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SYNTHESIS OF *S*-CONTAINING MALEOPIMARIC ACID DERIVATIVES

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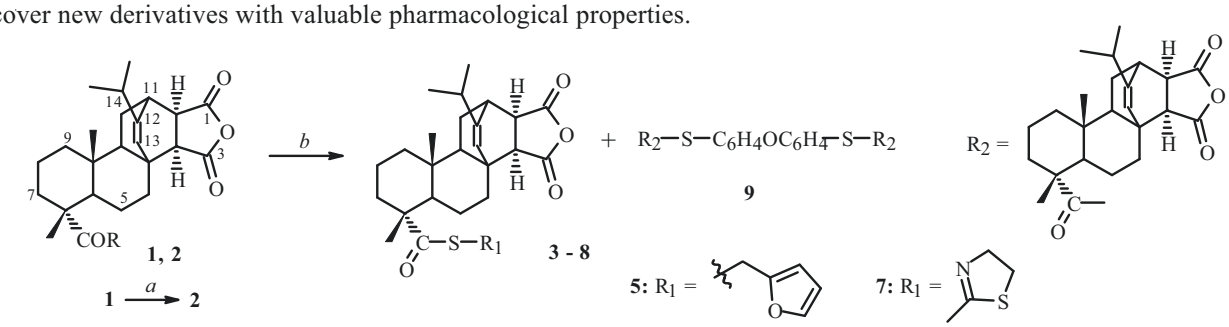
New S*-containing maleopimaric acid derivatives were synthesized. The structures of all synthesized compounds were elucidated using NMR spectroscopy and elemental analyses.*

Keywords: diterpenic acids, maleopimaric acid, *S*-containing derivatives.

S-Containing organic compounds are widely used in industry, agriculture, and medicine. For example, vitamins (biotin, thiamine, coenzyme A, lipoic acid), amino acids (cystine, cysteine, methionine), and alkaloids (peptides isolated from EtOH extract of *Amanita phalloides* mushroom, Cruciferae plants, Nymphaeaceae water lilies, etc.) are notable natural compounds with pharmacological activity. *S*-Containing modern drugs are used as antibacterial, antituberculosis, and anti-inflammatory medicines [1]. The presence of S atoms in organic molecules is well-known to be responsible for their high physiological activity and to reduce their toxicity [2].

Levopimaric acid occurs in resins of many conifer species and has recently been used as a scaffold for synthesizing biologically active compounds [3]. Diene adducts of levopimaric acid and maleic anhydride, i.e., maleopimaric acid (MPA, **1**) derivatives, are highly interesting because of their antibacterial, anti-inflammatory, and antiulcer properties [3]. Several *S*-containing levopimaric acid derivatives (quinopimaric acid framework derivatives) showed antihypoxic activity [4]. New *S*-containing MPA derivatives were synthesized by us to expand the repertoire of levopimaric acid derivatives and to discover new derivatives with valuable pharmacological properties.



1: R = OH; **2:** R = Cl; **3:** $R_1 = CH_2CO_2Me$; **4:** $R_1 = CH_2CO_2Et$; **6:** R_1 = Ph; **8:** $R_1 = C_6H_4OC_6H_4SH$
a. $SOCl_2$; *b*. R_1SH, CH_2Cl_2, Et_3N

S-Containing MPA derivatives were prepared in two steps using acid chlorides. First, the reaction of $SOCl_2$ and MPA (**1**) gave acid chloride **2**, which then was reacted with mercaptans. The thiols were methyl and ethyl mercaptoacetates, 2-furylmethylthiol, thiophenol, 2-mercaptothiazoline, and 4,4′-thiodiphenol. The reactions were performed at room temperature in CH_2Cl_2 with added Et_3N. Carbothioates **3**–**8** were obtained in 74–99% yields.

The reaction with 4,4′-thiodiphenol gave carbothioate **8** and a small amount (4%) of dimer **9**. Weak-field shifts of the carbonyl singlet (δ 185.54 ppm for MPA and 201–206 ppm for **3**–**9**) and the C-6 singlet (δ 46.85 ppm for MPA and 54 for **3**–**6**, **8**) and a strong-field shift of C-6 in **7** (δ_C 46.79 ppm) confirmed that carbothioates **3**–**9** had formed.

Thus, MPA carbothioates were synthesized for the first time by us by reacting MPA chloride with mercaptans.

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EXPERIMENTAL

General comments were published [4].

R_f values were determined using $CHCl_3$–MeOH (10:1).

MPA chloride (**2**) was synthesized as before [5]. All physicochemical properties of MPA chloride agreed with the literature.

Synthesis of *S*-Containing MPA Derivatives. MPA chloride (**2**, 0.7 g, 1.67 mmol) in anhydr. CH_2Cl_2 (30 mL) was stirred at room temperature and treated with mercaptan (1.75 mmol) and then Et_3N (0.23 mL, 1.67 mmol). When the reaction was finished (TLC monitoring), the solvent was evaporated at reduced pressure. The residue was treated with anhydr. Me_2CO (25 mL). The precipitate was filtered off and rinsed with anhydr. Me_2CO (10 mL). The filtrate was evaporated at reduced pressure. The solid was dried under vacuum and ground. If necessary, the product was purified by column chromatography over SiO_2 (eluents $CHCl_3$ and $CHCl_3$–MeOH gradient, 100:1, 50:1, 10:1).

Methyl {[{(6*R*,9a*R*)-12-Isopropyl-6,9a-dimethyl-1,3-dioxotetradecahydro-1*H*-3b,11-ethenophenanthro[1, 2-*c*]furan-6-yl}carbonyl]thio}acetate (3). $C_{27}H_{36}O_6S$. Yield 87%, R_f 0.61, mp 45–48°C, $[\alpha]_D^{20}$ –4.4° (*c* 5.7, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1842, 1779, 1744, 1681, 1463, 1385, 1297, 1232, 1159, 1084, 1003, 946, 918, 854. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.80 (CH_3, C-6), 16.83 (CH_3, C-9a), 17.07 (CH_2, C-8), 19.96 (CH_3, C-14), 20.57 (CH_3, C-14), 21.18 (CH_2, C-5), 27.28 (CH_2, C-10), 31.32 (CH_2, C-1′), 32.76 (CH, C-14), 34.69 (CH_2, C-4), 35.64 (CH, C-11), 37.62 (CH_2, C-7), 37.88 (CH_2, C-9), 37.96 (C, C-9a), 40.39 (C, C-3b), 45.67 (CH, C-11a), 50.22 (CH, C-5a), 52.75 (CH_3, COO<u>Me</u>), 53.05 (CH, C-3a), 53.31 (CH, C-9b), 54.35 (C, C-6), 125.16 (CH, C-13), 148.15 (C, C-12), 169.45 (C, COO), 170.92 (C, C-1), 172.71 (C, C-3), 206.32 (C, COS). Found, %: C 66.01; H 7.09; S 6.74. Calcd, %: C 66.37, H 7.43, S 6.56.

Ethyl {[{(6*R*,9a*R*)-12-Isopropyl-6,9a-dimethyl-1,3-dioxotetradecahydro-1*H*-3b,11-ethenophenanthro[1, 2-*c*]furan-6-yl}carbonyl]thio}acetate (4). $C_{28}H_{38}O_6S$. Yield 98%, R_f 0.68, mp 34–37°C, $[\alpha]_D^{20}$ –42° (*c* 0.9166, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1842, 1778, 1733, 1682, 1464, 1377, 1297, 1232, 1155, 1083, 946, 917. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 14.12 (CH_3, Me in Et), 15.79 (CH_3, C-6), 16.82 (CH_3, C-9a), 17.07 (CH_2, C-8), 19.95 (CH_3, C-14), 20.56 (CH_3, C-14), 21.17 (CH_2, C-5), 27.25 (CH_2, C-10), 31.57 (CH_2, C-1′), 32.74 (CH, C-14), 34.66 (CH_2, C-4), 35.63 (CH, C-11), 37.65 (CH_2, C-7), 37.84 (CH_2, C-9), 37.93 (C, C-9a), 40.38 (C, C-3b), 45.64 (CH, C-11a), 50.16 (CH, C-5a), 53.02 (CH, C-3a), 53.26 (CH, C-9b), 54.31 (C, C-6), 61.77 (CH_2, OCH_2), 125.14 (CH, C-13), 148.16 (C, C-12), 168.96 (C, COO), 170.96 (C, C-1), 172.75 (C, C-3), 206.39 (C, COS). Found, %: C 70.01; H 7.77; S 6.50. Calcd, %: C 66.90, H 7.62, S 6.38.

***S*-(2-Furylmethyl) (6*R*,9a*R*)-12-Isopropyl-6,9a-dimethyl-1,3-dioxotetradecahydro-1*H*-3b,11-etheno-phenanthro[1,2-*c*]furan-6-carbothioate (5).** $C_{29}H_{36}O_5S$. Yield 99%, R_f 0.77, mp 154–157°C, $[\alpha]_D^{20}$ –54.7 ± 0.1° (*c* 1.01, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1840, 1768, 1713, 1657, 1652, 1464, 1456, 1377, 1235, 1227, 1158, 1087, 1011, 945, 918, 854, 754. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.79 (CH_3, C-6), 16.83 (CH_3, C-9a), 17.11 (CH_2, C-8), 19.96 (CH_3, C-14), 20.56 (CH_3, C-14), 21.17 (CH_2, C-5), 25.92 (CH_2, C-1′), 27.26 (CH_2, C-10), 32.76 (CH, C-14), 34.69 (CH_2, C-4), 35.65 (CH, C-11), 37.66 (CH_2, C-7), 37.91 (CH_2, C-9), 37.96 (C, C-9a), 40.40 (C, C-3b), 45.65 (CH, C-11a), 50.18 (CH, C-5a), 53.04 (CH, C-3a), 53.32 (CH, C-9b), 54.41 (C, C-6), 104.92 (CH, C-4″), 110.61 (CH, C-3″), 125.17 (CH, C-13), 142.14 (CH, C-5″), 148.17 (C, C-12), 150.65 (C, C-2″), 170.94 (C, C-1), 172.70 (C, C-3), 206.73 (C, COS). Found, %: C 70.21; H 7.23; S 6.74. Calcd, %: C 70.13, H 7.31, S 6.46.

***S*-Phenyl (6*R*,9a*R*)-12-Isopropyl-6,9a-dimethyl-1,3-dioxotetradecahydro-1*H*-3b,11-ethenophenanthro[1, 2-*c*]furan-6-carbothioate (6).** $C_{30}H_{36}O_4S$. Yield 74%, R_f 0.71, mp 186–188°C, $[\alpha]_D^{20}$ –61.4 ± 0.1° (*c* 1.01, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1834, 1775, 1682, 1533, 1464, 1377, 1226, 1084, 945, 928, 915, 747. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.82 (CH_3, C-6), 17.01 (CH_3, C-9a), 17.16 (CH_2, C-8), 19.97 (CH_3, C-14), 20.57 (CH_3, C-14), 21.36 (CH_2, C-5), 27.26 (CH_2, C-10), 32.76 (CH, C-14), 34.73 (CH_2, C-4), 35.66 (CH, C-11), 37.71 (CH_2, C-7), 37.93 (CH_2, C-9), 37.99 (C, C-9a), 40.40 (C, C-3b), 45.65 (CH, C-11a), 50.15 (CH, C-5a), 53.06 (CH, C-3a), 53.31 (CH, C-9b), 54.93 (C, C-6), 125.15 (CH, C-13), 128.35 (C, C-1′), 129.13 (CH, C-2′, 6′), 129.21 (CH, C-4′), 135.13 (CH, C-3′, 5′), 148.21 (C, C-12), 171.07 (C, C-1), 172.77 (C, C-3), 205.98 (C, COS). Found, %: C 73.22; H 7.40; S 6.33. Calcd, %: C 73.14, H 7.37, S 6.51.

***S*-(4,5-Dihydro-1,3-thiazol-2-yl) (6*R*,9a*R*)-12-Isopropyl-6,9a-dimethyl-1,3-dioxotetradecahydro-1*H*-3b,11-ethenophenanthro[1,2-*c*]furan-6-carbothioate (7).** $C_{27}H_{35}NO_4S_2$. Yield 99%, R_f 0.51, mp 63–67°C, $[\alpha]_D^{20}$ –2.6° (*c* 5.6, $CHCl_3$). IR spectrum (ν, cm^{-1}): 3142, 1841, 1778, 1693, 1519, 1464, 1377, 1299, 1231, 1088, 1053, 947, 924. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.51 (CH_3, C-6), 16.51 (CH_3, C-9a), 17.29 (CH_2, C-8), 19.97 (CH_3, C-14), 20.57 (CH_3, C-14), 21.67 (CH_2, C-5), 27.22 (CH_2, C-10), 32.76 (CH, C-14), 33.66 (CH_2, C-5′), 34.80 (CH_2, C-4), 35.69 (CH, C-11), 36.77 (CH_2, C-7), 37.57 (C, C-9a), 37.99 (CH_2, C-9), 40.45 (C, C-3b), 45.69 (CH, C-11a), 46.79 (C, C-6), 49.09 (CH, C-5a), 51.44 (CH_2,

C-4′), 53.12 (CH, C-3a), 53.30 (CH, C-9b), 125.17 (CH, C-13), 148.17 (C, C-12), 171.07 (C, C-1), 172.83 (C, C-3), 184.29 (C, C-2′), 201.85 (C, COS). Found, %: C 64.84; H 7.29; N 3.03; S 12.74. Calcd, %: C 64.64, H 7.03, N 2.79, S 12.78.

***S*-[4-(4-Mercaptophenoxy)phenyl] (6*R*,9a*R*)-12-Isopropyl-6,9a-dimethyl-1,3-dioxotetradecahydro-1*H*-3b,11-ethenophenanthro[1,2-*c*]furan-6-carbothioate (8).** $C_{36}H_{40}O_5S_2$. Yield 96%, obtained together with dimer **9**, **8**–**9** ratio 96:4. Isolated pure by column chromatography. R_f 0.79, mp 151–154°C, $[\alpha]_D^{20}$ –36.7 ± 0.1° (*c* 1.01, $CHCl_3$). IR spectrum (ν, cm^{-1}): 1848 br.s, 1778, 1697, 1581, 1483, 1456, 1377, 1238, 1167, 1083, 1013, 947, 914. ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 15.54 (CH_3, C-6), 17.03 (CH_3, C-9a), 17.17 (CH_2, C-8), 19.99 (CH_3, C-14), 20.61 (CH_3, C-14), 21.41 (CH_2, C-5), 27.27 (CH_2, C-10), 32.79 (CH, C-14), 34.76 (CH_2, C-4), 35.65 (CH, C-11), 37.58 (CH_2, C-7), 37.91 (CH_2, C-9), 38.01 (C, C-9a), 40.43 (C, C-3b), 45.64 (CH, C-11a), 50.18 (CH, C-5a), 52.86 (CH, C-3a), 53.36 (CH, C-9b), 54.92 (C, C-6), 119.72 (CH, C-2″, 6″), 119.87 (CH, C-3′, 5′), 125.11 (CH, C-13), 131.05 (C, C-4″), 131.76 (C, C-1′), 136.89 (CH, C-2′, 6′), 138.80 (CH, C-3″, 5″), 148.23 (C, C-12), 156.56 (C, C-1″), 157.82 (C, C-4′), 171.05 (C, C-1), 172.74 (C, C-3), 206.44 (C, COS). Found, %: C 70.09; H 6.43; S 10.52. Calcd, %: C 70.10, H 6.54, S 10.40.

***S*,*S*′-[Oxy-*bis*(4,1-phenylene)] *bis*-[(6*R*,9a*R*)-12-Isopropyl-6,9a-dimethyl-1,3-dioxotetradecahydro-1*H*-3b,11-ethenophenanthro[1,2-*c*]furan-6-carbothioate] (9).** Yield 4% (according to spectral data), obtained together with carbothioate **8**, **8**–**9** ratio 96:4, not isolated pure. Characteristic resonances in the ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 124.98 (CH, C-13), 131.08 (CH, C-2′, 6′), 154.80 (C, C-12), 206.41 (C, C=S).

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