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Synthesis of alkylphenols lactamomethyl derivatives

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Abstract

In this paper we describe the synthesis of lactamomethyl derivatives of several alkylphenols (thymol and 2,4-di-*t*-butyl-phenol) with butyrolactam, valerolactam, caprolactam and 4-phenylpyrrolidone fragments. The development of such compounds is one of the modern trends for the search of new and effective antioxidants with low toxicity and, as a result, with wide range of possible usage. The structures of target compounds were confirmed by IR and NMR study. In IR spectra there are carbonyl group peaks in lower frequencies (about 1600 cm^{-1}) than expected due to the formation of inter- and intramolecular hydrogen bonds between this group and phenolic hydroxyl group. In ^1H NMR spectra the signals of protons of lactam fragments and phenolic alkyl substituents are located in the high field region (1.50-3.50 ppm) and have a form of corresponding multiplets. The value of the chemical shift of the "methylene bridge" (-CH_2-group) protons is about 4.00 ppm. This signal is a singlet in most cases. The signals of aromatic and hydroxylic protons are located in the weak-field region. For several products, containing a fragment of 4-phenylpyrrolidone, the signal of the methylene bridge is an AB system due to the presence of asymmetric nitrogen atom. *In silico* estimation of possible pharmacological effects and acute rat toxicity for target compounds was carried out using PASS-Online and GUSAR-Online services. It was shown, that studied compounds are expected to be nontoxic or low toxic (Class 5 or 4 of rat acute toxicity) and possess wide range of possible biological effects and. Energy of dissociation of ArO-H bond was calculated to reveal possible antioxidant activity of target compounds using quantum chemical method (semi-empirical PM6) in $ROO^{\cdot} + ArOH \rightarrow ROOH + ArO^{\cdot}$ reaction model. According to the calculation results, introducing of lactamomethyl fragment in the *para*-position of phenolic ring decreases energy of the dissociation of ArO-H bond. In case of *ortho*-substitution, increasing of the energy was observed due to the formation of hydrogen bond between phenolic hydroxyl group and lactam carbonyl group.

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