 (s, H-2).

Prenylcarboxylic Acid Amides 15, 16. A solution of **13** (0.15 g) in CH_2Cl_2 (2 mL) at 0°C was treated with Et_3N (0.05 mL) and *i*-Pr_2NH (0.05 mL) or morpholine (0.07 g). The reaction mixture at 0°C was treated dropwise with $POCl_3$ (0.03 mL) in CH_2Cl_2 (1 mL) and stirred for another 1 h at 0°C. The temperature was increased to 20°C. Stirring was continued for 1 h. Water (5 mL) was added. The product was extracted with diethylether. The organic layer was washed with $NaHCO_3$ solution (10%) and saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated. The solid was purified by chromatography (SiO_2, petroleum ether:ethylacetate, 4:1). Yield 0.15 g of diisopropylamides **15** or 0.11 g of morpholylamides **16**. IR spectrum (KBr, ν, cm^{-1}): 870 w, 960 m, 1660 m (C=C), 1580 m (COR).

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