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Synthesis of 5-Hydroxy-1,3-benzoxathiol-2-one and 2-Amino-1,3-benzothiazol-6-ol Derivatives from Chrysenequinonecarboxylic Acid

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Abstract—Diterpenoid 5-hydroxy-1,3-benzoxathiol-2-one and 2-amino-1,3-benzothiazol-6-ol derivatives were synthesized by reaction of methyl chrysenequinonecarboxylate with thiourea.

Resin acids and their derivatives exhibit biological activity; for example, levopimaric acid adducts with 1,4-benzoquinone, 2-acetaminoquinone, sulfonaphthoquinone, and 3-hexylsulfanyl-4,5-dihydrothiophen-4-one 1,1-dioxide show antiulcer and antiphlogistic activity [1–3], while diarylamino derivatives of dehydroabietic acid act as antioxidants [4]. Some diterpenoid indole alkaloids (paspaline, penitrem, terpendole, etc.) exhibit insecticide and fungicide properties [5, 6]. In continuation of our studies on the synthesis of heterocycles with a diterpenoid fragment [2, 7–9], in the present work we synthesized derivatives of 5-hydroxy-1,3-benzoxathiol-2-one and 2-amino-1,3-benzothiazol-6-ol on the basis of quinopimaric acid, an adduct of levopimaric acid and *p*-benzoquinone.

Addition of thiourea to quinones is known as an effective method for the preparation of benzoxathiol and benzothiazole derivatives. Reactions of thiourea with unsubstituted and di- and trisubstituted quinones were shown to afford the only adduct, whereas monosubstituted quinones give rise to complex mixtures of products, depending on the substituent nature [10, 11].

As initial compound we used methyl chrysenequinonecarboxylate (1a,4a-dehydroquinopimarate) (**II**) which is readily available from levopimaric acid, the latter being one of the main components of the acidic fraction of *Pinus Silvestris* pine pitch. Compound **II** was synthesized in 89% yield from methyl quinopimarate (**I**) via oxidation of its hydroquinone tautomer with $Ce(NH_4)_2(NO_3)_6$ in acetonitrile by analogy with the procedure described in [12]. In the ^{13}C NMR spectrum of **II**, signals from the C^{1a} and C^{4a} atoms appeared at δ_C 152.7 and 150.5 ppm, respectively, while no signals typical of 1a-H and 4a-H in methyl quinopimarate (**I**) (δ 2.73 and 2.91 ppm) were observed in the ^1H NMR spectrum.

Heterocyclic compounds **III**–**V** were synthesized by reaction of methyl ester **II** with thiourea. Depending on the reactant ratio and reaction conditions, the product was either a mixture of hydroxybenzoxathiolones **III** and **IV** or aminobenzothiazolol **V** as the only product (Scheme 1). Compounds **III** and **IV** were obtained in an overall yield of 87% (ratio 1:4) when the reaction of quinone **II** with 2 equiv of thiourea was carried out in a mixture of acetic and hydrochloric acids at 50–55°C. The process is likely to involve 1,4-addition of thiourea to protonated quinone **II** with formation of *S*-(1,4-dihydroxyaryl)thiuronium salt which undergoes ring closure to 5(4)-hydroxy-2(1')-imino-1,2-benzoxathiol.* Hydrolysis of the latter yields 5(4)-hydroxy-1,2-benzoxathiol-2(1')-one **III**, as in the synthesis of 5-hydroxy-1,3-benzoxathiol-2-ones from simple quinones and thiourea [10]. Likewise, 5(1)-hydroxy-1,2(3,4)-benzoxathiol-2(1')-one **IV** is formed when the reaction begins with protonation of the oxo group on C^4.

The IR spectra of compounds **III** and **IV** contain an absorption band at 3380–3375 cm^{-1} due to stretch-

* Hereinafter, in parentheses are given locants corresponding to the atom numbering shown in Scheme 1.

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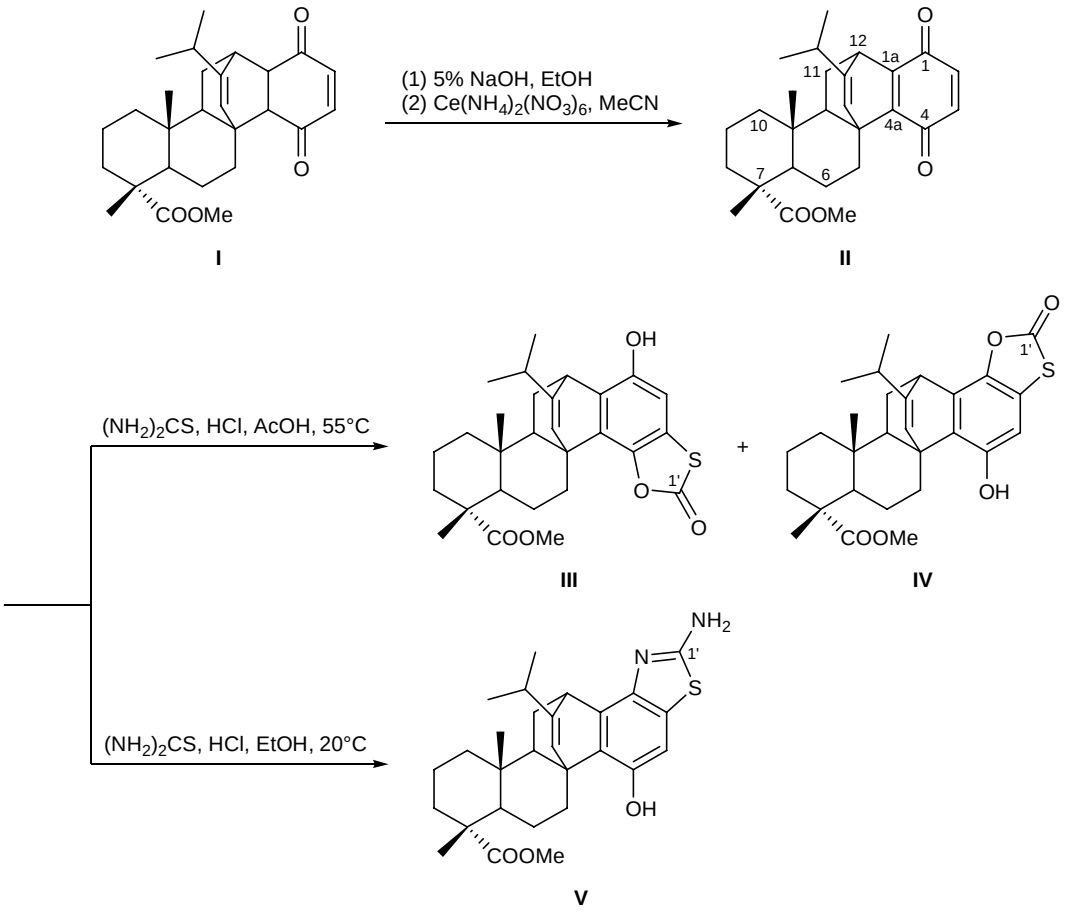
Scheme 1.



ing vibrations of the hydroxy group. The carbonyl carbon atom ($C^{1'}$) gives a signal at δ_C 152.2 ppm in the ^{13}C NMR spectrum. Signals from C^1 and C^4 in the hydroquinone fragment are located, respectively, at δ_C 148.9 and 125.4 ppm (**III**) or 130.4 and 132.2 ppm (**IV**). The C^2 and C^3 signals appear at δ_C 97.1 and 117.2 ppm (**III**) and δ_C 97.9 and 117.1 ppm (**IV**). The signals at δ_C 109.8 and 104.8 ppm in the spectra of both compounds belong to the doubly bonded C^{1a} and C^{4a} carbon atoms. In the ^1H NMR spectra, the OH signal from the hydroquinone fragment appears as a broadened singlet at δ 6.70 ppm.

In the reaction of quinone **II** with an equimolar amount of thiourea in ethanol in the presence of hydrochloric acid, followed by treatment with aqueous sodium acetate, we isolated aminobenzothiazolol **V** as the only product (yield 55%). Compound **V** showed in the IR spectrum an absorption band at 3390 cm^{-1} due to stretching vibrations of the amino group. The ^1H NMR spectrum of **V** contained broadened singlets at δ 4.90 and 6.70 ppm, which belong to the NH_2 and OH protons, respectively. The following signals were observed in the ^{13}C NMR spectrum of benzothiazole derivative **V**, δ_C, ppm: 152.3 ($C^{1'}$), 137.4 (C^1), 96.6 (C^2), 117.2 (C^3), 126.4 (C^4), 110.5 (C^{1a}), 101.6 (C^{4a}).

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The ^{13}C and ^1H NMR spectra were obtained on a Bruker AM-300 spectrometer at 75.5 and 300 MHz, respectively, using TMS as internal reference. The optical rotations were measured on a Perkin–Elmer MC-241 instrument from solutions in $CHCl_3$. The melting points were determined on a Boetius device. TLC was performed on Sulufol plates (Chemapol, Czechia) using $CHCl_3$–MeOH (20:1) as eluent; spots were detected by treatment with a 10% solution of phosphotungstic acid in ethanol, followed by heating at 100–120°C for 2–3 min. Methyl quinopimarate (**I**) was synthesized according to the procedure described in [13].

Methyl 20-isopropyl-5,9-dimethyl-14,17-dioxopentacyclo[10.6.2.0^{1,10}.0^{4,9}.0^{13,18}]icosa-13(18),15,19-

triene-5-carboxylate (II). To a solution of 0.42 g (1 mmol) of compound **I** in 30 ml of ethanol we added under stirring 3 ml of a 5% solution of sodium hydroxide. The mixture was stirred for 40 min and acidified with 3% hydrochloric acid, and the precipitate was filtered off, washed with water, dried, and recrystallized from ethyl acetate. Yield of the hydroquinone derivative 0.34 g (80%), mp 185–187°C, $[\alpha]_D^{20}$ = –91.0° (*c* = 1.0, $CHCl_3$). A 0.42-g (1-mmol) portion of the product was dissolved in 30 ml of anhydrous acetonitrile, 0.5 g of $Ce(NH_4)_2(NO_3)_6$ was added under stirring, and the mixture was stirred for 5–6 h until it became homogeneous and was left overnight. It was then poured into 50 ml of water and extracted with chloroform (20×3 ml), and the combined extracts were washed with water (20×2 ml), dried over $MgSO_4$, and evaporated under reduced pressure. Yield 0.37 g (89%), mp 199–200°C. $[\alpha]_D^{20}$ = –105.1° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 1730 ($COOCH_3$), 1680 (C=O), 1630 (–CH=CH–), 1480, 1390, 1330, 1315, 1260, 1210, 1160, 1125, 1070, 1035, 1015, 990, 880, 850, 745, 720. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.66 s (3H, 7-CH_3), 0.68–0.73 m (3H, 10-H_{ax}, 10-H_{eq}, 10b-H), 0.90 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 0.94 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 1.15 s (3H, 10a-CH_3), 1.18–1.32 m (5H, 6-H_{ax}, 6-H_{eq}, 9-H_{ax}, 9-H_{eq}, 11-H_{ax}), 1.40–1.68 m (6H, 8-H_{ax}, 8-H_{eq}, 5-H_{ax}, 5-H_{eq}, 6-H_{ax}, 11-H_{eq}), 2.08 sept [1H, C**H**$(CH_3)_2$, *J* = 6.9 Hz], 2.74 d.t (1H, 12-H, *J* = 8.0, 2.5, 2.6 Hz), 3.71 s (3H, $COOCH_3$), 5.60 br.s (1H, 14-H), 6.50 d.d [2H, 2-H, 3-H, *J* = 6.8 Hz]. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 185.2 (C^1), 152.7 (C^{1a}), 133.5 (C^2), 137.4 (C^3), 183.9 (C^4), 150.5 (C^{4a}), 47.1 (C^{4b}), 31.9 (C^5), 21.7 (C^6), 49.4 (C^{6a}), 49.1 (C^7), 36.4 (C^8), 17.1 (C^9), 39.3 (C^{10}), 38.5 (C^{10a}), 51.9 (C^{10b}), 27.0 (C^{11}), 36.3 (C^{12}), 150.9 (C^{13}), 127.2 (C^{14}), 32.3 (C^{15}), 20.5 (C^{16}), 20.2 (C^{17}), 16.7 (C^{18}), 16.3 (C^{19}), 179.1 (C^{20}), 54.7 (C^{21}). Found, %: C 76.65; H 8.20. $C_{27}H_{34}O_4$. Calculated, %: C 76.75; H 8.11.

Compounds III and IV. Compound **II**, 0.42 g (1 mmol), was dissolved in 50 ml of glacial acetic acid, and 1.0 g (13.2 mmol) of thiourea in 10 ml of 2 N hydrochloric acid was added with stirring. The mixture was stirred for 30 min at room temperature and slowly heated to 50–55°C. After 4 h, the mixture was cooled to room temperature and poured into 50 ml of water, and the precipitate was filtered off, washed with water, dried, and subjected to chromatography on aluminum oxide using benzene as eluent. We thus isolated 0.41 g (87%) of a mixture of compounds **III** and **IV** at a ratio of 1:4. ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 148.9 (0.80C, C^1), 130.4 (0.20C, C^1), 97.1 (0.80C, C^2), 117.1 (0.20C, C^2), 117.2 (0.80C, C^3), 97.9 (0.20C, C^3), 125.4 (0.80C, C^4), 132.2 (0.20C, C^4). IR spectrum, ν, cm^{-1}: 1780, 1730 (CO, ester), 1655, 1520, 1475, 1380, 1370, 1330, 1260, 1240, 1205, 1150, 1125, 1090, 1025, 950, 910, 890, 790, 770, 730. Found, %: C 68.35; H 7.15; S 6.59. $C_{28}H_{34}O_5S$. Calculated, %: C 69.68; H 7.10; S 6.64.

Methyl 14-hydroxy-23-isopropyl-5,9-dimethyl-18-oxo-17-oxa-19-thiahexacyclo[10.9.2.0^{1,10}.0^{4,9}.0^{13,21}.0^{16,20}]tricosa-13(21),14,16(20),22-tetraene-5-carboxylate (III). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.66 s (3H, 7-CH_3), 0.68–0.73 m (3H, 10-H_{ax}, 10-H_{eq}, 10b-H), 0.90 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 0.94 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 1.15 s (3H, 10a-CH_3), 1.18–1.29 m (5H, 6-H_{ax}, 6-H_{eq}, 9-H_{ax}, 9-H_{eq}, 11-H_{ax}), 1.45–1.68 m (6H, 8-H_{ax}, 8-H_{eq}, 5-H_{ax}, 5-H_{eq}, 6a-H, 11-H_{eq}), 2.08 sept [1H, C**H**$(CH_3)_2$, *J* = 6.9 Hz], 2.74 d.t (1H, 12-H, *J* = 8.0, 2.5, 2.6 Hz), 3.70 s (3H, $COOCH_3$), 4.70 br.s (1H, 14-H), 6.70 s (1H, 2-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 148.9 (C^1), 109.8 (C^{1a}), 97.1 (C^2), 117.2 (C^3), 125.4 (C^4), 104.8 (C^{4a}), 47.2 (C^{4b}), 32.9 (C^5), 20.3 (C^6), 51.7 (C^{6a}), 48.0 (C^7), 36.5 (C^8), 17.2 (C^9), 38.8 (C^{10}), 38.6 (C^{10a}), 54.2 (C^{10b}), 27.7 (C^{11}), 36.0 (C^{12}), 150.8 (C^{13}), 127.8 (C^{14}), 34.2 (C^{15}), 20.2 (C^{16}), 19.7 (C^{17}), 17.0 (C^{18}), 16.7 (C^{19}), 179.2 (C^{20}), 56.0 (C^{21}), 152.2 ($C^{1'}$).

Methyl 20-hydroxy-23-isopropyl-5,9-dimethyl-16-oxo-15-oxa-17-thiahexacyclo[10.9.2.0^{1,10}.0^{4,9}.0^{13,21}.0^{14,18}]tricosa-13(21),14(18),19,22-tetraene-5-carboxylate (IV). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.66 s (3H, 7-CH_3), 0.68–0.73 m (3H, 10-H_{ax}, 10-H_{eq}, 10b-H), 0.90 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 0.94 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 1.15 s (3H, 10a-CH_3), 1.18–1.29 m (5H, 6-H_{ax}, 6-H_{eq}, 9-H_{ax}, 9-H_{eq}, 11-H_{ax}), 1.45–1.68 m (6H, 8-H_{ax}, 8-H_{eq}, 5-H_{ax}, 5-H_{eq}, 6a-H, 11-H_{eq}), 2.08 sept [1H, C**H**$(CH_3)_2$, *J* = 6.9 Hz], 2.74 d.t (1H, 12-H, *J* = 8.0, 2.5, 2.6 Hz), 3.70 s (3H, $COOCH_3$), 4.70 br.s (1H, 14-H), 6.70 s (1H, 2-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 130.4 (C^1), 109.8 (C^{1a}), 117.1 (C^2), 97.9 (C^3), 132.2 (C^4), 104.8 (C^{4a}), 47.2 (C^{4b}), 32.9 (C^5), 20.3 (C^6), 51.7 (C^{6a}), 48.0 (C^7), 36.5 (C^8), 17.2 (C^9), 38.8 (C^{10}), 38.6 (C^{10a}), 54.2 (C^{10b}), 27.7 (C^{11}), 36.0 (C^{12}), 150.8 (C^{13}), 127.8 (C^{14}), 34.2 (C^{15}), 20.2 (C^{16}), 19.7 (C^{17}), 17.0 (C^{18}), 16.7 (C^{19}), 179.2 (C^{20}), 56.0 (C^{21}), 152.2 ($C^{1'}$).

Methyl 16-amino-20-hydroxy-23-isopropyl-5,9-dimethyl-17-thia-15-azahexacyclo[10.9.2.0^{1,10}.0^{4,9}.0^{13,21}.0^{14,18}]tricosa-13(21),14(18),15,19,22-pentaene-5-carboxylate (V). Compound **II**, 0.42 g (1 mmol), was dissolved in 50 ml of ethanol, and 0.5 g (6.58 mmol) of thiourea in 20 ml of ethanol and 1 ml of concentrated hydrochloric acid were added. The

mixture was stirred for 24 h at room temperature, poured into 50 ml of water, neutralized with aqueous sodium acetate, and extracted with chloroform (20× 3 ml). The combined extracts were washed with water (20×2 ml), dried over $MgSO_4$, and evaporated under reduced pressure, and the residue was subjected to chromatography on aluminum oxide using benzene as eluent. Yield 0.26 g (55%), mp 171–173°C, $[\alpha]_D^{20}$ = +110.4° (*c* = 1.0, $CHCl_3$). IR spectrum, ν, cm^{-1}: 3390 (NH_2), 1770, 1730 ($COOCH_3$), 1640, 1600, 1530, 1470, 1380, 1310, 1245, 1205, 1160, 1110, 1050, 1020, 990, 935, 895, 860, 760, 730. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.66 s (3H, 7-CH_3), 0.68–0.73 m (3H, 10-H_{ax}, 10-H_{eq}, 10b-H), 0.90 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 0.94 d [3H, CH(C**H**$_3$)$_2$, *J* = 6.9 Hz], 1.15 s (3H, 10a-CH_3), 1.20–1.35 m (5H, 6-H_{ax}, 6-H_{eq}, 9-H_{ax}, 9-H_{eq}, 11-H_{ax}), 1.40–1.67 m (6H, 8-H_{ax}, 8-H_{eq}, 5-H_{ax}, 5-H_{eq}, 6a-H, 11-H_{eq}), 2.07 sept [1H, C**H**$(CH_3)_2$, *J* = 6.9 Hz], 2.72 d.t (1H, 12-H, *J* = 8.0, 2.5, 2.6 Hz), 3.71 s (3H, $COOCH_3$), 4.68 br.s (1H, 14-H), 4.90 br.s (2H, NH_2), 6.70 s (1H, 2-H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 126.4 (C^1), 110.5 (C^{1a}), 96.6 (C^2), 117.2 (C^3), 137.4 (C^4), 101.6 (C^{4a}), 46.3 (C^{4b}), 32.1 (C^5), 18.0 (C^6), 49.8 (C^{6a}), 47.2 (C^7), 36.7 (C^8), 17.1 (C^9), 40.7 (C^{10}), 39.0 (C^{10a}), 51.6 (C^{10b}), 27.7 (C^{11}), 35.4 (C^{12}), 146.5 (C^{13}), 129.9 (C^{14}), 34.2 (C^{15}), 20.4 (C^{16}), 20.2 (C^{17}), 16.9 (C^{18}), 16.5 (C^{19}), 179.6 (C^{20}), 56.3 (C^{21}), 152.3 ($C^{1'}$). Found, %: C 68.35; H 7.45; N 5.59; S 6.60. $C_{28}H_{36}N_2O_3S$. Calculated, %: C 69.97; H 7.55; N 5.83; S 6.67.

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