Synthesis of polyprenylamines from plant polyprenols

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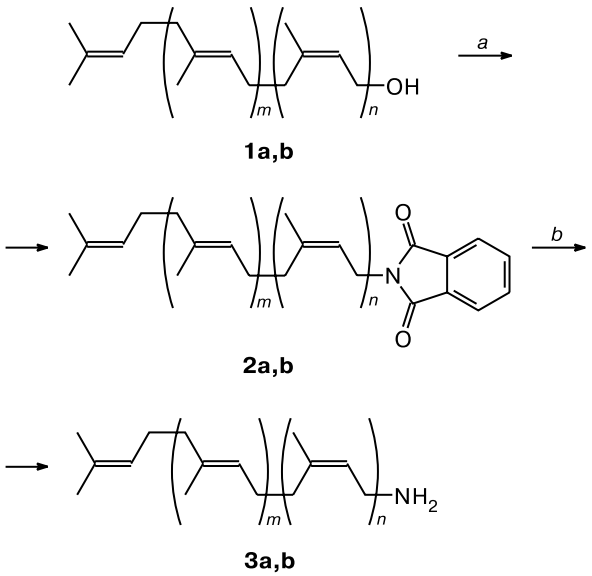
A simple method for the synthesis of polyprenylamines by a two-step transformation of plant polyprenol mixtures has been developed.

Key words: polyprenols, polyprenylamines, *N*-polyprenylphthalimides, Mitsunobu reaction.

Previously, it was reported that amino derivatives of linear isoprenoids possess immunomodulating, antiulcer, and antithrombotic activities (see Ref. 1 and references cited therein).

Here we report a simple method for the preparation of this type of compound based on readily available polyprenol mixtures from mulberry leaves (**1a**) and pine needles (**1b**). In view of the lability of the starting prenols and their derivatives, we used an approach developed by Mitsunobu and coworkers[2] for direct conversion of aliphatic alcohols into *N*-alkylphthalimides, whose hydrazinolysis smoothly yields alkylamines (Scheme 1). Previously,[3] this strategy has been employed successfully to prepare C_{15}-prenylamine from farnesol.

Scheme 1



m = 3, *n* = 7, 8 (**a**); *m* = 2, *n* = 11—14 (**b**)

Reagents and conditions: *a*. phthalimide/$(NCO_2Et)_2$/Ph_3P, THF, 20 °C; *b*. $N_2H_4 \cdot H_2O$, THF — MeOH, 50 °C.

The transformation of long-chain allylic alcohols **1a** and **1b** into *N*-prenylphthalimides **2a** and **2b** also proved to be rather efficient. Mixtures **2a** and **2b** obtained in ~70% yield after purification by chromatography were subsequently treated with $N_2H_4 \cdot H_2O$. This reaction proceeded most smoothly in MeOH—THF ensuring homogeneity of the reaction mixture. The yields of the target products **3a** and **3b** were 43 and 53%, respectively, which can be considered quite satisfactory in view of the product lability and high molecular weights.

The structures of compounds **2** and **3** obtained for the first time were proved by spectral and elemental analyses. In particular, their ^{1}H NMR spectra exhibit signals typical of this type of polyolefin.[4] The ^{1}H NMR spectra of phthalimides **2** and amino derivatives **3** contain a doublet for the CH_2N group (δ ~4.3 and δ ~3.2, respectively) and signals for the aromatic protons in the case of phthalimides. The IR spectra of amines **3** display typical NH absorption bands at 3440 and 3460 cm^{-1}.

Thus, we developed a facile route to polyprenylamines based on relatively accessible plant polyprenols. Study of the pharmacological properties of these compounds appears to be of interest.

Experimental

IR spectra were recorded for solutions in $CHCl_3$ on a Specord M-80 instrument. ^{1}H NMR spectra were measured for solutions in $CDCl_3$ using a Bruker AC-200 spectrometer. The ^{1}H and ^{13}C chemical shifts were referred to the solvent signals (δ_H 7.27, δ_C 77.0). TLC was performed on Silufol plates.

A sample of polyprenols **1a** with the ratio of the major homologs $C_{55}H_{90}O : C_{60}H_{98}O \approx 2 : 1$ (*cf.* Ref. 5) was kindly provided by L. L. Danilov (N. D. Zelinsky Institute of Organic Chemistry, RAS) and the sample of polyprenols **1b**, $C_{70}H_{114}O : C_{75}H_{122}O : C_{80}H_{130}O : C_{85}H_{138}O \approx 6 : 13 : 14 : 7$ (*cf.* Refs. 5, 6),

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by V. I. Roshchin (St.-Petersburg Forestry Engineering Academy).

Commercial phthalimide, triphenylphosphine, diethyl azodicarboxylate, and $N_2H_4 \cdot H_2O$ (Aldrich) were used. The solvents were purified by standard procedures.

Column chromatography was performed on SiO_2 (40/100) and Al_2O_3 (alkaline, 40/250) produced by Chemapol (Czechia).

Polyprenylphthalimides (2a). Diethyl azodicarboxylate (0.07 g, 0.40 mmol) was added with stirring at 20 °C (Ar) to a solution of polyprenols **1a** (0.27 g, ~0.34 mmol), phthalimide (0.06 g, 0.41 mmol), and Ph_3P (0.11 g, 0.42 mmol) in 2 mL of THF. The reaction mixture was kept for 2 h at 20 °C and concentrated to dryness *in vacuo*. The residue was triturated with ether and the insoluble material was filtered off. The filtrate was concentrated *in vacuo* and the residue (0.5 g) was chromatographed on 15 g of SiO_2 in ether—hexane (1 : 4, v/v) to give 0.22 g (~69%) of a mixture of homologs **2a** as a colorless oil with R_f 0.5 (ether—hexane, 1 : 4). IR, ν/cm^{-1}: 795, 805, 900, 1045, 1052, 1262, 1330, 1350, 1665, 1720, 2860, 2930, 3000. ^{1}H NMR, δ: 1.61 (br.s, *cis*-Me); 1.69 (br.s, *trans*-Me); 1.73 (br.s, MeC(3)); 1.93—2.17 (m, CH_2); 4.28 (br.d, HC(1), J = 8.0 Hz); 5.15 (m, HC=); 5.29 (br.t, HC(2), J = 8.0 Hz); 7.65—7.88 (m, HC arom.). Found (%): N, 1.81. $C_{63}H_{93}NO_2$, $C_{68}H_{101}NO_2$. Calculated (%): N, 1.56, 1.45, respectively.

Polyprenylphthalimides (2b). The reaction of polyprenols **1b** (0.76 g, ~0.71 mmol) with phthalimide (0.13 g, 0.88 mmol), Ph_3P (0.24 g, 0.92 mmol), and diethyl azodicarboxylate (0.14 g, 0.80 mmol) in 5 mL of THF was carried out as described above to give 0.58 g (~68%) of a mixture of homologs **2b** as a colorless oil with R_f 0.58 (ether—hexane, 1 : 4). IR, ν/cm^{-1}: 790, 805, 905, 1035, 1040, 1050, 1265, 1340, 1360, 1660, 1720, 2870, 2930, 3010. ^{1}H NMR, δ: 1.61 (br.s, *cis*-Me); 1.70 (br.s, *trans*-Me); 1.72 (br.s, MeC(3)); 1.95—2.20 (m, CH_2); 4.29 (br.d, HC(1), J = 7.7 Hz); 5.14 (m, HC=); 5.30 (br.t, HC(2), J = 7.7 Hz); 7.67—7.87 (m, HC arom.). Found (%): N, 1.40. $C_{78}H_{117}NO_2$, $C_{83}H_{125}NO_2$, $C_{88}H_{133}NO_2$, $C_{93}H_{141}NO_2$. Calculated (%): N, 1.27, 1.20, 1.13, 1.07, respectively.

Polyprenylamines (3a). A solution of phthalimides **2a** (0.44 g, ~0.47 mmol) and $N_2H_4 \cdot H_2O$ (0.24 g, 4.7 mmol) in a mixture of THF (3.5 mL) and MeOH (1.5 mL) was heated for 3 h at 50 °C (Ar) and diluted with ether. The solution was washed with a saturated solution of $NaHCO_3$ and water. The organic layer was dried with Na_2SO_4, the solvent was evaporated *in vacuo*, and the residue (0.6 g) was chromatographed on 30 g of Al_2O_3. Chloroform—methanol gradient elution (up to 5% of methanol) gave 0.16 g (~43 %) of a mixture of homologs **3a** as a colorless oil with R_f 0.65 ($CHCl_3$: MeOH : H_2O, 45 : 15 : 1, v/v). IR, ν/cm^{-1}: 840, 1000, 1250, 1310, 1380, 1450, 1580, 1665, 2715, 2860, 2920, 2960, 3020, 3380, 3440. ^{1}H NMR, δ: 1.60 (br.s, *cis*-Me); 1.71 (br.s, *trans*-Me); 1.73 (br.s, MeC(3)); 1.90—2.15 (m, CH_2); 3.26 (br.d, HC(1), J = 7.1 Hz); 5.13 (m, HC=); 5.28 (br.t, HC(2), J = 7.1 Hz). Found (%): N, 2.12. $C_{55}H_{91}N$, $C_{60}H_{99}N$. Calculated (%): N, 1.83, 1.68, respectively.

Polyprenylamines (3b). The reaction of phthalimides **2b** (0.76 g, ~0.63 mmol) with $N_2H_4 \cdot H_2O$ (0.36 g, 7.1 mmol) in a mixture of THF (7 mL) and MeOH (3 mL) carried out as described above gave 0.36 g (53%) of amines **3b** as a colorless oil with R_f 0.78 ($CHCl_3$: MeOH : H_2O, 45 : 15 : 1, v/v). IR, ν/cm^{-1}: 835, 1190, 1215, 1375, 1450, 1510, 1660, 2720, 2860, 2915, 2970, 3010, 3380, 3460. ^{1}H NMR, δ: 1.61 (br.s, *cis*-Me); 1.70 (br.s, *trans*-Me); 1.72 (br.s, MeC(3)); 1.92—2.17 (m, CH_2); 3.24 (br.d, HC(1), J = 7.4 Hz); 5.14 (m, HC=); 5.29 (br.t, HC(2), J = 7.4 Hz). Found (%): N, 1.50. $C_{70}H_{115}N$, $C_{75}H_{123}N$, $C_{80}H_{131}N$, $C_{85}H_{139}N$. Calculated (%): N, 1.44, 1.35, 1.27, 1.19, respectively.

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