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REGIOSELECTIVE OXIDATION OF THE METHYL ESTER OF MALEOPIMARIC ACID BY DIMETHYLDIOXIRANE

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*Reaction of the methyl ester of maleopimaric acid and dimethyldioxirane resulted in regioselective oxidation of the bridging double bond to form the 13(15)-en-14*S*-hydroxy derivative.*

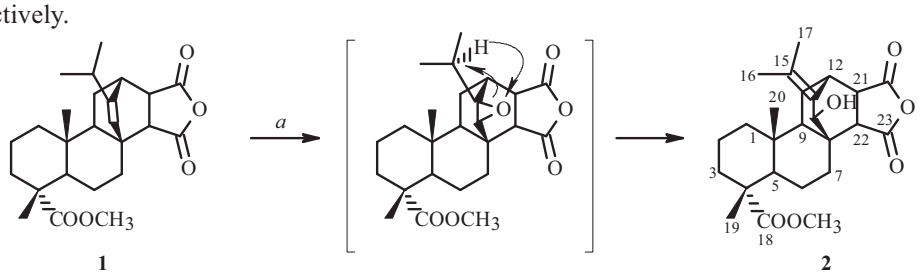
Keywords: levo-pimaric acid, maleopimaric acid, oxidation, dimethyldioxirane.

Diene adducts of levo-pimaric acid and their synthetic derivatives are significant for the preparation of compounds with new structures, e.g., diterpene heterocycles and several other compounds with an original structure and valuable biological activity. Their oxidative transformations are especially interesting. The *endo*-configuration of the majority of diene adducts of levo-pimaric acid hinders functionalization of the ring-C bridging double bond. As a result, the double bond is incapable of reacting with most oxidants [1, 2]. The first reports of the oxidation of maleopimaric acid appeared already in the 1930s [3, 4]. It was assumed that ozonation of maleopimaric acid opened the ring-C bridging double bond and retained the anhydride ring. However, the structure of the obtained compound was not confirmed [3]. It was shown later that ozonolysis of maleopimaric acid in CH_2Cl_2 at 0°C in the presence of a catalytic amount of tetracyanoethylene formed a mixture of the epoxide and the 1,2,4-ozonide at the C13–C14 double bond [5]. Cleavage of the double bond in CH_2Cl_2:MeOH at 0°C formed a tetra-acid for which anti-inflammatory and antiulcer activity was observed [6, 7].

The bridging double bond of maleopimaric acid is stable to the action of *m*-CPBA in $CHCl_3$. However, it undergoes oxidation by CF_3CO_3H or *p*-$NO_3C_6H_4CO_3H$ to the C13–C14 epoxide [1]. Oxidation of maleopimaric acid by $KMnO_4$ formed a mixture of C14–O–C23 and C14–O–C24 lactones depending on the amount of used equivalents of oxidant [8].

In continuation of research on oxidative transformations of diene adducts of levo-pimaric acid [6, 7, 9, 10], we carried out the oxidation of the methyl ester of maleopimaric acid by dimethyldioxirane (DMD). It was shown previously that the reaction of DMD with dihydroquinopimaric acid proceeded through epoxidation of the C13–C14 double bond, opening of the epoxide ring, formation of a double bond at the C13–C15 position, and cyclization into a hemiacetal at the C14–C4 position [10].

Reaction of the methyl ester of maleopimaric acid (**1**) with three equivalents of DMD in Me_2CO at room temperature formed **2** in 84% yield (Scheme 1). The structure of **2** was established using NMR spectroscopy. Thus, the PMR spectrum of **2** exhibited a singlet for H-14 at δ 5.04 ppm whereas the resonance of H-15 at δ 2.25 ppm that was characteristic of the spectrum of **1** was missing. The ^{13}C NMR spectrum contained resonances for C-13, C-14, and C-15 at δ 135.1, 79.7, and 126.7 ppm, respectively.



1 **2**

a. 3 equiv. DMD, Me_2CO

Scheme 1

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The proposed formation mechanism of **2** was analogous to the oxidation of dihydroquinopimaric acid and concluded with epoxidation of the C13−C14 double bond and a subsequent 1,2-sigmatropic shift and opening of the epoxide ring to form a C13−C15 double bond and a C-14 hydroxyl.

Thus, the reaction of maleopimaric acid and DMD, like for quinopimaric acid derivatives [9, 10], was an effective approach to the oxidation of the bridging double bond to form the previously inaccessible 13(15)-en-14*S*-hydroxy derivative.

EXPERIMENTAL

PMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker AM-300 spectrometer (75.5 and 300 MHz, respectively). Chemical shifts are given in ppm relative to the resonance of $SiMe_4$ internal standard. Melting points were determined on a Boetius microstage. Specific rotation angles were taken on a Perkin–Elmer 241 MC polarimeter in a 1-dm tube. The methyl ester of maleopimaric acid (**1**) was prepared as before [8]; the solution of DMD in acetone, according to the literature [11].

Methyl (4*R*,10*R*)-14-Hydroxy-4,10-dimethyl-13-(15-methylethylidene)-23,24-dioxotetradecahydro-1*H*-8,12-ethanophenanthro[1,2-*c*]furan-4-carboxylate (2). A solution of the methyl ester of maleopimaric acid (**1**, 100 mg) in Me_2CO (10 mL) was stirred continuously at room temperature, treated with small portions of DMD (3 equiv., 1 equiv. ~ 0.08 M) in Me_2CO, and stirred until the DMD was completely consumed (monitoring by peroxide iodometry). When the reaction was finished, the solvent was distilled off in vacuo. The solid was crystallized from Me_2CO. Yield 84 mg (84%), mp 152°C, $[\alpha]_D^{20}$ −9° (*c* 0.033, $CHCl_3$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 5.04 (1H, s, H-14), 3.68 (3H, s, OCH_3), 3.12 (1H, m, H-12), 2.89 (1H, dd, J = 3, 11, H-21), 2.48 (1H, d, J = 11, H-22), 2.05 (1H, dt, J = 3, 14, H-7), 1.80 (3H, s, H-16), 1.79 (1H, t, H-9), 1.78 (3H, s, H-17), 1.71 (1H, t, H-5), 1.65–1.25 (9H, m, H-2, 3, 6, 7, 11), 1.15 (3H, s, H-19), 1.01-0.92 (2H, t, H-1), 0.74 (3H, s, H-20).

^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 13.9 (C-20), 16.5 (C-19), 17.1 (C-2), 19.9 (C-16), 20.2 (C-17), 21.3 (C-6), 29.5 (C-11), 31.0 (C-12), 33.1 (C-7), 36.7 (C-3), 37.3 (C-1), 37.5 (C-10), 43.8 (C-21), 45.1 (C-5), 45.8 (C-8), 47.1 (C-4), 49.6 (C-9), 50.2 (C-22), 52.1 (OCH_3), 79.7 (C-14), 126.7 (C-15), 135.1 (C-13), 175.9 (C-23), 177.3 (C-24), 179.0 (C-18).

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